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Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: A systematic review and meta-analysis

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ABSTRACT

Study objectives: Recently, less invasive methods have emerged as potential alternatives for staging with tissue confirmation of suspected metastatic mediastinal lymph nodes in lung cancer. The objective of this review was to assess the overall diagnostic accuracy of EBUS-TBNA in detecting metastatic mediastinal lymph node in lung cancer with a meta-analysis.
Methods: The MEDLINE, EMBASE, Cancerlit and Cochrane Library database, from January 1995 to September 2008, were searched for studies evaluating EBUS-TBNA accuracy. Meta-analysis methods were used to pool sensitivity and specificity and to construct summary receiver-operating characteristic.
Results: A total of 11 studies with 1299 patients, who fulfilled all of the inclusion criteria, were considered for the analysis. No publication bias was found. EBUS-TBNA had a pooled sensitivity of 0.93 (95% CI, 0.91–0.94) and a pooled specificity of 1.00 (95% CI, 0.99–1.00). The subgroup of patients who were selected on the basis of CT or PET positive results had higher pooled sensitivity (0.94, 95% CI 0.93–0.96) than the subgroup of patients without any selection of CT or PET (0.76, 95% CI 0.65–0.85) ($p < 0.05$). Study sensitivity was not correlated with the prevalence of lymph node metastasis. Only two complications occurred (0.15%).
Conclusion: EBUS-TBNA was an accurate, safe and cost-effective tool in lung cancer staging. The selection of patients who had positive results of suspected lymph node metastasis in CT or PET may improve the sensitivity of EBUS-TBNA. High-quality prospective studies regarding EBUS-TBNA in lung cancer staging are still needed to be conducted.

1. Introduction

Lung cancer is the leading cause of cancer death with a 5-year survival rate of only 15%.[1] The stage of disease dictates the choice of therapy. Surgery is most appropriate for patients in whom disease is confined to the lung and hilar lymph nodes. For patients with ipsilateral mediastinal lymph node metastases, the benefit of surgery as primary therapy is questionable. For patients with contralateral mediastinal lymph node metastases, surgery is generally not indicated, and chemotherapy, radiotherapy or both are considered the standard of care.[2] Therefore, adequate staging before surgery is of paramount importance to better stratify the therapeutic approach and to limit the number of futile thoracotomies.

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Mediastinoscopy has been the diagnostic standard for staging with tissue confirmation of suspected metastatic mediastinal lymph nodes.[3] However, less invasive methods have emerged as potential alternatives. Recently, Micames and colleagues[4] have reported in a meta-analysis of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in lung cancer mediastinal staging indicating that EUS-FNA is an accurate, cost-effective means of evaluating patients with lung cancer. Nevertheless, the research also pointed out that the main limitation of EUS-FNA was the inability to visualise mediastinal lymph nodes anterior to the trachea. Unlike EUS-FNA, endo-bronchial ultrasound-guided fine-needle aspiration (EBUS-TBNA) can precisely detect anterior mediastinal lymph nodes, since it is also a minimally invasive method, EBUS-TBNA is possible to be a valuable tool for mediastinal lymph node staging in lung cancer.

Since a large number of studies exploring the role of EBUS-TBNA in staging of lung cancer have been published, a comprehensive systematic review would be useful to synthesise the currently available bulk of information. The objective of this review was to assess the overall diagnostic value of EBUS-TBNA in detecting metastatic mediastinal lymph node in lung cancer with a meta-analysis, which to our knowledge, had not previously been studied.

2. Materials and methods

2.1. Literature search

A comprehensive computer literature search[5] was performed to identify articles about the diagnostic performance of EBUS-TBNA in detecting mediastinal lymph nodes in lung cancer. The MEDLINE and EMBASE databases, from January 1995 to September 2008, were used with the following key words: 'endobronchial ultrasound' OR 'endoscopic ultrasound' OR 'endosonography' OR 'transbronchial ultrasound', and 'fine-needle' OR 'fine-needle aspiration'. Other databases such as Cancerlit, Cochrane Library were also searched for relevant articles. Reference lists of included studies and review articles were manually searched.

2.2. Selection of studies

Two investigators (GP and ZYZ) independently checked retrieved articles. Disagreements were resolved in consensus. The inclusion criteria were (a) articles were published in English. (b) Real-time EBUS-TBNA was used in pretreatment patients with suspected or previously diagnosed lung cancer for staging of mediastinal lymph nodes. (c) Histopathology analysis and/or close clinical follow-up for at least six months were used as the reference standard. (d) For per-patient statistics, sufficient data were presented to calculate the true-positive (TP), false-negative (FN), false-positive (FP) and true-negative (TN) values. (e) 10 or more patients were included. (f) When data or subsets of data were presented in more than one article, the article with most details or the most recent article was chosen. The authors of abstracts and studies not reporting with sufficient data were contacted to request for additional information.

2.3. Data extraction

The same investigators (GP and ZYZ) independently extracted relevant data about study characteristics and examination results by using a standardised form. To resolve disagreement between reviewers, a third reviewer (HBH) assessed all discrepant items, and the majority opinion was used for analysis.

Relevant studies were further examined with Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria.[6] To perform accuracy analyses, we extracted the following items: description of study population (age); study design (prospective, retrospective or unknown); patient enrollment (consecutive or not); interpretation of the test results (blinded or not); stations examined by EBUS-TBNA; whether patients selected on the basis of CT or PET positive results or not; using histopathology alone or combined with clinical follow-up as the reference standard; prevalence of mediastinal lymph node metastasis; providing on-site cytopathology or not; the numbers of true-positive (TP), false-negative (FN), false-positive (FP) and true-negative (TN) results in the detection of mediastinal lymph nodes in suspected or previously diagnosed lung cancer. Positive EBUS-TBNA result was considered a true-positive, since the chance of contamination is rare.[7]

2.4. Statistical analysis

We used likelihood ratio I^2 index and χ^2 test to assess heterogeneity. I^2 index is a measure of the percentage of total variation across studies due to heterogeneity beyond chance, if its values over 50% indicate heterogeneity.[8] To likelihood ratio χ^2 test, $p < 0.05$ was considered having apparent heterogeneity. If heterogeneity existed,[9] a random effect model was used for the primary meta-analysis to obtain a summary estimate for sensitivity with 95% confidence intervals (CI). Studies in which positive EBUS-TBNA results were confirmed by other method were conducted a pooled specificity with 95% CI. Summary receiver operating characteristic (SROC) curves as described by Moses and colleagues[10] were constructed to summarise the results quantitatively. To assess sources of possible variation in study results, we performed subgroup analysis. Comparisons of diagnostic accuracy between subgroups were made by comparing the diagnostic odds ratio (DOR) between subgroups. Linear regression was not only used to analyse whether difference of DOR between subgroups was statistically significant, but used to evaluate potential relationship between sensitivity and prevalence of mediastinal metastasis lymph nodes as well. We also tested publication biases assessed by funnel plots.

All of the statistical analyses were undertaken using SAS statistical software version 8.2 (SAS Institute Inc., Cary, NC, United States) and Meta-DiSc (Version 1.4).[11] (Meta-DiSc, produced by Javier.zamora, is freeware software to perform systematic review of studies of evaluation of diagnostic and screening tests.). p-Values of <0.05 were considered to be statistically significant.

3. Results

3.1. Literature search and study design characteristics

Our research yielded 121 primary studies, of which 101 were excluded after reviewing the title and abstract, nine articles were excluded after reviewing the full article (Fig. 1), the reasons for exclusion were (a) EBUS-TBNA was used for restaging of mediastinal lymph nodes in patients after chemotherapy/radiotherapy or for detecting lymph node in patients with metastatic lung tumour.[12–14] (b) Data or subsets of data were presented in more than one article, the article with fewest details was excluded.[7,15,16] (c) Sufficient data were not presented to calculate the TP, TN, FP and FN values.[17,18] (d) Study was not published in English.[19] A total of 11 studies[20–30] with 1299 patients, who fulfilled all of the inclusion criteria, were considered for the analysis (Table 1).

3.2. Study description and study quality

The median number of participants per study was 118 (range 11–502). The median age of the participants was 61 years. Our study reported the results by using individual patient as the unit of analysis; the median prevalence of mediastinal metastasis was 68%. All studies used ultrasound bronchoscope with 22-gauge needle produced by Olympus Ltd., which was exclusively designed for real-time EBUS-TBNA. Eight studies enrolled patients who were selected on the basis of CT or PET positive results,[20,21,23–25,28–30] five studies used only histopathologic evidence as reference standard.[20,27–30] Two studies[27,28] were performed on surgery to confirm positive EBUS-TBNA result. Rapid on-site cytopathological examinations were conducted in two studies.[23,25] Two studies had an addition check to confirm true-positive results of EBUS-TBNA.[27,30]

Of all 11 studies, eight studies[21–24,26,27,29,30] enrolled patients prospectively. Two studies[20,25] were retrospective database reviews. Six studies enrolled patients in a consecutive manner,[23–27,30] including two studies,[27,30] in which TBUS-TBNA operator was blinded to prior test results.

3.3. Diagnostic accuracy of EBUS-TBNA

3.3.1. Publication bias and heterogeneity

To assess a possible publication bias, scatter plots were designed using the log diagnostic odd ratios (DORs) of individual studies against their sample size. The plot of this meta-analysis (Fig. 2) showed symmetric, demonstrating that there was probably no publication bias.

Heterogeneity was found between sensitivity of 11 enrolled studies (Table 2). No heterogeneity was found in specificity. Therefore, a random effect model was used for the primary meta-analysis to obtain a summary estimate for sensitivity and specificity with 95% confidence intervals (CI). To explore the possible source of heterogeneity, subgroup analyses were applied (Table 2). No heterogeneity was found between the subgroup with or without abnormal mediastinal lymph nodes confined by CT or PET. Hence, patient selection on the basis of CT or PET results was the possible source of heterogeneity in EBUS-TBNA.

3.3.2. Pooled sensitivity, pooled specificity and AUC

EBUS-TBNA had a pooled sensitivity of 0.93 (95% CI, 0.91–0.94) and a pooled specificity of 1.00 (95% CI, 0.99–1.00) (Table 2). Results for sensitivity in individual studies ranged from 69% to 100% (Fig. 3). The lowest sensitivity (69%) occurred in an individual study.[26] This study enrolled consecutive patients with suspected lung cancer, with or without enlarged mediastinal lymph nodes, with no selection for the location of lymphadenopathy. They did not use rapid on-site evaluation of the cytologic samples to determine adequacy either. The median prevalence of mediastinal metastasis was 68%. Linear regression suggested that study sensitivity was not correlated with the prevalence of lymph node metastasis (Fig. 4). When the prevalence rose from 40% to 80%, sensitivity only increased from 87% to 92%. Other factors which might have impact on pooled sensitivity were analysed in subgroup analyses (Table 2). Eight studies enrolled patients who were selected on the basis of CT or PET positive results,[20,21,23–25,28–30] the pooled sensitivity was 0.94 (95% CI, 0.93–0.96). The remaining three studies[22,26,27] which enrolled patients regardless of the results

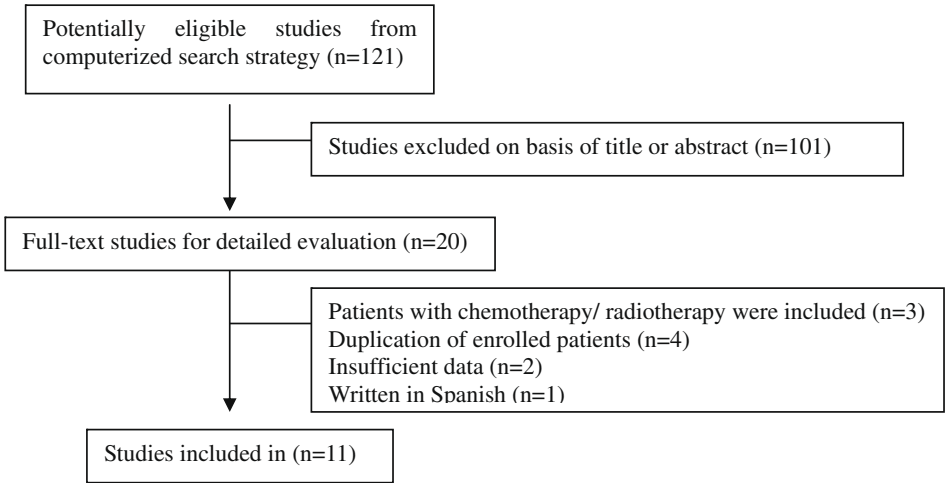

Fig. 1 – Results of search strategy.

Table 1 – Main characteristics of 11 studies.

Author	Year	No. of patients	Age (Average)	Study design	Patients enrollment	Patients selection	Confirmation of EBUS-TBNA positive results	Stations examined by EBUS-TBNA	Sensitivity (%)	Specificity (%)	Prevalence[c] (%)
Krasnik[20]	2003	11	58	Retrospective	ND*	Selected[a]	–	1.2.4.7.10	100.0	100.0	90.9
Rintoul[21]	2005	18	65	Prospective	ND*	Selected[a]	–	2.3.4.7.10.11	84.6	100.0	72.2
Vilmann[22]	2005	28	61	Prospective	ND*	Unselected[b]	–	1.2.4.5.7.10.11	85.0	100.0	71.4
Yasufuku[23]	2005	108	65	Prospective	Consecutive	Selected[a]	–	1.2.4.7.10.11	94.1	100.0	63.0
Herth[24]	2006	502	59	Prospective	Consecutive	Selected[a]	–	2.3.4.7.10.11	94.0	100.0	99.2
Vincent[25]	2008	146	60	Retrospective	Consecutive	Selected[a]	–	2.3.4.7.10.11	99.1	100.0	78.1
Wallace[26]	2008	138	69	Prospective	Consecutive	Unselected[b]	–	1.2.3.4.5.6.7	69.0	100.0	30.4
Herth[27]	2008	97	52	Prospective	Consecutive	Unselected[b]	Surgery	2.4.7.10.11	88.9	100.0	9.3
Lee[28]	2008	95	64	ND*	ND*	Selected[a]	–	2.4.7	93.8	100.0	33.7
Bauwens[29]	2008	90	64	Prospective	ND*	Selected[a]	–	2.4.7.10.11	95.1	100.0	67.8
Ernst[30]	2008	66	60	Prospective	Consecutive	Selected[a]	Mediastinoscopy and surgery	2.4.7	88.1	100.0	89.4

* ND = not document.
a Patients were selected on the basis of CT or PET positive results.
b Patients were enrolled without the results of CT or PET.
c Prevalence of mediastinal lymph node metastasis using individual patient as the unit of analysis. Studies that did not surgically confirm all EBUS-TBNA results assumed that the false-positive rate was zero.

of CT or PET had a pooled sensitivity of 0.76 (95% CI, 0.65–0.85). The difference in diagnostic accuracy between studies enrolling patients with abnormal lymph node in CT or PET was statistically significant ($p = 0.02$). The on-site evaluation of cytologic specimens had the highest pooled sensitivity, 0.97 (95 CI, 0.94–0.99); however, because of potential heterogeneity, when its pooled sensitivity was compared with that of other subgroups, no statistical significance was found ($p > 0.05$). Other factors such as the stations examined by EBUS-TBNA and using histopathology alone or combined with clinical follow-up as the reference standard did not influence the overall sensitivity significantly ($p > 0.05$).

3.3.3. *Complication rate*

In all 1299 patients involved in this metaanalysis, one major complication occurred (0.07%). This patient[29] with chronic obstructive pulmonary (COPD) was confirmed with a pneumothorax that required chest tube drainage after the procedure. The remaining studies only reported one minor complication. This patient was a 74-year-old male[28] with COPD, he suffered from hypoxemia during the procedure, however, he recovered from hypoxemia soon after EBUS-TBNA. No other complication was reported.

4. Discussion

Accurate staging of lung cancer is essential in order to plan effective treatment and to optimise survival rate. Generally, the procedures for lymph node staging can be divided into non-invasive and invasive strategies. Invasive techniques are further subdivided into surgical and non-surgical (minimally invasive) procedures.

Non-invasive methods such as CT and PET are safe but have limited sensitivity and specificity. Dwamena and colleagues[31] conducted a meta-analysis, which included 29 studies (2226 patients) from 1990–1998, to evaluate the accuracy of CT in lung cancer mediastinal staging. Only research with third- or fourth- generation CT equipment was accepted. The sensitivity was 0.60 (95% CI, 0.58–0.62), specificity 0.77 (95% CI, 0.75–0.79), and accuracy 0.75 (95% CI, 0.74–0.76). Another systematic review[32] concerning the utility of PET in staging of the mediastinal lymph nodes in lung cancer was published in 2003. This research included 18 studies with a total of 1045 patients involved. The pooled sensitivity was 0.84 (95% CI, 0.78–0.89), and the pooled specificity was 0.89 (95% CI, 0.83–0.93). Compared with CT, the performance of PET in lung cancer staging significantly improved. However, the overall accuracy was still not satisfactory.

Recently, a new American College of Chest Physicians (AACP) evidence-based practice guidelines (2nd edition) for lung cancer staging suggested that patients with abnormal lymph nodes on CT or PET should undergo invasive procedures (grade of recommendation, 1B).[33] Mediastinoscopy is one of those invasive methods, which has been the gold standard[34] in staging mediastinal lymph nodes. The average sensitivity of mediastinoscopy is 80%, however, it has a 2% risk of major morbidity and a 0.08% risk of mortality and is substantially costly.[33,35,36] Other less invasive methods such as TBNA, EUB-FNA and EBUS-TBNA have emerged as potential alternatives. In a meta-analysis written by Holty and colleagues,[37] 13

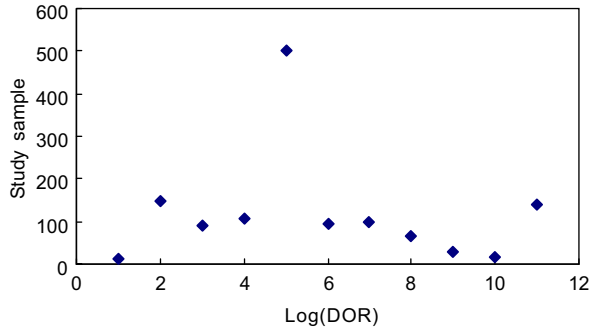

Fig. 2 – Funnel plot of included studies. The plot of this meta-analysis showed symmetric, demonstrating that there was probably no publication bias.

studies met the inclusion criteria, TBNA had a relatively high specificity (99%), while the sensitivity was extremely low (39%), and the pooled major complication rate was 0.3%. Recently, Micames[4] reported in a meta-analysis that EUS-FNA identified 0.83 of patients (95% CI, 0.78–0.87) with positive mediastinal lymph nodes and 0.97 of patients (95% CI, 0.96–0.98) with negative mediastinal lymph nodes. The research, which included 18 eligible studies with a total of 1201 patients, also pointed out that higher sensitivity was obtained when EUS-FNA was used to confirm metastasis to mediastinal lymph nodes seen on CT scans.

In this meta-analysis, we mainly focused on the accuracy of EBUS-TBNA in detecting lymph node metastasis in lung cancer, which to our knowledge had not previously been studied. When compared with the results of several other meta-analyses, in which non-invasive or minimally invasive modalities were used in lung cancer staging, EBUS-TBNA demonstrated the highest sensitivity as 0.93 (95% CI, 0.91–0.94) and the highest specificity as 1.00 (95% CI 0.99–1.000). This result was also consistent with the results of other well-designed studies. Herth and colleagues[27] demonstrated that despite negative CT and PET scan results, EBUS-TBNA of mediastinal lymph nodes was positive for metastatic disease in eight patients and only missed one patient. The sensitivity, specificity and negative predictive value were 89%, 100%, and 99%, respectively. Vilmman and colleagues[22] reported that EBUS-TBNA had higher sensitivity and specificity than EUB-FNA in detecting lymph node metastasis. In another study,[26] although EBUS-TBNA and EUB-FNA had same sensitivity (69%), in the subgroup analysis, EBUS-TBNA was more sensitive than EUS-FNA in detecting 'EBUS-suited' lymph nodes (upper paratracheal, lower paratracheal, or subcarinal location), while EUS-FNA was not significantly more sensitive than EBUS-TBNA in detecting 'EUS-suited' lymph nodes (subaortic, subcarinal, paraesophageal or pulmonary ligament location).

In subgroup analysis, we found that selection of patients who had positive results of suspected lymph node metastasis in CT or PET might increase the sensitivity of EBUS-TBNA in lung cancer staging. According to our data, the subgroup of patients selected on the basis of CT or PET positive results had higher pooled sensitivity (0.94, 95% CI 0.93–0.96) than the subgroup of patients without any selection of CT or PET (0.76, 95% CI 0.65–0.85) ($p < 0.05$). Therefore, our result supported the recommendations by AACP guidelines that patients with abnormal lymph nodes on CT or PET should undergo invasive procedures such as EBUS-TBNA. Rapid on-site evaluation might be another way to improve diagnostic accuracy. Previous studies had suggested that on-site evaluation of TBNA specimens increase the cytologic yield.[38] In our meta-analysis, we also found this tendency, however, heterogeneity between the studies hampered us to get a satisfactory result. Other factors such as the choice of gold standard

Table 2 – Diagnostic accuracy and heterogeneity.

	No. of patients	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	AUC	Likelihood ratio I^2 (%)	$\chi 2$ test (p value)
Total*	1299	0.93 (0.91–0.94)	1.00 (0.99–1.00)	0.9796	74.40	39.03 (0.00)
Selected patients[b]	1036	0.94 (0.93–0.96)[a]	–	0.9834	48.90	13.71 (0.06)
Unselected patient[c]	263	0.76 (0.65–0.85)[a]	–	0.9436	33.40	3 (0.22)
No on-site cytopathology	1045	0.92 (0.89–0.94)	–	0.9606	70.50	27.09 (0.00)
On-site cytopathology	254	0.97 (0.94–0.99)	–	0.9969	74.50	3.92 (0.04)
Histopathology and clinical follow-up	940	0.93 (0.91–0.95)	–	0.9852	85.80	35.12 (0.00)
Histopathology alone	359	0.92 (0.87–0.96)	–	0.9889	60.20	25.12 (0.00)

(Only studies in which positive EBUS-TBNA results were confirmed by other methods were conducted a pooled specificity with 95% CI).

* Diagnostic accuracy and heterogeneity of all 11 enrolled studies.

a The difference in diagnostic accuracy between studies enrolling patients with abnormal lymph node in CT or PET was statistically significant ($p = 0.02$).

b Patients were selected on the basis of CT or PET positive results.

c Patients were enrolled without the results of CT or PET.

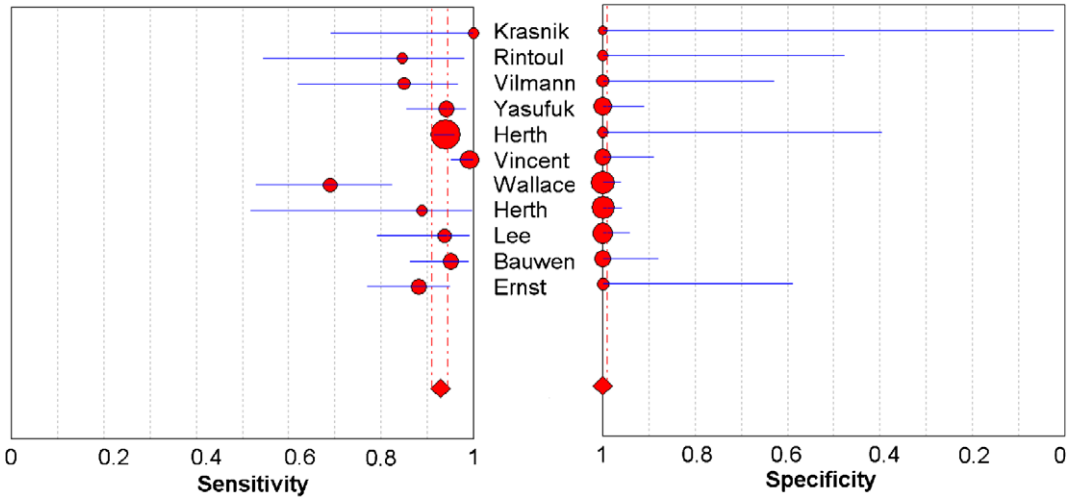

Fig. 3 – Results for sensitivity and specificity. Cycle icon = sensitivity and specificity of individual studies. Diamond icon = pooled sensitivity and pooled specificity of all 11 enrolled studies.

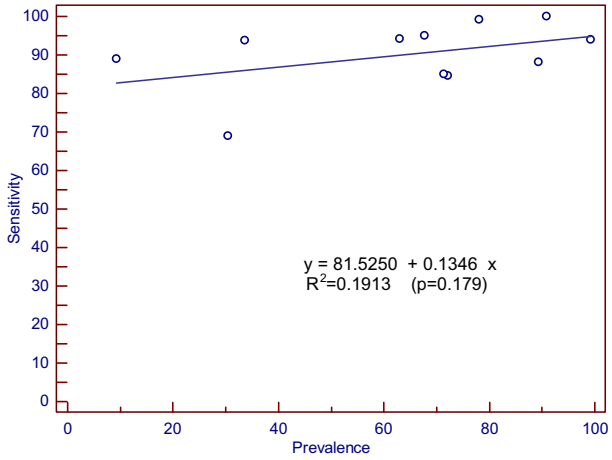

Fig. 4 – Relationship between prevalence of mediastinal lymph node metastasis. Our meta-analysis used individual person as the unit of analysis. Both the linear regression equation and R^2 were shown. Study sensitivity was not correlated with the prevalence of lymph node metastasis ($p = 0.179$).

(histopathology or histopathology combined with clinical follow-up) and the stations examined by EBUS-TBNA did not show statistical significance with the diagnostic accuracy.

One study[39] had conducted a cost-effective analysis regarding EBUS-TBNA. They calculated that the introduction of an EBUS-TBNA service would save the local National Health Service (NHS) economy by £32 631 per year (including capital costs). In our meta-analysis on all the 1299 patients involved, only two complications occurred (0.15%). Thus, we believed that with high sensitivity and low incidence of complications, EBUS-TBNA might be an accurate, safe and cost-effective tool in lung cancer staging.

One of the main limitations of EBUS-TBNA was that some lymph node stations such as levels 5, 6, 8 and 9 are not accessible. This can be overcome by endoscopic ultrasound with fine-needle aspiration which was more suitable for detecting lymph nodes in a subaortic, subcarinal, paraesophageal or pulmonary ligament location. Some studies[40,41] had suggested that combined EBUS-TBNA and EUS-FNA could achieve near-complete minimally invasive mediastinal staging. It seemed therefore logical to assume that the combination of EUS-FNA and EBUS-TBNA will replace more invasive methods such as mediastinoscopy for diagnosis and staging of lung cancers in the near future. However, through a comprehensive search, only two articles[22,26] were eligible, which is insufficient for a meta-analysis.

To be sure, our study has some drawbacks. Despite rigorous application of QUADAS criteria, most results showed heterogeneity in the assessment of sensitivity. One possible reason was that the sensitivity of EBUS-TBNA partially depended on the experience of the operator, inadequate training or lack of combined endoscopic and brochoscopic expertise may frustrate final results. Another reason may be the different times of aspirations in the same lymph node. Previous study[28] showed that the sensitivity could be raised by 25% from one time aspiration to three times aspiration. Unfortunately, those information were rarely provided. Despite random effect model, asymmetric SROC curves were used to make the results of meta-analysis more robust in our research, high-quality prospective studies were still needed.

5. Conclusion

EBUS-TBNA was an accurate, safe and cost-effective tool in lung cancer staging. The selection of patients who had positive results of suspected lymph node metastasis in CT or PET may improve the sensitivity of EBUS-TBNA. High-quality prospective studies regarding EUBS-TBNA in lung cancer staging are still needed to be conducted.

Conflict of interest statement

We would like to submit the enclosed paper entitled “Endobronchial Ultrasound-Guided Transbronchial Needle Aspira-

tion for Staging of Lung Cancer: A Systematic Review and Metaanalysis". It is submitted to be considered for publication as an origin article in European Journal of Cancer.

This paper is original. Neither the entire paper nor any part of its content has been published or has been accepted elsewhere. We disclose any financial and personal relationships with other people or organizations that could inappropriately influenceour work. There is no conflict interest related to the article or the research described.

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