Systematic Review and Meta-Analysis

Comparison between endobronchial ultrasound-guided transbronchial biopsy and CT-guided transthoracic lung biopsy for the diagnosis of peripheral lung cancer: a systematic review and meta-analysis

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Background: With the release of the National Lung Screening Trial results, the detection of peripheral pulmonary lesions (PPLs) is likely to increase. Computed tomography (CT)-guided percutaneous transthoracic needle biopsy (PTNB) and radial probe endobronchial ultrasound (r-EBUS)-guided transbronchial lung biopsy (TBLB) are recommended for tissue diagnosis of PPLs.

Methods: A systematic review of published literature evaluating the accuracy of r-EBUS-TBLB and CT-PTNB for the diagnosis of PPLs was performed to determine point sensitivity and specificity, and to construct a summary receiver-operating characteristic curve.

Results: This review included 31 publications dealing with EBUS-TBLB and 14 publications dealing with CT-PTNB for the diagnosis of PPLs. EBUS-TBLB had point sensitivity of 0.69 (95% CI: 0.67–0.71) for the diagnosis of peripheral lung cancer (PLC), which was lower than the sensitivity of CT-PTNB (0.94, 95% CI: 0.94–0.95). However, the complication rates observed with EBUS-TBLB were lower than those reported for CT-PTNB.

Conclusions: This meta-analysis showed that EBUS-TBLB is a safe and relatively accurate tool in the investigation of PLC. Although the yield remains lower than that of CT-PTNB, the procedural risks are lower.

Keywords: Computed tomography-guided percutaneous transthoracic needle biopsy (CT-PTNB); radial probe endobronchial ultrasound-guided transbronchial lung biopsy (r-EBUS-TBLB); peripheral pulmonary lesions; diagnosis; meta-analysis

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Introduction

With the established role of low-dose helical computed tomography (CT) screening for lung cancer (1,2) and the wide application of high-resolution CT (HRCT), pulmonary lesions are increasingly detected (3). Peripheral pulmonary lesions (PPLs) are a common problem in pulmonary practice. PPLs are defined as focal radiographic opacities that may be characterized as nodules (<3 cm) or masses (>3 cm). Solitary pulmonary nodule (SPN) is defined as a single, well-circumscribed radiographic opacity ≤30 mm in diameter that is completely surrounded by aerated lung and is not associated with atelectasis, hilar enlargement, or pleural effusion (4). With HRCT, PPLs can be categorized in a more accurate and detailed way. A ground-glass opacity (GGO) is a specific morphological type of pulmonary nodule (5).

To establish a tissue diagnosis, multiple approaches including sputum cytology, bronchoscopic sampling, and CT-guided percutaneous transthoracic needle biopsy (PTNB), may be undertaken. Conventional bronchoscopy has been used for several decades to diagnose PPLs (i.e., lesions that are not endobronchially visible), but its diagnostic yield is lower than 20% (6,7). The addition of imaging and guidance technology, such as radial probe endobronchial ultrasound (r-EBUS) and electromagnetic navigational bronchoscopy, has been shown by some studies to improve the diagnostic performance of transbronchial lung biopsy (TBLB). Several groups have now published their experience with r-EBUS-TBLB of PPLs. While there are a number of published case series evaluating the sensitivity and specificity of this diagnostic modality, the population recruited in each study was small and, therefore, the precision of the derived estimates varied widely. The aims of our study were to perform a systematic review of r-EBUS-TBLB and to ascertain the pooled sensitivity and specificity of this modality compared with published results of CT-PTNB for the diagnosis of peripheral lung cancer (PLC).

Methods

Publication search

Electronic databases of Medline (using PubMed as the search engine), Embase, Cochrane, and China National Knowledge Infrastructure were searched to identify suitable studies. Articles were identified with the use of the related articles function in PubMed. The references of the articles identified were also searched manually. The search terms used in this meta-analysis were "endobronchial ultrasound", "lung biopsy", "peripheral lung cancer", "peripheral pulmonary lesions", "computed tomography", "CT", "sensitivity and specificity", and "accuracy". An upper date limit of Aug 01, 2016 was applied; no lower date limit was used.

Inclusion criteria

We sought to identify all studies that used R-EBUS-TBLB and/or CT-PTNB for the investigation of PPLs. For inclusion, the studies must have met the following criteria: (I) evaluated the sensitivity (true-positive rate) and the specificity (false-positive rate) of r-EBUS-TBLB and/or CT-PTNB for the diagnosis of PPLs; (II) included at least 20 patients with PPLs for R-EBUS-TBLB and 200 patients with PPLs for CT-PTNB, since studies with smaller population may be vulnerable to selection bias; (III) histopathology analysis and/or close clinical follow-up for at least one year was used as the reference standard; and (IV) the search was performed without any restrictions on language and focused on studies that had been conducted in humans. Conference abstracts and letters to journal editors were excluded because of the limited data presented. Two reviewers (P Zhan and QQ Zhu) independently evaluated the study eligibility for inclusion. Disagreements were resolved by consensus.

Data extraction and quality assessment

The studies included were assessed independently by two reviewers who were blinded to publication details; disagreements were resolved by consensus. Extracted data included the following items: participant characteristics, publication year, patient enrolment and study design, use of reference standards, methodological quality, sensitivity data, and complication rate.

We assessed the methodological quality of the studies using guidelines published by the standards for reporting diagnostic accuracy (QUADAS) tool (8), with a maximum score of 14. Appraisal of the quality of the diagnostic accuracy of the primary studies was based on empirical evidence, expert opinion, and formal consensus.

Statistical analysis

The standard methods recommended for meta-analyses of diagnostic test evaluations were used (9). Meta-analyses

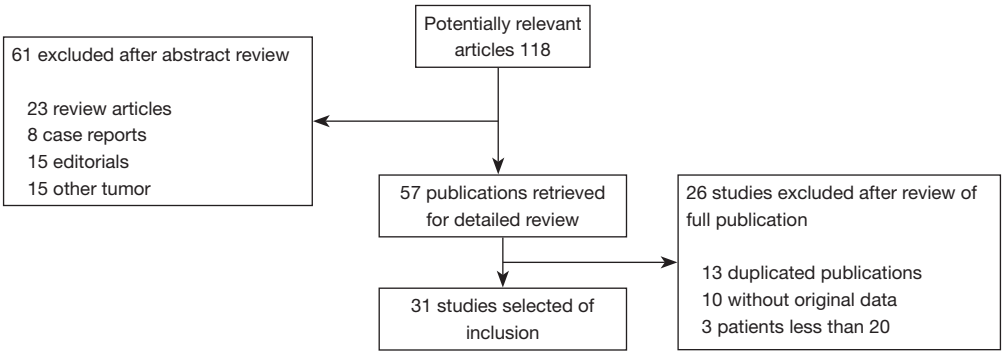

Figure 1 Identification, inclusion, and exclusion of studies on r-EBUS-TBLB. r-EBUS, radial probe endobronchial ultrasound; TBLB, transbronchial lung biopsy.

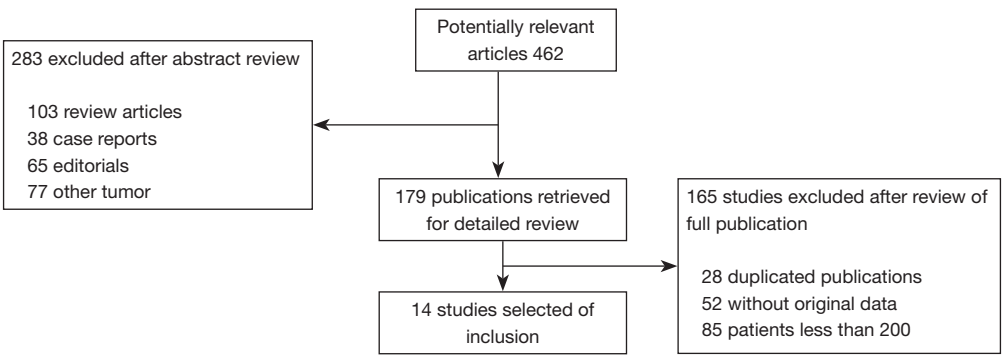

Figure 2 Identification, inclusion, and exclusion of studies on CT-PTNB. CT, computed tomography; PTNB, percutaneous transthoracic needle biopsy.

were performed using a statistical software program (Meta-DiSc Version 1.4; XI Cochrane Colloquium; Barcelona, Spain). We computed the following measures of test accuracy for each study: sensitivity; specificity; positive likelihood ratio (PLR); negative likelihood ratio (NLR); and diagnostic odds ratio (DOR).

The analysis was based on a summary receiver operating characteristic (SROC) curve (9,10). The sensitivity and specificity for the single test threshold identified for each study were used to plot an SROC curve (11). A random effects model was used to calculate the average sensitivity, specificity, and other measures across studies (12,13). The term heterogeneity, when used in relation to meta-analyses, referred to the degree of variability in results across studies. We used the χ^2 and Fisher exact tests to detect statistically significant heterogeneity, as appropriate. The relative DOR (RDOR) was calculated according to standard methods to analyze the change in diagnostic precision in a study per unit increase in the covariate (14,15).

Results

Study characteristics

After independent review, 31 publications (16-39) and (40-46) on r-EBUS-TBLB and 15 publications (47-61) on CT-PTNB for the diagnosis of PPLs were considered to be eligible for inclusion in the analysis. The study search process is shown in *Figures 1* and *2*. The QUADAS scores of these studies are outlined in *Table 1*. *Tables 2* and *3* present the principal characteristics of these studies. Among the 14 CT-PTNB publications, 12 were published in English and 2 were in Chinese. Among the 31 published studies on r-EBUS-TBLB, 29 were in English and 2 were in Chinese.

Diagnostic accuracy

Among 31 studies that evaluated the sensitivity of r-EBUS-TBLB for the diagnosis of PPLs, point sensitivity for pooled data was 0.69 (95% CI: 0.67–0.71) (*Figure 3*) and the area

Table 1 Main characteristics of selected studies on r-EBUS-TBLB

Author-year	No. of patients	Study design	Reference/comparison test	Q score
Herth-2002	50	Prospective randomizedcross-over study: EBUS versus fluoroscopy	Surgical resection	8
Yang-2004	122	Retrospective audit	Histology by alternate means or clinical surveillance	3
Shirakawa-2004	50	Prospective case series versus retrospective controls	Histology by alternate means	3
Kurimoto-2004	150	Prospective case series	Histology by alternate means	3
Paone-2005	87	Prospective, randomized, blinded study	Histology by alternate means	3
Asahina-2005	30	Unclear	Histology by alternate means	3
Herth-2006	54	Prospective case series	Surgical resection	4
Eberhardt-2007	39	Prospective RCT	Surgical resection	3
Yoshikawa-2007	121	Prospective case series	Histology by alternate means	3
Yamada-2007	155	Retrospective	NA	2
Asano-2008	31	Prospective case series	Surgical resection	3
Huang-2009	83	Retrospective audit	Histology by alternate means or surveillance	4
Eberhardt-2009	100	Prospective case series	Histology by alternate means	4
Oki-2009	86	Prospective study	Histology by alternate means or clinical surveillance	4
Chao-2009	88	Prospective, randomized trial.	NA	8
Disayabutr-2010	152	Prospective cross-sectional study	Histology by alternate means or clinical surveillance	6
Mizugaki-2010	107	Retrospective	Histology by alternate means or clinical surveillance	3
Steinfort-2011	51	Prospective randomized	Histology by alternate means or clinical surveillance	8
Fielding-2012	64	Prospective, randomized trial, EBUS-GS or CT-guided	Histology by alternate means or clinical surveillance	8
Hsia-2012	40	Retrospective	NA	2
Lin-2012	39	Retrospective	Surgical resection	3
Ishida-2012	65	Retrospective	NA	2
Oki-2012	203	Prospective EBUS-TBB under 3.4-mm or 4.0-mm thin bronchoscope with GS	Histology by alternate means or clinical surveillance	8
Fuso-2013	662	Retrospective	Histology by alternate means or clinical surveillance	3
Li-2014	75	Retrospective	Histology by alternate means	4
Chavez-2014	212	Retrospective	Histology by alternate means	4
Zhang-2015	117	Retrospective	Histology by alternate means	4
Durakovic-2015	147	Retrospective	Histology by alternate means or clinical surveillance	4
Tang-2016	105	Retrospective	Histology by alternate means or clinical surveillance	4
Fukusumi-2016	27	Retrospective	Histology by alternate means	4
Hayama-2016	27	Retrospective	Histology by alternate means or clinical surveillance	4

r-EBUS, radial probe endobronchial ultrasound; TBLB, transbronchial lung biopsy; Q, QUAD; NA, not applicable; CT, computed tomography.

Table 2 Characteristics of included studies on r-EBUS-TBLB

Study-year	No. of patients with LC	TP	FN	Complication	
				Severe bleeding	Pneumothorax with tube
Herth-2002	45	36	9	2	1
Yang-2004	122	80	42	NA	NA
Shirakawa-2004	24	17	7	NA	NA
Kurimoto-2004	101	82	19	0	0
Paone-2005	87	60	17	0	0
Asahina-2005	23	17	6	0	0
Herth-2006	39	28	11	0	1
Eberhardt-2007	32	23	9	0	2
Yoshikawa-2007	103	65	38	0	0
Yamada-2007	128	90	38	NA	NA
Asano-2008	27	23	4	NA	NA
Huang-2009	65	39	26	0	0
Eberhardt-2009	87	41	16	0	2
Oki-2009	44	35	9	0	0
Chao-2009	72	57	15	0	0
Disayabutr-2010	99	58	41	0	0
Mizugaki-2010	91	66	25	NA	NA
Steinfort-2011	32	25	7	0	0
Oki-2012	82	58	24	0	0
Fielding-2012	23	17	6	0	2
Hsia-2012	17	12	5	0	0
Lin-2012	39	30	9	NA	NA
Ishida-2012	50	38	12	0	1
Fuso-2013	359	255	104	NA	NA
Li-2014	32	27	5	0	0
Chavez-2014	212	143	69	0	0
Zhang-2015	88	66	22	0	0
Durakovic-2015	147	39	108	0	2
Tang-2016	14	12	2	0	0
Fukusumi-2016	18	12	6	NA	NA
Hayama-2016	27	20	7	0	0
Total complication (%)				0.087	0.48

r-EBUS, radial probe endobronchial ultrasound; TBLB, transbronchial lung biopsy; LC, lung cancer; TP, true-positive; FN, false-negative; NA, not applicable.

Table 3 Characteristics of included studies on CT-PTNB

Study-year	No. of patients with LC	Source	TP	FN	Complication (%)	
					Severe bleeding	Pneumothorax with tube
Yang-2015	217	China	215	2	11	3
Brandén-2014	463	Sweden	NA	NA	NA	27 patients (6%)
Lee-2014	766	South Korea	733	33	1 patient	13 patients
Wang-2013	623	China	618	5	0	8 patients (1.3%)
Wang-2014	342	China	333	9	0	5 patients (1.5%)
Choi-2013	290	South Korea	270	20	NA	NA
Loh-2013	399	Singapore	381	18	1 patient	12 patients (4.3%)
Yuan-2011	1014	China	962	52	1 patient	15 patients (1.5%)
Wei-2011	329	China	305	24	NA	NA
Laspas-2008	409	Greece	384	25	0	1 patient
D'Alessandro-2007	583	Italy	542	41	0	29 patients (18%)
Priola-2007	612	Italy	552	60	NA	NA
Tomiyama-2006	6881	Japan	NA	NA	22	14
Yeow-2003	631	China	587	44	NA	NA
Casamassima-1988	419	Italy	367	52	NA	NA
Total complication (%)					0.32	1.09

CT, computed tomography; PTNB, percutaneous transthoracic needle biopsy; LC, lung cancer; TP, true-positive; FN, false-negative; NA, not applicable.

under the SROC curve was 0.955 (SE =0.03) (*Figure 4*). Among 13 studies that evaluated the sensitivity of CT-PTNB for the diagnosis of PPLs, the point sensitivity for pooled data was 0.94 (95% CI: 0.94–0.95) (*Figure 5*) and the area under the SROC curve was 0.994 (SE =0.0023) (*Figure 6*).

Complication rates

The main limitation of CT-PTNB for the diagnosis of PPLs was the rate of complications, including pneumothorax and bleeding. The pooled rate across all included studies was 0.32% (36 out of 11,234) for severe bleeding and 1.09% (127 out of 11,697) for pneumothorax that needed chest tube drainage. On the other hand, the complication rates observed with r-EBUS-TBLB were low. The pooled rate across all included studies was 0.087% (2 out of 2,284) for severe bleeding and 0.48% (11 out of 2,284) for pneumothorax that needed chest tube drainage.

Discussion

The present meta-analysis showed that r-EBUS-TBLB had a point sensitivity of 0.69 (95% CI: 0.67–0.71) for the diagnosis of PLC, which was lower than the sensitivity of CT-PTNB (0.94, 95% CI: 0.94–0.95). Although the diagnostic yield was not superior to that of CT-PTNB, the major advantage of r-EBUS-TBLB over CT-PTNB was its safety profile. Our meta-analysis demonstrated overall rates of only 0.087% for severe bleeding and 0.48% for pneumothorax that needed chest tube drainage. In comparison, many studies describing CT-PTNB reported 0.32% rate of severe bleeding and 1.09% overall rate for pneumothorax requiring chest tube drainage.

Since Haaga and Alfidi reported the first case of CT-PTNB in 1976 (62), the procedure had been constantly developed and is currently widely employed as a routine diagnostic technique for PPLs, owing to its simplicity and minimal invasiveness. Recently, we performed a

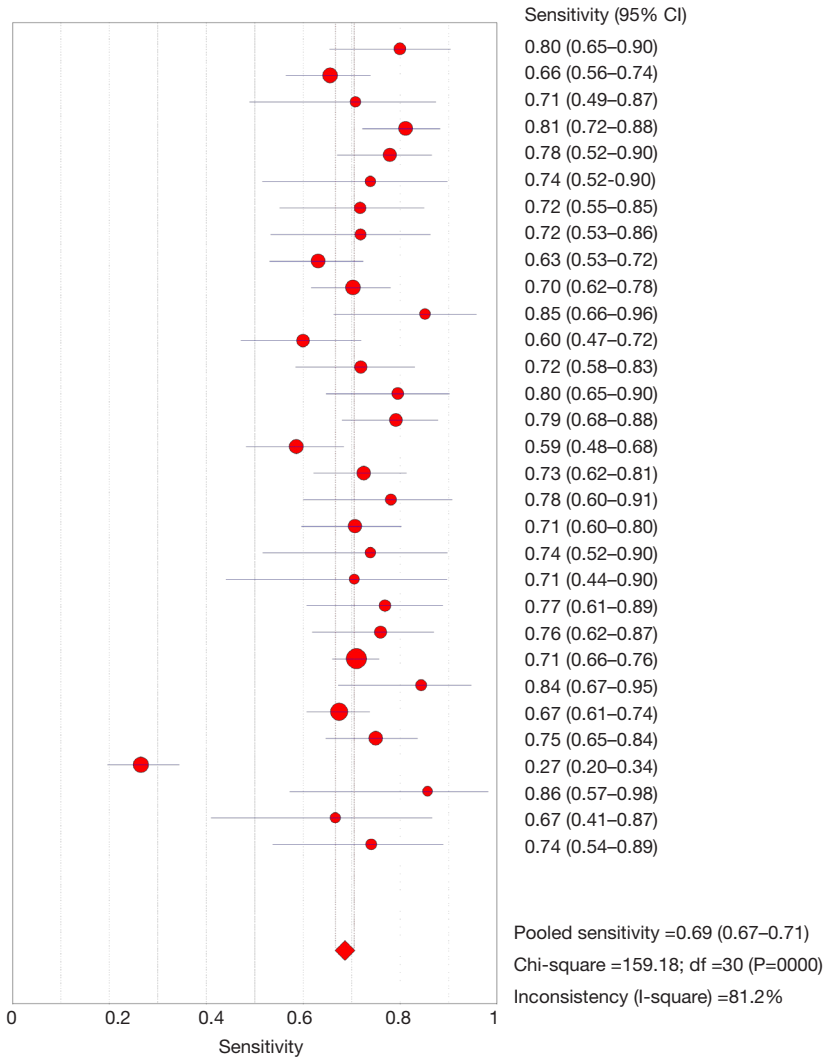

Figure 3 Forest plot: sensitivity analysis for of r-EBUS-TBLB for the diagnosis of PPLs. r-EBUS, radial probe endobronchial ultrasound; TBLB, transbronchial lung biopsy; PPL, peripheral pulmonary lesion.

retrospective study (47) to evaluate the diagnostic accuracy of CT-PTNB for SPN. Out of the 311 patients with SPN, 2 were false-positive cases, 12 were false-negative cases, and 8 were undiagnosed, resulting in a 92.9% diagnostic accuracy of CT-PTNB. However, PTNB has been known to have major complications of pneumothorax and pulmonary hemorrhage, with reported incidence rates of 10–40% and 26–33%, respectively (63). In our previous study (47), there were 55 cases of pneumothorax (17.7%), 2 cases needed thoracentesis and 1 case needed chest tube drainage. In addition, the diagnostic yield was influenced by size of the lesion, size of the needle, number of passes, and use of rapid on-site evaluation (64,65).

On the other hand, conventional bronchoscopy for PPLs can be performed using several instruments and sampling methods, including transbronchial biopsy forceps, transbronchial brush, transbronchial needle aspiration, and bronchoalveolar lavage. However, the sensitivity of traditional bronchoscopic biopsy was only 14–34% for nodules <2 cm (66). The sensitivity increased to 63% when nodules were >2 cm in size, but decreased as the distance from the hilum increased. Recently, image guidance has been used during bronchoscopy. One of which is r-EBUS that uses a 20-MHz ultrasound probe that can be passed through the working channel of a bronchoscope into the lung periphery. The r-EBUS probe can be passed within

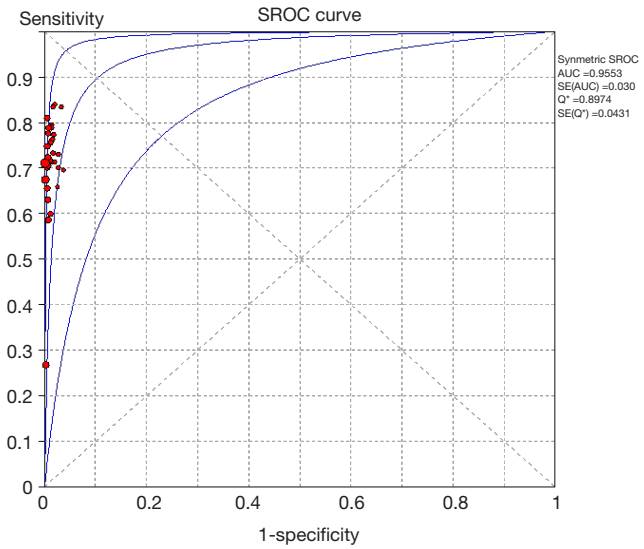

Figure 4 Summary receiver operating characteristics plot: r-EBUS-TBLB for the diagnosis of PPLs. r-EBUS, radial probe endobronchial ultrasound; TBLB, transbronchial lung biopsy; PPL, peripheral pulmonary lesion.

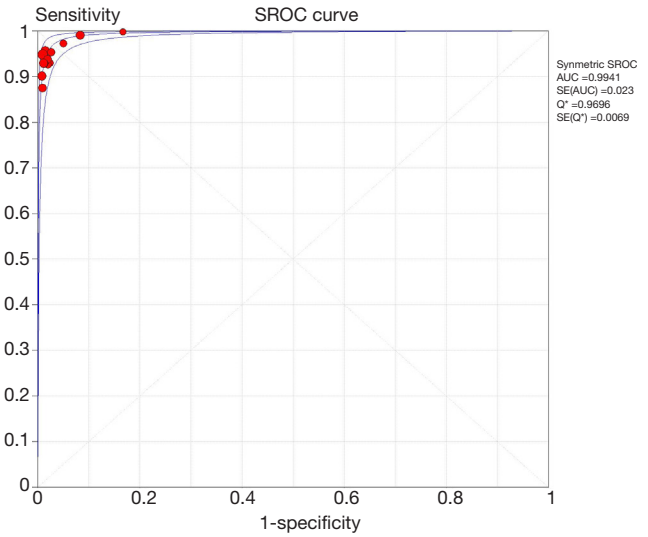

Figure 6 Summary receiver operating characteristics plot: CT-PTNB for the diagnosis of PPLs. CT, computed tomography; PTNB, percutaneous transthoracic needle biopsy; PPL, peripheral pulmonary lesion.

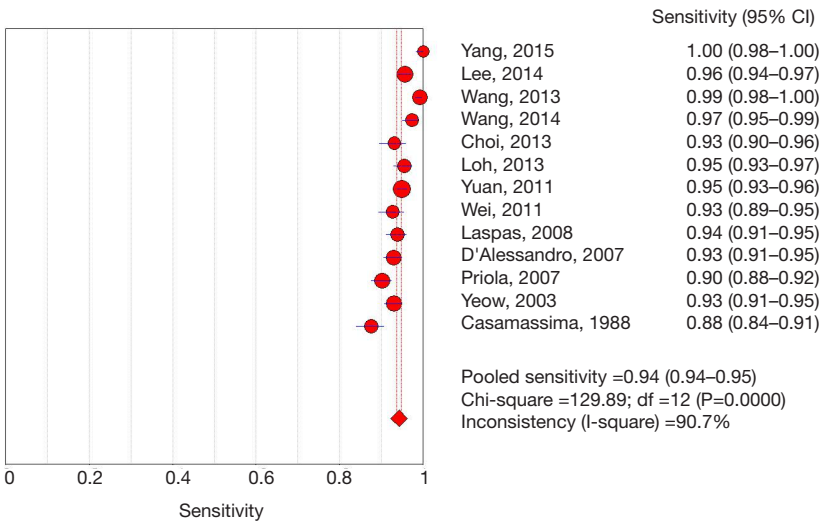

Figure 5 Forest plot: sensitivity analysis for of CT-PTNB for the diagnosis of PPLs. CT, computed tomography; PTNB, percutaneous transthoracic needle biopsy; PPL, peripheral pulmonary lesion.

a disposable guide sheath or by itself. Two previous meta-analyses have evaluated the performance of r-EBUS for the investigation of PPLs. The one by Steinfort *et al.* (67) on 16 studies of 1,420 patients that underwent r-EBUS for diagnosis of PPLs showed a pooled sensitivity of 73% (95% CI: 70–76%). Another meta-analysis (68) reported pooled diagnostic yields of 73.2% (95% CI: 64.4–81.9%) for r-EBUS with a guide sheath and 71.1% (95% CI: 66.5–75.7%) for r-EBUS without a guide sheath.

It has been reported that several guided-bronchoscopy technologies could improve the yield of transbronchial biopsy for PPLs diagnosis, such as electromagnetic navigation bronchoscopy (ENB), virtual bronchoscopy (VB), r-EBUS, ultrathin bronchoscope, and guide sheath.

Wang Memoli *et al*. study (68) performed the meta-analysis to determine the overall diagnostic yield of guided bronchoscopy using one or a combination of these technologies. They found that the pooled diagnostic yield was 70%, which is higher than the yield for traditional transbronchial biopsy. The yield increased as the lesion size increased. Only a few studies have focused on impact of the "bronchus sign", defined as a bronchus leading directly into the lesion on transverse CT imaging, although we have recognised the importance of the "bronchus sign" for the diagnosis of PPLs within our own practice.

The major limitation of our findings was the quality of studies included in the meta-analysis. The consistency of the patient populations in the individual studies was unclear because the selection criteria were not clear in the majority of studies. Therefore, it is difficult to know whether the spectrum of study subjects was representative of patients who would undergo r-EBUS-TBLB in clinical practice. In addition, some factors influencing the performance of r-EBUS-TBLB were not described in most papers included in our meta-analysis. These factors include bronchoscopist experience, number of biopsies taken, proximity of the PPL to central airways, and radiologic appearance of PPLs.

In summary, our meta-analysis confirmed that the overall diagnostic performance of r-EBUS-TBLB for PPLs was relatively accurate, although lower than that of CT-PTNB. However, our results indicate a favorable safety profile of EBUS-TBLB, supporting EBUS-TBLB as a viable investigation in patients with PPLs. This data once more suggests that radial EBUS may be the initial test of choice for the diagnosis of PPLs in those patients deemed at higher risk of a pneumothorax from CT-PTNB such as in the context of severe emphysema. The diagnostic sensitivity of r-EBUS-TBLB may be influenced by the prevalence of malignancy in the patient cohort being examined. Further randomized-controlled trials are required to evaluate the generalizability of our results to more clearly defined patient populations.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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