



Radial probe endobronchial ultrasound for the diagnosis of peripheral lung cancer: systematic review and meta-analysis

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ABSTRACT: Improved diagnostic sensitivity of bronchoscopy for the investigation of peripheral pulmonary lesions (PPLs) with the use of radial probe endobronchial ultrasound (EBUS) has been reported, although diagnostic performance varies considerably.

A systematic review of published literature evaluating radial probe EBUS accuracy was performed to determine point sensitivity and specificity, and to construct a summary receiver-operating characteristic curve. Sub-group analysis and linear regression was used to identify possible sources of study heterogeneity.

16 studies with 1,420 patients fulfilled inclusion criteria. Significant inter-study variation in EBUS method was noted. EBUS had point specificity of 1.00 (95% CI 0.99–1.00) and point sensitivity of 0.73 (95% CI 0.70–0.76) for the detection of lung cancer, with a positive likelihood ratio of 26.84 (12.60–57.20) and a negative likelihood ratio of 0.28 (0.23–0.36). Significant inter-study heterogeneity for sensitivity was observed, with prevalence of malignancy, lesion size and reference standard used being possible sources.

EBUS is a safe and relatively accurate tool in the investigation of PPLs. Diagnostic sensitivity of EBUS may be influenced by the prevalence of malignancy in the patient cohort being examined and lesion size. Further methodologically rigorous studies on well-defined patient populations are required to evaluate the generalisability of our results.

KEYWORDS: Biopsy, bronchoscopy, pneumothorax, solitary pulmonary nodule

Peripheral pulmonary lesions (PPL) are focal radiographic opacities that may be characterised as nodules (≤ 3 cm) or masses (> 3 cm). While referral for lobectomy in patients with a PPL with a very high pre-test probability of malignancy is suggested by some guidelines [1], computed tomography (CT) screening studies have shown that 18–34% of such operations are performed in patients with benign nodules [2–4]. Consequently, attempts at minimally invasive diagnosis are strongly favoured.

Multiple approaches may be undertaken to establish a tissue diagnosis, including sputum cytology, percutaneous image-guided aspiration/biopsy and bronchoscopic sampling. Diagnostic yield for routine bronchoscopy for investigation of peripheral pulmonary lesions (*i.e.* lesions not endobronchially visible) may be $< 20\%$ [5, 6]. Diagnostic yield is improved by the use of fluoroscopic guidance during performance of transbronchial lung biopsies (TBLB) [6, 7], although it varies

considerably across studies from $< 45\%$ [6, 8, 9] to $> 70\%$ [10, 11]. The highest diagnostic yield for bronchoscopic evaluation of PPLs appears to be associated with use of radial probe endobronchial ultrasound (EBUS).

Radial probe EBUS employs a flexible catheter housing a rotating ultrasound transducer which produces a 360° (“radial”) ultrasound image and was first used to guide TBLB by HERTH *et al.* [12]. The transducer is passed into bronchial subsegments until the characteristic ultrasound signal indicating the presence of a solid lesion is demonstrated (fig. 1). TBLB and other methods of sampling tissue are then performed from this bronchus.

Numerous groups have now published their experience with EBUS-guided evaluation of PPLs. Synthesis of this information may be valuable to assess the effectiveness and safety of EBUS-TBLB for the evaluation of PPLs. With this systematic review we sought to establish this *via*

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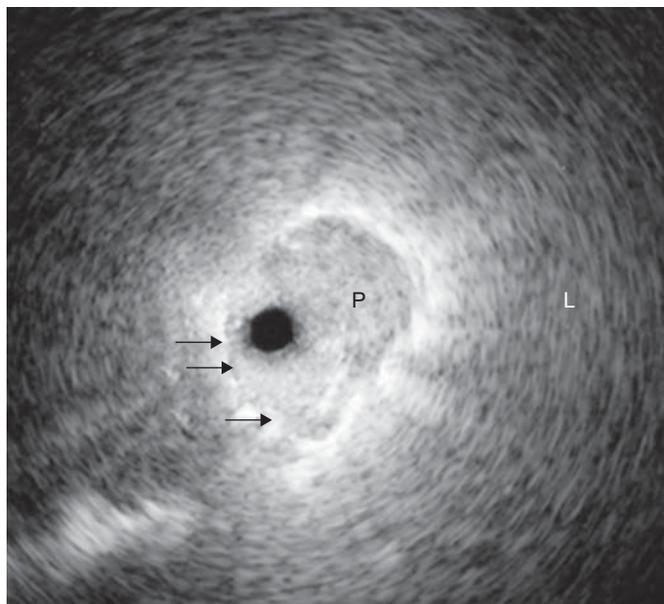


FIGURE 1. Radial probe endobronchial ultrasound image indicating presence of peri-bronchial mass lesion. The position of the probe is indicated by the central black circle and the hyper-echoic line (arrows) demonstrates the solid tissue-air interface between the peribronchial pulmonary mass lesion (P) and the surrounding lung (L).

performance of meta-analysis which, to our knowledge, has not previously been performed.

METHODS

Literature search

A systematic search of the medical literature was performed in December 2009 to identify all studies that used radial probe EBUS for investigation of PPLs. Both Medline and PubMed were searched with a common search strategy (table 1). A manual search of references cited in review papers as well as in all original papers identified by the search was also performed to complete the search.

Selection of studies

All articles identified by our search strategy were independently assessed by two authors (D.P. Steinfort and R.L. Manser) for inclusion in this review. Discordance was resolved by consensus. Abstracts of all identified articles were initially examined according to pre-established selection criteria. Studies were selected for inclusion in the review only after both reviewers assessed the full text articles. We considered all studies that examined EBUS for the diagnosis of PPLs. Inclusion criteria were: 1) radial probe EBUS for diagnosis of PPL; 2) diagnoses confirmed histologically or by close clinical follow-up for at least 6 months used as the reference standard; and 3) enrolled at least 30 patients.

We excluded review articles, non peer-reviewed papers and papers not published in English. When multiple papers were published from a single institution we included papers where there were no overlapping study periods. In the event of multiple publications with overlapping study periods we included only one publication to prevent double counting of the patient cohorts.

Data extraction

Two authors (Y.H. Khor and D.P. Steinfort) extracted relevant data regarding study characteristics and investigation results. Extracted data included the following items: description of study population (age, prevalence of malignancy, lesion size and lobar location); study design (prospective, retrospective or unknown); patient enrolment (consecutive or not); interpretation of the test results (blinded or not); and use of guidance modalities.

Further examination of included studies was performed using the QUADAS tool to assess study quality [13]. This is a validated tool that assesses 14 domains of design and the presentation of studies of diagnostic accuracy.

Two-by-two contingency tables were created for each study, with patients categorised into one of four options: true positive, false positive, false negative and true negative.

TABLE 1 Bibliographic search strategy

1. (Title=bronchoscopy OR (Topic=bronchoscopy OR MeSH Heading:exp=Bronchoscopy)) OR (MeSH Major Topic:exp=bronchoscopy)
2. (Title=bronchoscopic OR Topic=bronchoscopic) OR MeSH Major Topic=bronchoscopic
3. (Title=bronchial OR (Topic=bronchial OR MeSH Heading:exp=Bronchi)) OR MeSH Major Topic=bronchial
4. (Title=endobronchial OR Topic=endobronchial) OR MeSH Major Topic=endobronchial
5. ((Title=endobronchial AND Title=ultrasonography) OR (Topic=endobronchial AND (Topic=ultrasonography OR MeSH Heading:exp=Ultrasonography))) OR MeSH Major Topic=endobronchial ultrasonography
6. ((Title=endobronchial AND Title=ultrasound) OR (Topic=endobronchial AND (Topic=ultrasound OR MeSH Heading:exp=Ultrasonography))) OR MeSH Major Topic=endobronchial ultrasound
7. (Title=ultrasound OR (Topic=ultrasound OR MeSH Heading:exp=Ultrasonography)) OR MeSH Major Topic=ultrasound
8. (Title=ultrasonography OR (Topic=ultrasonography OR MeSH Heading:exp=Ultrasonography)) OR (MeSH Major Topic:exp=ultrasonography)
9. (Title=sonography OR (Topic=sonography OR MeSH Heading:exp=Ultrasonography)) OR MeSH Major Topic=sonography
10. (Title=sonographic OR Topic=sonographic) OR MeSH Major Topic=sonographic
11. (Title=ultrasonographic OR Topic=ultrasonographic) OR MeSH Major Topic=ultrasonographic
12. (Title=ultrasonographic OR Topic=ultrasonographic) OR MeSH Major Topic=ultrasonographic
13. #6 OR #5 OR #4 OR #3 OR #2 OR #1
14. #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5
15. #14 AND #13

Statistical analysis

Cohen's kappa (κ) co-efficient was calculated using GraphPad quickcalcs (www.graphpad.com/quickcalcs) to determine the inter-observer agreement for selection of studies.

Meta-analysis was performed using Meta-DiSc (Version 1.4) [14]. A p -value <0.05 was considered to be statistically significant. Extracted data was pooled with weighted averages applied, in which the weight of each study was its sample size. As no diagnostic threshold exists for histological diagnoses, symmetrical summary-receiver operating characteristic (SROC) curves, as described by MOSES *et al.* [15], were constructed to summarise the results quantitatively.

Study heterogeneity was assessed by the I^2 index, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance [16]. A value $>50\%$ may be considered indicative of significant heterogeneity [17]. If heterogeneity was demonstrated, sub-group analysis was performed according to common methodological/clinical features of the studies to identify possible sources of heterogeneity.

Linear regression was performed to analyse relationships between continuous variables using GraphPad Prism 5 for Mac OS X (GraphPad Software, La Jolla, CA, USA).

RESULTS

Literature search and study selection

The bibliographic search identified 968 papers for consideration. Following review of abstracts, 24 articles were selected for full text review. Of these, eight were excluded: two papers enrolled less than 30 patients [18, 19]; three papers examined ultrasound features of malignancy but did not report diagnostic performance of EBUS [20–22]; two papers were not published in English [23, 24]; and one paper was a review article [25]. Therefore 16 studies formed the basis of our systematic review [12, 26–40]. Inter-observer agreement for selection of studies was high: $\kappa=0.855$ (95% CI 0.587–1.132).

Study description and quality assessment

The mean number of participants per study was 89 (median 87; range 30–158), with a total of 1,420 subjects. The prevalence of malignancy was reported in 13 studies, with the median study prevalence being 68% (range 50–84%), and overall pooled prevalence being 72%. There was wide variation in the conditions under which EBUS-TBLB was performed, with several studies utilising additional guidance devices including guide sheaths [26–28, 30–33, 36, 37, 40], fluoroscopy [27, 28, 30, 32, 37], electromagnetic navigation [33] and virtual bronchoscopy [36, 37]. Study characteristics are recorded in table 2.

Our application of the QUADAS tool revealed that there were generally low scores in all of the eligible papers (see supplementary data). Only one study performed EBUS-TBLB in comparison to a traditional biopsy method which could serve as a reference standard [12]. As a result, all other studies were only assessable in six of the QUADAS domains. The highest score was only 8 out of a possible 14 [12], the lowest was only 2 (out of a possible 6), with a mean of 3.3. In all studies it was unclear if the spectrum of study subjects was representative of the patients who would receive the test in practice, and in only seven studies were selection criteria clearly described.

Test performance: meta-analysis

Results for sensitivity for detection of malignancy in individual studies ranged from 49% [40] to 88% [26]. Only 13 studies presented data sufficient to allow inclusion in meta-analysis [12, 26–33, 36, 37, 39, 40]: one study did not present raw data [35], and two studies reported incomplete data [34, 38]. Meta-analysis from these 13 studies (1,090 patients) demonstrated a point specificity for pooled data of 1.00 (95% CI 0.99–1.00). No heterogeneity in specificity was found (I^2 0.0%; Chi-squared 0.00; $p=1.00$).

The point sensitivity for pooled data was 0.73 (95% CI 0.70–0.76) (fig. 2) and the area under the SROC curve (fig. 3) was 0.9376 (SE 0.049). Diagnostic odds ratio was 103.75 (95% CI 46.4–231.7). The results correspond to a positive likelihood ratio of 26.84 (95% CI 12.60–57.20) and a negative likelihood ratio of 0.28 (95% CI 0.23–0.36). Significant heterogeneity between sensitivity of individual studies was observed (I^2 75%; Chi-squared 47.92; $p<0.0001$). To explore the possible source of heterogeneity, subgroup analyses were applied (table 3).

No heterogeneity was found among studies with prevalence of malignancy greater than 75% (sensitivity 0.83 (95% CI 0.78–0.88); I^2 37%; Chi-squared 4.73; $p=0.193$). Further analysis using linear regression demonstrated a weak positive association between prevalence of malignancy and sensitivity ($p=0.0872$). Using the robust regression method [41] we identified two studies as outliers. The excluded studies were a retrospective chart review performed to “evaluate factors predicting the visualisation of EBUS in PPL” [39], and a prospective series of 100 patients with PPL <2 cm where mean size was just 15 mm (range 9–20 mm) [40]. Exclusion of these studies from linear regression analysis demonstrated a significant relationship between prevalence of malignancy and study sensitivity (y 41.1 ± 8.1 ; $r^2=0.676$; $p=0.002$) (fig. 4).

Analysis of studies with prevalence of malignancy $<75\%$ following removal of studies identified as outliers demonstrated no heterogeneity (sensitivity 0.73 (95% CI 0.69–0.77); I^2 20%; Chi-squared 8.8; $p=0.268$). Therefore, we identified prevalence of malignancy as a possible source of heterogeneity in EBUS-TBLB.

Significant heterogeneity was noted between studies with median lesion size <25 mm, and also between studies with median lesion size >25 mm (data not shown). Removal of outliers resulted in a finding of no heterogeneity was found between studies with median lesion size <25 mm (I^2 13%; Chi-squared 5.74; $p=0.332$), although significant heterogeneity was still seen for studies with median lesion size ≥ 25 mm. Linear regression analysis demonstrated no significant relationship between prevalence of malignancy and lesion size (y 9.54 ± 8.6 ; $r^2=0.269$; $p=0.124$), or between lesion size and study sensitivity (y 9.35 ± 9.4 ; $r^2=0.186$; $p=0.161$). Variation in size of PPLs may also contribute to heterogeneity, although the evidence supporting this contention is less clear.

Sub-group analysis according to the means of confirmation of diagnosis of non-diagnostic EBUS-TBLB demonstrated no heterogeneity among studies in whom all subjects underwent histological confirmation by alternate means (sensitivity 0.83 (95% CI 0.78–0.88); I^2 37%; Chi-squared 4.73; $p=0.193$). Significant heterogeneity was noted among studies who used

TABLE 2 Main characteristics of selected studies

First author [ref.]	Patients n	Mean age yrs	Study design	Prevalence of lung cancer %	Patient selection	Additional guidance tools	Reference/comparison test	QUADAS score#
ASAHINA [36]	30	62.2	Unclear	63	Referral for diagnosis of PPL	Guide sheath VB	Histology by alternate means	3
CHUNG [35]	158	59.4	Prospective RCT: EBUS ± distance	71	PPL not visible at routine bronchoscopy	Distance measured: n=57	Histology by alternate means	3
DOOMS [34]	50	69	Prospective case series	ND	Referral for diagnosis of PPL	Nil	ND	2
EBERHARDT [33]	39	53	Prospective RCT	69	Patients with PPL referred to interventional pulmonology service	Guide sheath (n=39)	Surgical resection	3
FIELDING [32]	140	63	Prospective case series	50	Referral for diagnosis of PPL	Guide sheath fluoroscopy	ND	2
HERTH [31]	54	46	Prospective case series	57	Referral for diagnosis of PPL	Guide sheath	Surgical resection	4
HERTH [12]	50	62	Prospective randomised case cross-over study: EBUS versus fluoroscopy	84	Referral for diagnosis of PPL	Nil	Surgical resection	8
KURIMOTO [30]	150	ND	Prospective case series	66	Referral for diagnosis of PPL	Guide sheath fluoroscopy ± angulated curette	Histology by alternate means or radiologic surveillance	3
PAONE [29]	87	65	Prospective RCT	67	Referral for diagnosis of PPL	Nil	Histology by alternate means	3
SHIRAKAWA [28]	50	68	Prospective case series (versus retrospective controls)	50	PPL not visible at routine bronchoscopy	Fluoroscopy ± angulated curette guide sheath (n=21)	Histology by alternate means	3
YAMADA [27]	155	ND	Retrospective audit	68	ND	Guide sheath fluoroscopy ± angulated curette	Unclear	2
YOSHIKAWA [26]	121	66	Prospective case series	84	Referral for diagnosis of PPL	Guide sheath ± angulated curette	Histology by alternate means	3
ASANO [37]	31	72	Prospective case series	unclear	PPL not visible at routine bronchoscopy	Guide sheath fluoroscopy virtual bronchoscopy	Surgical resection or follow-up to radiological resolution	3
HUANG [39]	83	60	Retrospective audit	78	Unclear	Distance measured	Histology by alternate means or radiological surveillance	4
YANG [38]	122	66	Retrospective audit	100	Patients with confirmed lung cancer	Nil	Histology by alternate means or clinical surveillance	3
EBERHARDT [40]	100	52	Prospective case series	61	PPL <20 mm with CT characteristics of malignancy	Guide sheath	Histology by alternate means	4

RCT: randomised controlled trial; EBUS: endobronchial ultrasound; PPL: peripheral pulmonary lesion; ND: no data available; CT: computed tomography; VB: virtual bronchoscopy. #: refer to supplementary file 1 for detailed presentation of individual study scores for each QUADAS domain.

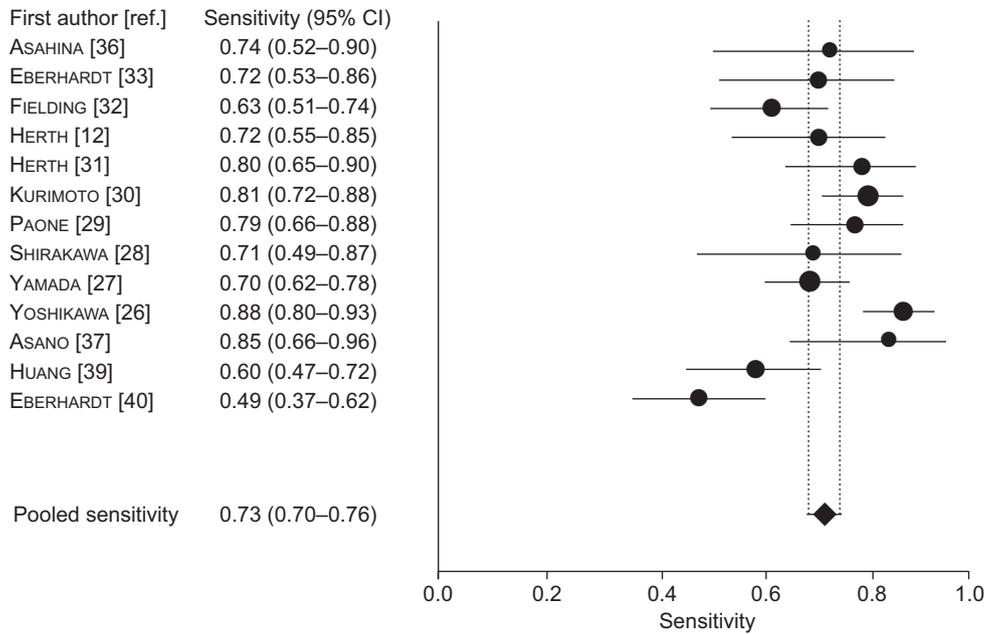


FIGURE 2. Forest plot of sensitivity.

non-histological methods to determine a diagnosis in subjects with non-diagnostic EBUS-TBLB or studies which did not specify how diagnoses were determined (sensitivity 0.71 (95% CI 0.68–0.76); I^2 56%; Chi-squared 16.1; $p=0.025$).

Several studies reported diagnostic performance based on lesion size. Only two studies presented sufficient data to allow pooling of data [36, 37]. Therefore, we were unable to perform meta-analysis. However, 10 studies reported overall diagnostic yield for lesions ≤ 20 mm and for lesions >20 mm. Pooled statistics demonstrated a diagnostic yield of 56.3% (95% CI 51–61%) and 77.7% (95% CI 73–82%) for lesions ≤ 20 mm (364 patients) and lesions >20 mm (367 patients), respectively. This difference was significant ($p=0.007$).

Descriptive review

Several studies examined the influence of specific clinical/radiological features on diagnostic performance. No studies

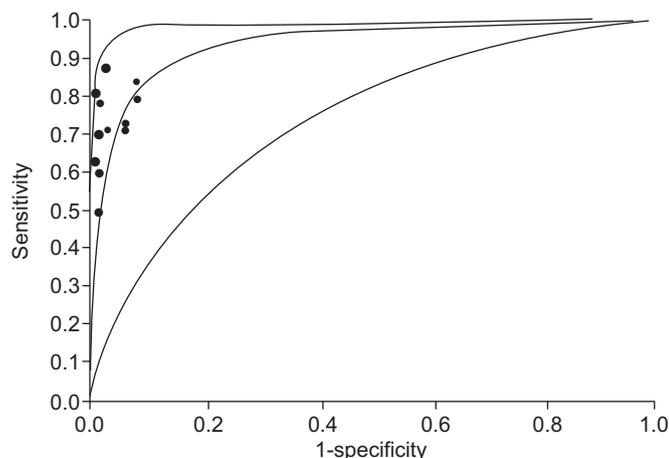


FIGURE 3. Summary receiver-operator characteristic curve.

presented sufficiently detailed data to allow meta-analysis of these features. Eight studies examined the effect of lobar position of PPL on diagnostic yield. YAMADA *et al.* [27] noted a higher yield for PPLs positioned in the right middle lobe and lingular lobe, EBERHARDT *et al.* [40] noted higher yield in the right middle and right lower lobes and KURIMOTO *et al.* [30] noted a significantly lower yield for the apicoposterior left upper lobe segment. However, the remaining five studies noted no significant effect of lobar position on diagnostic yield [27, 33, 35, 36, 39].

While two studies indicated a higher sensitivity for detection of malignant compared to benign lesions [33, 35], six studies reported no difference in diagnostic sensitivity based on lesion pathology [26, 27, 30, 32, 39, 40].

Unsurprisingly, identification of PPL position by the EBUS probe was associated with higher diagnostic sensitivity in all seven studies that examined this clinical feature [27, 28, 30, 34, 35, 39, 40]. In addition, proximity of PPL to the pulmonary hilum was reported to be associated with increased diagnostic yield in both studies describing this feature [32, 39]. Only two studies examined the effect of number of samples taken on diagnostic yield, and both noted an improved yield to a plateau of five biopsies [27, 36].

Complication rates

Complication rates were not reported in two studies [27, 28]. Complication rates in the remaining 14 studies varied from 0% [29, 36–38] to 7.4% [31]. The highest complication rate was noted in a single study and three out of the four patients experiencing complications in this study experienced only minor self-limiting bleeding [31]. No patients in any study experienced bleeding requiring intervention. Pneumothorax rate varied from 0% [29, 30, 34, 36–39] to 5.1% [33], with a pooled rate of pneumothorax across 14 studies of 1.0% (11 out of 1,090). The pooled rate of

TABLE 3 Results of pooled analysis and heterogeneity

	Studies n	Patients n	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	AUC (SE)	Likelihood ratio I ² %	Chi-squared test (p-value)
All studies	13	1,090	0.73 (0.70–0.76)	1.00 (0.99–1.00)	0.9376 (0.046)	75	30.13 (p<0.0001)
Outliers removed	11	907	0.76 (0.73–0.80)	1.00 (0.99–1.00)	0.9199 (0.062)	55	22.4 (p=0.013)
Use fluoroscopy							
Yes	5	526	0.73 (0.68–0.78)		0.9378 (0.081)	60	9.98 (p=0.041)
No	8	564	0.73 (0.68–0.77)		0.9409 (0.075)	82	37.9 (p<0.0001)
Use guide sheath							
Yes	10	841	0.73 (0.69–0.76)		0.9407 (0.051)	78	40.6 (p<0.0001)
No	3	249	0.69 (0.63–0.75)		0.9126 (0.114)	67	9.16 (p=0.027)
Without VB	11	1,029	0.72 (0.69–0.75)		0.9483 (0.050)	78	45.4 (p<0.0001)
Median size							
<25 mm	7	580	0.71 (0.66–0.75)		0.9356 (0.071)	73	22.2 (p=0.001)
≥25 mm	6	510	0.75 (0.70–0.79)		0.9364 (0.066)	80	24.3 (p<0.0001)
<25 mm outliers removed	5	480	0.75 (0.70–0.80)		0.8940 (0.124)	27	5.5 (p=0.240)
Prevalence[#]							
<75%	9	688	0.70 (0.66–0.74)		0.9127 (0.103)	85	23.05 (p=0.003)
>75%	4	402	0.83 (0.78–0.88)		0.9338 (0.117)	37	4.73 (p=0.193)
<75 % outliers removed	8	588	0.73 (0.69–0.77)		0.8578 (0.169)	20	8.79 (p=0.268)
Reference standard							
Histology only	7	452	0.79 (0.75–0.84)		0.9176 (0.103)	33	9.0 (p=0.174)
Alternate means/not stated	6	638	0.71 (0.68–0.76)		0.9023 (0.118)	56	16.1 (p=0.025)

AUC: area under the curve; VB: virtual bronchoscopy. [#]: prevalence of malignancy in lesions investigated using endobronchial ultrasound-transbronchial lung biopsies.

intercostal catheter drainage of pneumothorax was 0.4%. No deaths were reported in any studies.

DISCUSSION

Narrative reviews on EBUS-TBLB have previously been published [42]; however, to our knowledge this is the first systematic evaluation and first meta-analysis of published

literature on EBUS-TBLB. The results of our analysis indicate very good diagnostic performance of EBUS-TBLB for evaluation of PPLs. Meta-analysis of 13 studies determined a point sensitivity and specificity of 0.73 (95% CI 0.70–0.76) and 1.00 (95% CI 0.99–1.00), respectively. Heterogeneity in sensitivity of EBUS-TBLB was noted (I² 75%; Chi-squared 47.92; p<0.0001). Sub-group analysis strongly suggested that the prevalence of malignancy in the patient cohort undergoing EBUS-TBLB is a source of heterogeneity in diagnostic sensitivity among studies.

Our results also support previous observations that yield of EBUS-TBLB is influenced by PPL size. Subgroup analysis suggested variation in lesion size (table 3) may explain some of the observed heterogeneity in diagnostic sensitivity; however, this remains uncertain as heterogeneity was still seen in studies with median lesion size ≥25 mm. Probability of malignancy in PPLs is recognised to increase with increasing lesion size in both clinical studies [43–45], and in lung cancer screening studies using low-dose CT [46–48]. This may explain the potential influence of lesion size on diagnostic sensitivity, although regression analysis failed to demonstrate a significant relationship among the studies analysed. Due to limited availability of data in the primary studies included in the meta-analysis, we were unable to determine if lower prevalence of malignancy in smaller nodules contributed to the observation that sensitivity of EBUS-TBLB is reduced for smaller lesions.

Significant variation is noted in the technique of EBUS-TBLB between institutions, particularly with respect to guidance tools (e.g. fluoroscopy, guide sheath use, etc.). We did not identify any such characteristics as influencing sensitivity.

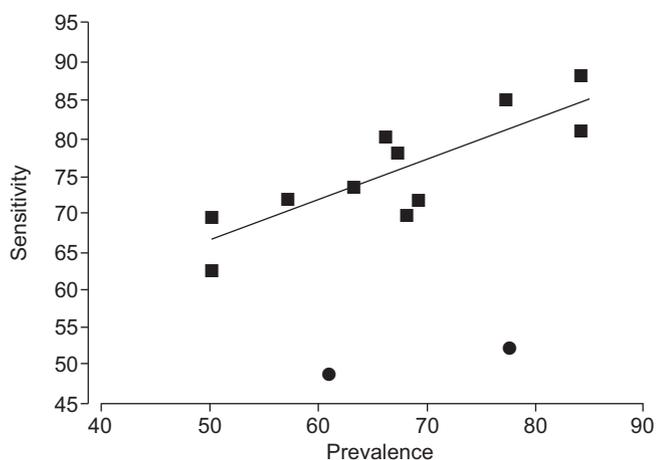


FIGURE 4. Results of linear regression examination of a relationship between prevalence of malignancy and reported sensitivity of individual studies. Each study is represented by ■. The outliers have not been included in calculation of the regression line. Study sensitivity was correlated with prevalence of malignancy in patients with peripheral pulmonary nodules. y: 41.1±8.1; r²: 0.676; p=0.002. ●: studies detected as outliers.

The only procedural feature consistently associated with improved diagnostic sensitivity was the ability to locate a PPL with the EBUS probe.

The two modalities commonly utilised to investigate PPLs are bronchoscopy or CT-guided percutaneous needle biopsy/aspiration (CT-PNB). To our knowledge, no systematic review of CT-PNB for investigation of PPLs has previously been published. Recently, published evidence-based clinical practice guidelines reviewed CT-guided needle biopsy and observed that sensitivity for detection of malignancy using CT-PNB in most studies exceeds 90%; however, ~20% of procedures were non-diagnostic [49], reflecting the lower yield of CT-PNB in benign conditions.

Investigation of PPL with bronchoscopy, while associated with a low complication rate [1], was previously limited by poor diagnostic performance, even with fluoroscopic guidance. Previous meta-analysis of this technique noted an overall diagnostic sensitivity of 33% for lesions with diameter ≤ 2 cm, and 62% for lesions > 2 cm [50]. EBUS-TBLB has improved diagnostic yield of bronchoscopic investigation of PPLs to a level more comparable to CT-PNB, with improvement in sensitivity most apparent for smaller lesions. While diagnostic yield in routine bronchoscopy is notably lower for smaller PPLs [1, 5, 6], we noted a pooled diagnostic yield for PPLs ≤ 20 mm of 56.3% (95% CI 51–61%), which is only slightly reduced in comparison to PPL > 20 mm (yield 77.7% (95% CI 73–82%)).

While diagnostic yield does not exceed CT-PNB, the major advantage of EBUS-TBLB over CT-PNB is its safety profile. Our meta-analysis demonstrated an overall pneumothorax rate of just 1.0%, and an overall intercostal drain insertion rate of 0.4%. In comparison, many studies describing CT-PNB report pneumothorax rates $> 25\%$ [49, 51–54], and as high as 69% [55], with many of these patients requiring admission or even intercostal catheter drainage. Pulmonary haemorrhage is less frequent, but still complicates 1–10% of CT-PNB [51, 52].

Limitations

The major limitation of our findings is the quality of studies included in the meta-analysis. It is unclear whether the patient populations in individual studies are consistent, as selection criteria were not clear in a majority of studies. Therefore, it is unclear if the spectrum of study subjects was representative of patients who would undergo EBUS-TBLB in clinical practice. This may induce heterogeneity in sensitivity in between studies, and potentially limits the generalisability of our results.

In addition, a number of features influencing performance of EBUS-TBNA were not described in most papers included in our meta-analysis. These include bronchoscopist experience, number of biopsies taken, proximity of PPL to central airways and radiological appearance of PPLs (*e.g.* solid *versus* ground-glass opacity).

While two studies determined that lobar location of PPLs may influence diagnostic sensitivity, a majority of studies that examined the influence of lobar position did not detect any effect on sensitivity. No studies presented sufficient data to allow meta-analysis; therefore, the effect of lobar position on sensitivity of EBUS-TBLB remains unresolved.

Implications for practice and future research

Our analysis calculated a negative likelihood ratio of 0.28 (0.23–0.36) for EBUS-TBLB. It is clear that non-diagnostic EBUS-TBLB should not serve as sufficient reassurance of the absence of malignancy and patients with negative results following EBUS-TBLB should be strongly considered for further investigation to exclude the possibility of cancer.

The relationship demonstrated between prevalence of malignancy and sensitivity of EBUS-TBLB has significant implications for clinical management of incidentally detected pulmonary nodules. It suggests that diagnostic yield of EBUS-TBLB may be influenced by the probability of malignancy for a given patient. The incidence of malignancy in nodules detected by low-dose CT in lung cancer screening trials is much lower than observed in studies included in this meta-analysis, varying from 13% [46] to $< 2\%$ [56, 57]. Incidental PPLs are frequently detected on imaging performed for other clinical indications [58–60], and such lesions may warrant a different approach to tissue diagnosis than clinically apparent PPLs.

Selection between EBUS-TBLB and CT-PNB may be possible based on clinical and radiological features of individual patients. For example, radiological findings may predict a lower sensitivity of EBUS-TBLB (*e.g.* lesions positioned in apicoposterior bronchial segments [30], or pleurally based or sub-pleural lesions [32, 39]) or a higher rate of complications with CT-PNB (*e.g.* perihilar lesions [32, 51, 52, 54, 61], COPD/emphysema [51–53, 61] or lesion size [51, 53, 61].) Other factors, such as “bronchus sign” [62] or even clinical models, predicting the probability of malignancy in PPLs [43], may be helpful in determining optimal investigation approaches for individual patients. Future studies are required to inform construction of such a clinical algorithm.

Future studies reporting on EBUS-TBLB need to clearly outline the selection process for inclusion and should ideally describe clinicoradiologic characteristics and include a description of each of these performance issues to allow improved understanding of the features that predict diagnostic yield of EBUS-TBLB. This could then be used to inform clinical decisions regarding the optimal approach to investigation for individual patients. Given the discrepancy in sensitivity and complication rates between EBUS-TBLB and CT-PNB, we suggest economic analyses are also warranted. The lower complication rate of EBUS-TBLB may mean that, despite a lower diagnostic yield, the procedure may still be cost-effective. Such evidence may also guide clinicians in the future investigation of patients presenting with PPLs.

Conclusions

Our study confirms overall test performance characteristics of EBUS-TBLB for the investigation of PPLs is very good in the population of patients included in the studies in this review, with excellent specificity and sensitivity markedly higher than for routine bronchoscopy, although lower than for CT-PNB. However, our results indicate an extremely favourable safety profile of EBUS-TBLB, supporting initial investigation of patients with PPLs using EBUS-TBLB. Diagnostic sensitivity of EBUS-TBLB may be influenced by the prevalence of malignancy in the patient cohort being examined. Further

methodologically rigorous studies are required to evaluate the generalisability of the results to more clearly defined patient populations. Studies examining the influence on test performance of prevalence of malignancy, as well as other specific clinical and radiological features, particularly PPL position, are still required.

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STATEMENT OF INTEREST

A statement of interest for D.P. Steinfort can be found at www.ersjournals.com/site/misc/statements.xhtml

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