Transbronchial needle aspiration in peripheral pulmonary lesions: a systematic review and meta-analysis

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ABSTRACT Fluoroscopy-guided transbronchial needle aspiration (TBNA) has long been used in the diagnosis of peripheral pulmonary lesions (PPLs), although its diagnostic performance varies considerably.

We conducted a systematic review and meta-analysis evaluating the accuracy of TBNA in the diagnosis of PPLs, comparing its diagnostic yield with transbronchial biopsy (TBB) and assessing the main predictors of a successful aspirate.

In 18 studies, the overall TBNA yield was 0.53 (95% CI 0.44–0.61). TBNA showed a higher accuracy when directly compared to TBB (0.60 (95% CI 0.49–0.71) *versus* 0.45 (95% CI 0.37–0.54)). The subgroup analyses documented a higher TBNA yield when the computed tomography (CT) bronchus sign was present (0.70 (95% CI 0.63–0.77) *versus* 0.51 (95% CI 0.38–0.64)), when rapid on-site evaluation (ROSE) was performed (0.62 (95% CI 0.43–0.79) *versus* 0.51 (95% CI 0.42–0.60)), in the case of malignant lesions (0.55 (95% CI 0.44–0.66) *versus* 0.17 (95% CI 0.11–0.24)) and for lesions >3 cm (0.81 (95% CI 0.73–0.87) *versus* 0.55 (95% CI 0.47–0.63)).

Conventional TBNA is a useful sampling technique for the diagnosis of PPL, with a higher diagnostic yield than TBB. The presence of CT bronchus sign, an underlying malignant process, lesion size >3 cm and ROSE employment are predictors of a higher yield.

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Introduction

Peripheral pulmonary lesions (PPLs) are defined as focal radiographic opacities not detectable beyond the visual segmental bronchi by flexible bronchoscopy [1, 2]. In recent years, due to the widespread diffusion of imaging techniques, the detection of PPLs has become even more frequent. The goal, in this context, is to quickly identify malignant nodules in order to allow a curative surgical resection, while avoiding unnecessary invasive interventions in case of benign lesions. In fact, up to 60% of removed nodules are not malignant, underlining the importance of a diagnostic test that better enables lung preservation [3]. Mini-invasive approaches to establish a tissue diagnosis include imaging-guided transthoracic and bronchoscopic sampling techniques. Although transthoracic needle aspiration, also named percutaneous needle aspiration, is characterised by a higher sensitivity than transbronchial needle aspiration (TBNA), bronchoscopy is widely considered as the first diagnostic step, due to the better safety profile and the advantages of obtaining information on mediastinal staging and airway involvement, and ruling out the possibility of synchronous lesions, during a single examination [4, 5].

Despite the recent introduction of innovative and more powerful imaging-guided techniques, such as endobronchial ultrasounds (EBUSs) and electromagnetic navigation, the lack of resources and specific skills in most centres worldwide have strongly limited their diffusion in clinical practice. As a result, traditional fluoroscopy-guided TBNA still plays a relevant role in this context [6].

A limited number of studies have specifically assessed the diagnostic yield of conventional TBNA in diagnosing PPLs, showing a great heterogeneity in terms of sensitivity [5–14]. This could be related to differences in study design, as well as to a number of selected other factors, including both baseline clinical characteristics and procedural aspects. However, the results on such predictors have been often conflicting and the real value of each one has yet to be definitely assessed. Therefore, the aim of the present systematic review was to summarise the available literature in order to provide a pooled estimate of TBNA diagnostic yield and to identify the main predictive factors of a positive transbronchial aspirate according to different clinical conditions.

Material and methods

This systematic review was conducted according to the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [15] and the inter-rater agreement was analysed for quality assessment of the articles included in the review.

Search strategy

We selected studies that evaluated the TBNA yield for the diagnosis of PPLs. We searched PubMed and EMBASE until December 2014. The following key words and their related MeSH (Medical Subjects Heading) terms were searched in the databases: “transbronchial needle aspiration”, “conventional transbronchial needle aspiration”, “transbronchial fine needle aspiration”, “transbronchial needle biopsy” and “transbronchial needle aspiration biopsy”. Only publications in the English language were considered.

Study selection and data extraction

Observational/interventional studies of accuracy and/or its predictors of fluoroscopy-guided conventional TBNA in the diagnosis of PPLs were included. The following exclusion criteria were employed. 1) Manuscripts describing observational/interventional studies evaluating TBNA for the diagnosis of PPLs with the guidance of radial probe EBUS, electromagnetic navigation, virtual bronchoscopy and computed tomography (CT) fluoroscopy. 2) Manuscripts describing observational studies also evaluating the yield of TBNA for mediastinal lymphadenopathies/endobronchial lesions where the outcome of interest was not available separately for PPLs, mediastinal nodes and endobronchial lesions. 3) Manuscripts describing studies with sample size <20. 4) Abstracts, editorials, letters, review articles and case reports. 5) Manuscripts published not in English language.

Two independent authors (M. Mondoni and E.M. Parazzini) firstly reviewed all titles/abstracts to identify potentially relevant articles. Then, study selection, based on a full-text review, was performed according to the aforementioned predefined inclusion/exclusion criteria and disagreements were resolved by discussion.

The following data were extracted: authors, title, year of publication, country, enrolment period, sample size, study design, diagnostic yield, study population, lesion size and complications.

Study quality assessment

The inter-rater agreement was 100%. Quality assessment of individual studies was deemed necessary to identify potential sources of bias and to limit the bias effects on the estimates and the conclusions of the review. We assessed the study for methodological quality using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [16]. It consists of four key domains that discuss patient

selection, index test, flow of patients selection, timing of the index tests and reference standard. Through specified questions, each domain is assessed about risk of bias and the first three items also in terms of concerns about applicability.

Statistical analysis

Forest plots were constructed to assess graphically both the variability of the estimates of the diagnostic parameters and the weight of every sample size in the calculation of the pooled estimates (weighted means). A random-effects meta-analysis was performed in order to account for the expected between-study variability. The statistical software used was Stata13.0 (StataCorp, College Station, TX, USA) and StatsDirect 2.8.0, version 1.4 (StatsDirect Ltd, Altrincham, UK). Inconsistency (statistical heterogeneity) among studies was assessed by the conventional Chi-squared test for heterogeneity and by calculating the I^2 statistic in order to highlight the effect of true variability rather than sampling error on the overall variation in the diagnostic yield.

Results

Out of 2089 articles selected from the electronic databases, 18 studies were eligible for a qualitative and quantitative analysis (figure 1). The pooled sample size included 1687 patients enrolled from 10 countries (USA [7–9, 17, 18], Japan [14, 19, 20], Italy [4, 5], Spain [6, 10], Poland [21], Greece [11], Turkey [22], India [12], Norway [23], and Switzerland [13]). Mean±SD age of the population target was 60.4±5.8 years, although data were reported only in eight studies [5–7, 11–14, 22].

The majority of the studies were prospective cohort studies (11 (61%) out of 18) [4–9, 11, 12, 17, 18, 22], whereas seven (39%) out of 18 [10, 13, 14, 19, 20, 21, 23] were retrospective investigations. Some studies (nine (50.0%) out of 18) [7, 9, 10, 14, 19, 20–23] enrolled patients with suspected or known pulmonary malignancy; the remaining selected studies included subjects with undefined nodules. The diagnostic yield

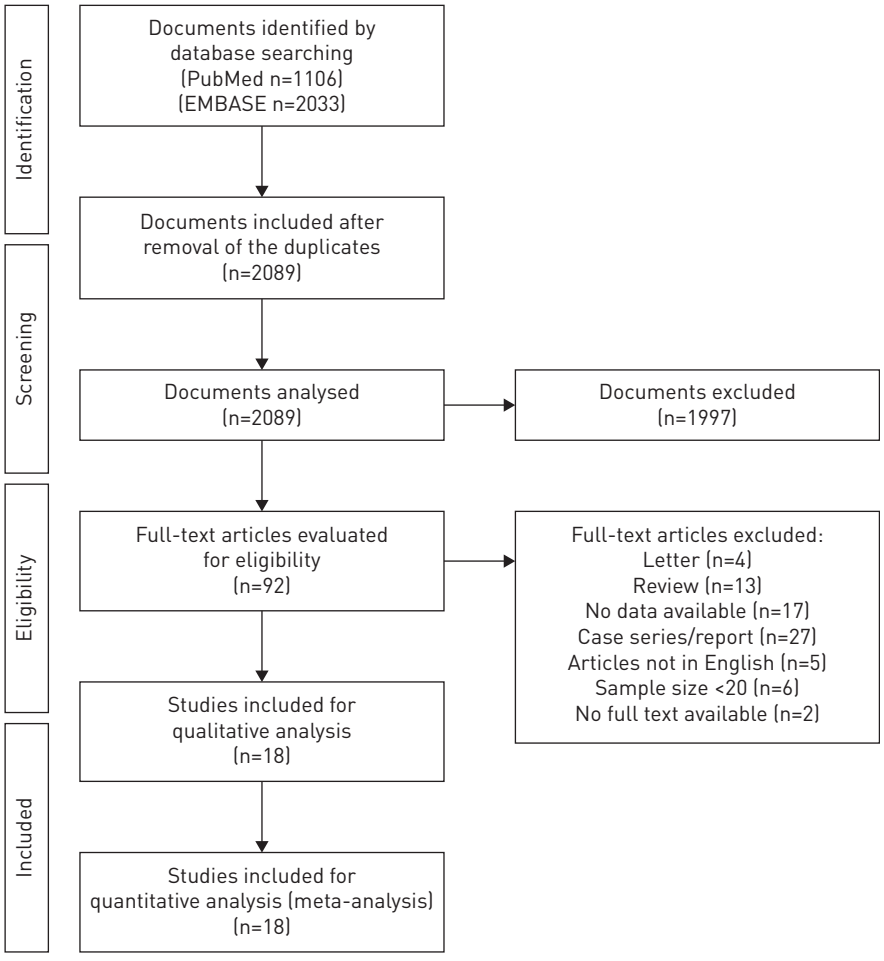

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 flow diagram.

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TABLE 1 Characteristics of the selected studies

First author [ref.]	Country	Study design	Patients	Age years	Yield results	Population	Yield according to				TBNA *versus* TBB comparison	Complications
							Lesion size	ROSE	CT bronchus sign	Disease type		
Baba [19]	Japan	RCS	78		66.6%	Suspected/known malignancy		Reported (present)		Reported (malignant)		
Bilaçeroglu [22]	Turkey	PCS	92	51 (mean)	52.0%	Suspected/known malignancy		Reported (absent)	Reported		Performed	1 PNT 1 moderate bleeding
Castella [10]	Spain	RCS	45		69.0%	Suspected/known malignancy	Reported	Reported (absent)				None
Checkani [17]	USA	PCS	37		51.0%	Unselected		Reported (absent)				3 moderate bleeding
Gasparini [4]	Italy	PCS	435		59.1%	Unselected		Reported (present)		Reported (malignant/ benign)	Performed	1 PNT
Gupta [12]	India	PCS	21	52 (mean)	61.9%	Unselected						None
Kawaraya [20]	Japan	RCS	69		34.8%	Suspected/known malignancy				Reported (malignant)		
Katis [11]	Greece	PCS	37	44–78	62.1%	Unselected		Reported (absent)			Performed	None
Iyoda [14]	Japan	RCS	296	62.2 (mean)	83.4%	Suspected/known malignancy		Reported (present)		Reported (malignant)	Performed	
Leiro-Fernández [6]	Spain	PCS	36	65.6 (mean)	30.6%	Unselected		Reported (present)				
Pirozynski [21]	Poland	RCS	24		58.3%	Suspected/known malignancy				Reported (malignant)		
Reichenberger [13]	Switzerland	RCS	152	63 (mean)	35.5%	Unselected				Reported (malignant/ benign)		
Roth [23]	Norway	RCS	21		19.0%	Suspected/known malignancy		Reported (absent)		Reported (malignant)		
Schenk [9]	USA	PCS	42		40.0%	Suspected/known malignancy				Reported (malignant)		None
Shure [7]	USA	PCS	42	46–77	52.4%	Suspected/known malignancy		Reported (absent)		Reported (malignant)	Performed	None
Trisolini [5]	Italy	PCS	218	66.7 (mean)	65.0%	Unselected	Reported		Reported	Reported (malignant/ benign)	Performed	4 PNT 4 major bleeding
Wang [8]	USA	PCS	20		55.0%	Unselected		Reported (absent)				1 PNT
Wang [18]	USA	PCS	22		36.3%	Unselected		Reported (absent)			Performed	None

ROSE: rapid on-site evaluation; CT: computed tomography; TBNA: transbronchial needle aspiration; TBB: transbronchial biopsy; RCS: Retrospective Cohort Study; PCS: Prospective Cohort Study; PNT: pneumothorax.

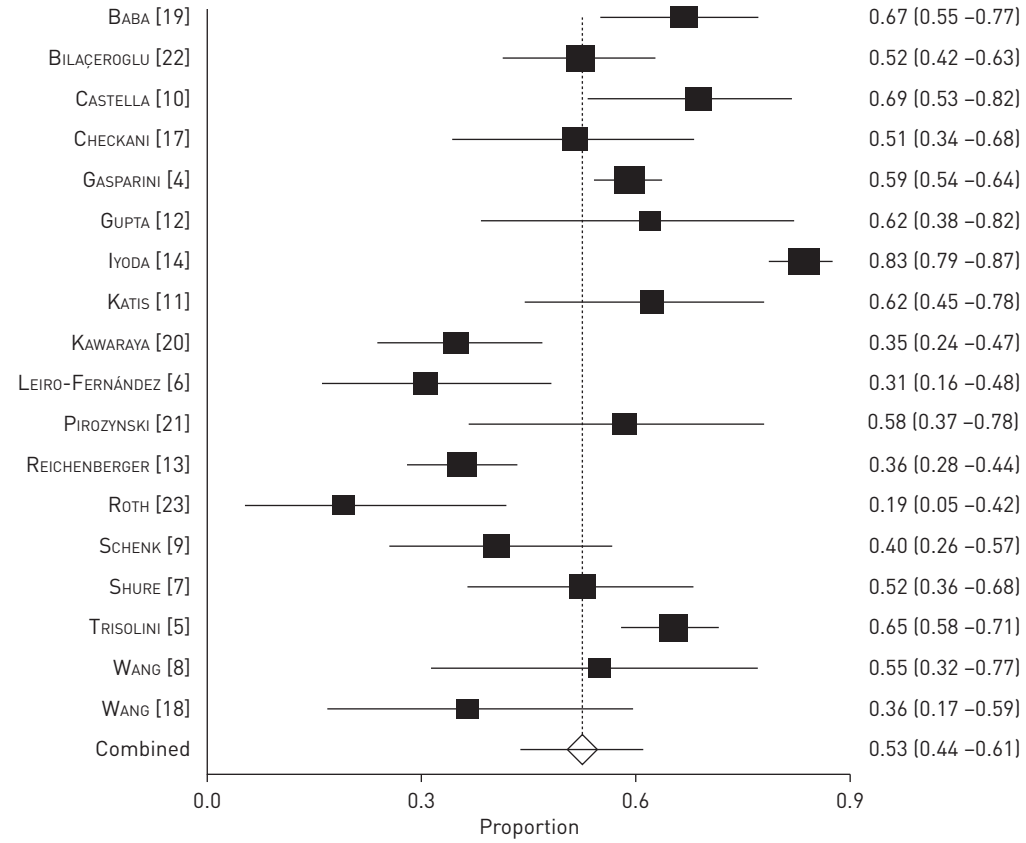

FIGURE 2 Diagnostic yield of transbronchial needle aspiration in the included studies. I^2 90.9% (95% CI 87.7–93.0%). Error bars represent 95% confidence intervals.

according to nodule size was reported by two (11.1%) out of 18 [5, 10] and according to the presence/absence of CT bronchus sign by two (11.1%) out of 18 [5, 22]. The presence/absence of rapid on-site evaluation (ROSE) was reported in 12 (66.7%) out of 18 studies [4, 6–8, 10, 11, 14, 17–19, 22, 23]. Malignant and benign diseases were diagnosed through TBNA in 10 (55.6%) out of 18 [4, 5, 7, 9, 13, 14, 19, 20, 21, 23] and three (16.7%) out of 18 [4, 5, 13], respectively. TBNA-related complications were reported by five (22.2%) out of 18 [4, 5, 8, 17, 22] articles: seven patients with pneumothorax [4, 5, 8, 22], eight cases of moderate bleeding [5, 17, 22] and four cases of major bleeding [5] were described in the entire cohort. The comparison of the diagnostic yield between TBNA and transbronchial biopsy (TBB) was performed in seven (38.9%) out of 18 studies [4, 5, 7, 11, 14, 18, 22] (table 1).

The pooled TBNA yield, computed on 18 individual studies [4–14, 17–23], was 0.53 (95% CI 0.4–0.6) (I^2 90.9%, 95% CI 87.7–93.0%) (figure 2). According to the CT bronchus sign [5, 22], the pooled TBNA yield was 0.70 (95% CI 0.6–0.8) (I^2 not available) when the bronchus sign was present and 0.51 (95% CI 0.4–0.6) (I^2 not available) when it was absent (figure 3). A pooled TBNA yield of 0.51 (95% CI 0.4–0.6) (I^2 63.0%,

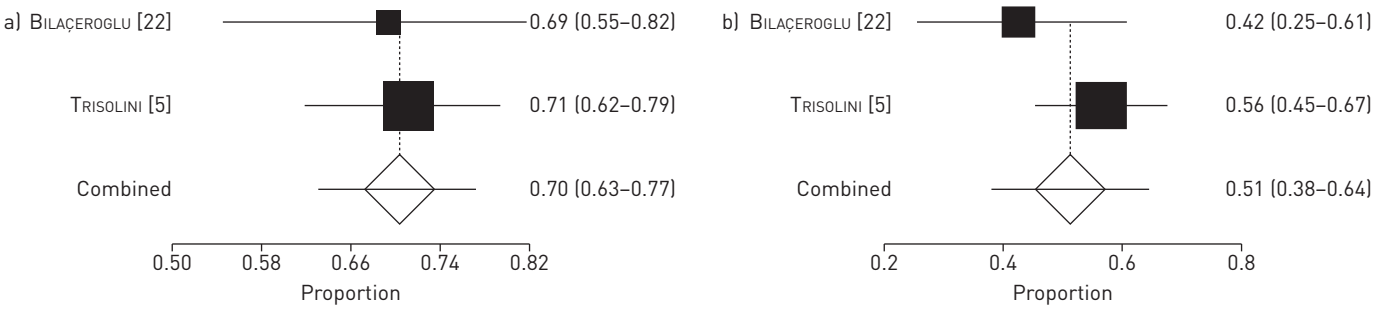

FIGURE 3 Diagnostic yield of transbronchial needle aspiration according to the computed tomography (CT) bronchus sign. a) CT bronchus sign positive. b) CT bronchus sign negative. Error bars represent 95% confidence intervals.

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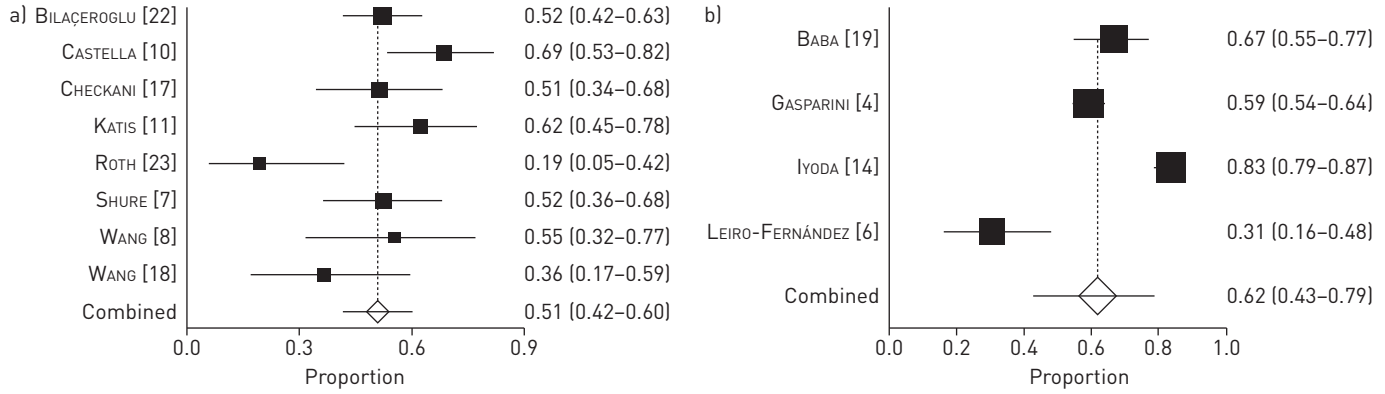

FIGURE 4 Diagnostic yield of TBNA according to the rapid on-site evaluation (ROSE) presence. a) ROSE absent. I^2 63% (95% CI 0–81%). b) ROSE present. I^2 96% (95% CI 93.2–97.3%). Error bars represent 95% confidence intervals.

95% CI 0.0–81.0%) was found when ROSE was not carried out [7, 8, 10, 11, 17, 18, 22, 23] and 0.62 (95% CI 0.4–0.8) (I^2 96%, 95% CI 93.2–97.3%) when it was performed [4, 6, 14, 19] (figure 4). In the case of malignant lesions [4, 5, 7, 9, 13, 14, 19, 20, 23], pooled TBNA yield was higher (0.55, 95% CI 0.4–0.7) (I^2 93.2%, 95% CI 90.2–95.0%) if compared with cases of benign lesions [4, 5, 13] (0.17, 95% CI 0.1–0.2) (I^2 0.0%, 95% CI 0.0–72.9%) (figure 5). When the authors evaluated lesions >3 cm [5, 10], the TBNA diagnostic yield was 0.81 (95% CI 0.7–0.9) (I^2 not available); the pooled proportion was 0.55 (95% CI 0.5–0.6) (I^2 not available) in cases of lesions ⩽3 cm [5, 10] (figure 6). TBNA showed a higher diagnostic yield (0.60) (I^2 92.2%, 95% CI 86.9–94.7%) than TBB (0.45) (I^2 85%, 95% CI 68.5–91%) [4, 5, 7, 11, 14, 18, 22] (figure 7).

The application of the QUADAS-2 tool revealed an overall low methodological quality. It presents the judgement of risk of bias, concerns about applicability for each domain, and the final summarised proportion of studies deemed as at "low" or "high" risk of bias and having "low" or "high" concerns regarding applicability of the review question (online supplementary figure S1). Overall, five studies were judged to be at low risk of bias [4, 5, 7, 11, 17], seven as having low concerns about applicability [4, 5, 7, 8, 10, 11, 17] and, out of these, two studies met both the conditions [5, 7].

Discussion

The present systematic review and meta-analysis firstly provides an extensive description and synthesis of the main results from all published studies evaluating fluoroscopy-guided TBNA yield and predictors for the diagnosis of PPL. Overall, the pooled estimate documented an acceptable diagnostic performance (0.53, 95% CI 0.4–0.6). Major predictors of a higher sensitivity included the presence of CT bronchus sign, the malignant nature of the abnormalities, diameter of the lesions >3 cm and ROSE employment. Data on comparison between TBNA and TBB, resulting only from studies in which both procedures were performed in the same patients, showed a significant superiority of TBNA. Considering that, based on the

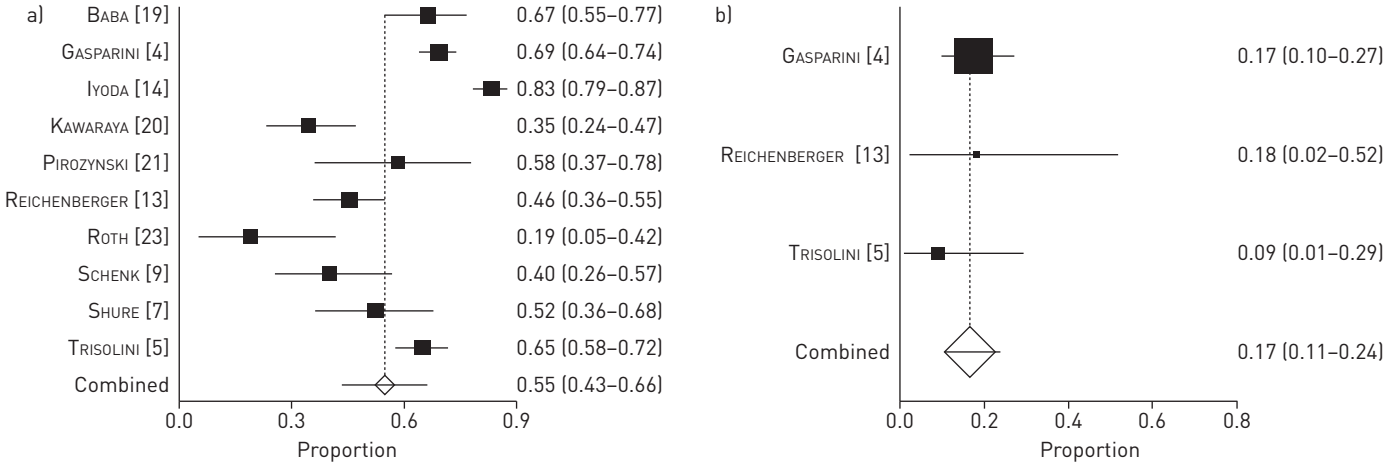

FIGURE 5 Diagnostic yield of transbronchial needle aspiration according to the malignancy of the lesions. a) Malignant lesions. I^2 93.2% (95% CI 90.2–95%). b) Benign lesions. I^2 0% (95% CI 0–72.9%). Error bars represent 95% confidence intervals.

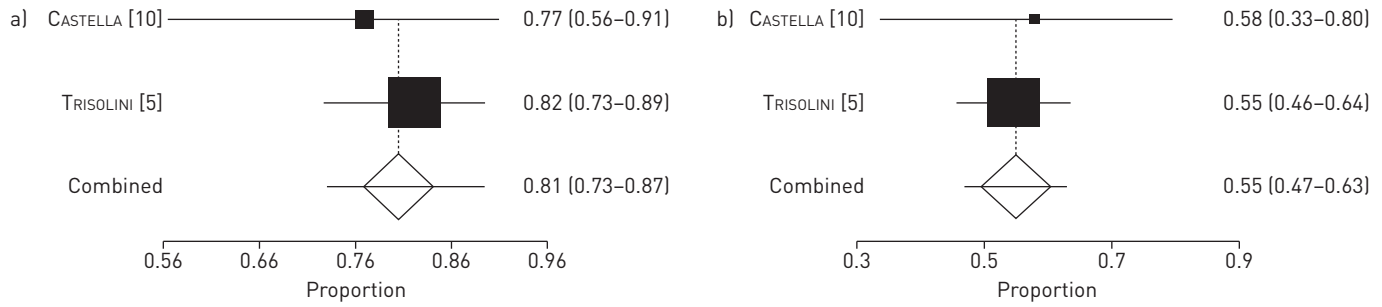

FIGURE 6 Diagnostic yield of transbronchial needle aspiration according to lesion size. a) >3 cm. b) ⩽3 cm. Error bars represent 95% confidence intervals.

literature, TBNA is still largely underused while TBB is the most employed technique in this context, this result is of great relevance [1, 5, 6].

Randomised controlled trials have previously suggested the importance of ROSE of needle aspirates in both central malignant lesions, and hilar and mediastinal adenopathies. In the former, the immediate cytological assessment may improve the sensitivity of this sampling technique; in the latter, it may reduce the number of biopsy sites and the complication rate of bronchoscopy without enhancing the yield of TBNA [24, 25]. In sampling peripheral lesions, the only data available came from uncontrolled studies [26, 27]. However, our subgroup analysis suggested ROSE as a potential predictor of a better yield. Furthermore, the ROSE technique may allow bronchoscopists to stop sampling when sufficient material has been harvested for traditional diagnosis and molecular studies, thus potentially avoiding useless TBBs or brushings [28, 29].

Further subanalyses support the previous findings that malignant lesions [4, 5, 13] and the presence of a CT bronchus sign [5, 22] are associated with a better yield. Actually, it should be noted that even in the absence of CT bronchus sign, TBNA offers a good diagnostic performance (pooled yield of 51%). As suggested by some authors, this aspect might be explained by the peculiar ability of this sampling method to pierce the bronchial wall, reaching lesions with a peribronchial growth [5, 7, 8].

TBNA showed a higher yield in sampling peripheral masses than in diagnosing nodules. Moreover, it is worth noting that the diagnostic performance of TBNA in lesions with a diameter ⩽3 cm is not negligible (pooled yield of 53%). These results encourage performing conventional TBNA during the first bronchoscopic examination in every PPL that is visible by fluoroscopy; in about half of cases, this might spare the patients from undergoing diagnostic procedures with a higher risk of complications, such as transthoracic needle aspiration [5]. Our analysis suggests that TBNA is also a safe procedure with a limited number of adverse events, pneumothorax and bleeding being the most frequent complications.

Although less powerful and technologically advanced in comparison with electromagnetic navigation and EBUS guidance, fluoroscopy-guided bronchoscopic procedures should be learnt after specific training to improve technical skills. Furthermore, adequate infrastructures and equipment, as well as the possible inclusion of other healthcare workers (*e.g.* radiology technicians and pathologists), may be deemed as potential limitations in terms of costs, time and radiation exposure.

Some limitations of the present review have to be acknowledged. In particular, there was a high baseline heterogeneity among studies in terms of design, sample size and outcome measures. Moreover, several

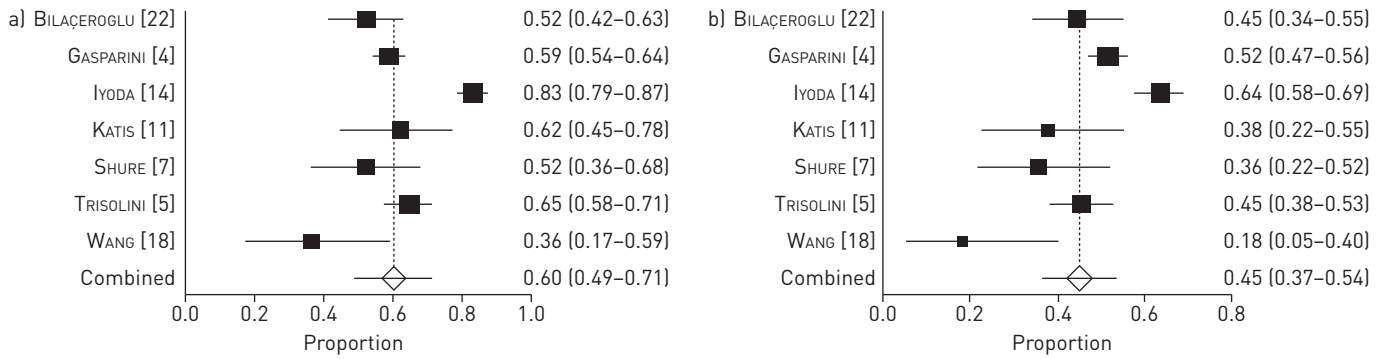

FIGURE 7 Diagnostic yield of transbronchial needle aspiration (TBNA) compared with transbronchial biopsy (TBB). a) TBNA yield. I^2 92.2% (95% CI 86.9–94.7%). b) TBB yield. I^2 85.0% (95% CI 68.5–91%). Error bars represent 95% confidence intervals.

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confounding factors could have affected the performance and interpretation of index test, as TBNA was often performed by different operators and with different numbers of passes within the same study. Indeed, the majority of the studies did not include important information on operators' skills (experienced endoscopists/fellows, and number and experience of pathologists), sampling method and equipment (bronchoscope and needle type, needle pass number, and presence/absence of ROSE) and targeted lesions (method of nodule/mass measurement). A further limitation includes the definition of "diagnostic samples" among studies. In the era of targeted lung cancer therapy, a sample should be considered as diagnostic only if provides an amount of cells suitable for both immunocytochemical and molecular studies, but in most of investigations, it was unclear whether this was routinely obtained. Finally, considering that a nondiagnostic or negative result does not rule out the possibility of malignancy, the lack of a standardised reference test, as documented by our QUADAS-2 results, is also highly likely to influence the interpretation of results. However, the evidence provided could help scientists for the design of novel studies on this topic, addressing the aforementioned limitations.

Conclusions

Our systematic review and meta-analysis suggests that fluoroscopy-guided TBNA is a useful and safe diagnostic technique for the diagnosis of PPLs, but its accuracy seems to be related to selected clinical and procedural aspects, such as presence of CT bronchus sign, an underlying malignant process, diameter of the lesions >3 cm and ROSE employment.

Despite the above mentioned limitations, our results are particularly remarkable in this era of new advances in endoscopic procedures. Although these innovative technologies have recently broadened the bronchoscopist's horizons, their diffusion is still limited, particularly in developing countries, and the routinely diagnostic approach to PPLs is still represented by fluoroscopy-guided transbronchial and percutaneous sampling. In this context, it is reasonable to propose a sequential diagnostic algorithm, as previously suggested [4], in which flexible bronchoscopy with TBNA should be performed first, due to the acceptable sensitivity and the safer profile, especially in presence of predictors of positive aspirates.

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