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Endobronchial Ultrasound for the Diagnosis of Centrally Located Lung Tumors: A Systematic Review and Meta-Analysis

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Lung cancer · Diagnosis · Endobronchial ultrasound · Tumor

Abstract
Introduction: Obtaining a tissue diagnosis of centrally located lung tumors in patients presenting without endobronchial abnormalities is challenging, and therefore a considerable diagnostic problem. ***Objective:*** The objective of this study was to evaluate the performance of linear endobronchial ultrasound guided-transbronchial-needle aspiration (EBUS-TBNA) for the diagnosis of centrally located lung tumors. ***Methods:*** We performed a systematic review (PROSPERO, CRD42017080968) and searched MEDLINE, Embase, BIOSIS Previews, and Web of Science till November 18, 2018 for studies that evaluated the yield and/or sensitivity of EBUS-TBNA for diagnosing centrally located lung tumors. We assessed the study quality using QUADAS-2 and performed random-effects meta-analysis. ***Results:*** A total of 5,657 manuscripts were identified; of these 14 were considered for the study, including 1,175 patients who underwent EBUS-TBNA for diagnosing an intrapulmonary tumor. All studies had a high risk of bias or applicability concerns, predominately regarding patient selection. The average yield of EBUS-TBNA for diagnosing centrally located lung tumors was 0.89 (95% CI 0.84–0.92) and average sensitivity for diagnosing malignant tumors was 0.91 (95% CI 0.88–0.94). Among studies reporting this information, EBUS-related complications occurred in 5.4% of patients (42/721). ***Conclusion:*** EBUS-TBNA has a high yield and sensitivity for diagnosing centrally located lung tumors and is safe in selected patients. Prospective studies are recommended to evaluate the routine use of this procedure for diagnosing intrapulmonary tumors.

Introduction

Lung cancer is the leading cause of cancer-related mortality in the world [1]. If lung cancer is suspected, a tissue diagnosis should be obtained to establish a definite diagnosis. In patients with centrally located lung tumors suspected for lung cancer, current clinical guidelines recommend conventional flexible bronchoscopy with biop-

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sy or transbronchial-needle aspiration (TBNA) to obtain a diagnosis [2]. However, bronchoscopy is non-diagnostic in a considerable proportion of patients, especially in the absence of endobronchial abnormalities [3]. Computed tomography (CT) guided transthoracic needle aspiration can be used to obtain a diagnosis, but for centrally located lung tumors this technique has a high risk of complications including pneumothorax and bleedings [3]. Moreover, such tumors are frequently inaccessible for a transthoracic approach, and the diagnostic yield is lower than for peripheral lung tumors [4, 5].

Current staging guidelines advocate endobronchial and esophageal ultrasound (EBUS and EUS-[B]) as the techniques of choice for mediastinal nodal tissue staging of non-small cell lung cancer [6–8]. In patients in whom CT imaging shows a centrally located lung tumor adjacent to the major airways, endobronchial endoscopic ultrasound-guided fine-needle aspiration (EBUS-TBNA) is suggested for diagnostic purposes following a non-diagnostic conventional bronchoscopy [6, 9].

Although the EBUS technique for mediastinal nodal staging of lung cancer has rapidly spread, its role in obtaining an adequate tissue sample directly from intrapulmonary tumors has received much less attention. If sufficiently feasible and accurate, diagnosing lung tumors through EBUS could have major logistic advantages, as tumor and mediastinal nodal staging can be performed in the same session [6, 10].

Various reports regarding the role of EBUS-TBNA in the diagnosis of centrally located lung tumors have been published, but its feasibility, yield, sensitivity, and safety are not well-established [6]. Therefore, we conducted a systematic review and meta-analysis with the aim of obtaining summary estimates of the yield and sensitivity of EBUS-TBNA for diagnosing centrally located lung tumors in patients with suspected lung cancer.

Material and Methods

The protocol of this systematic review was prospectively registered at PROSPERO under registration number CRD42017080968. This review is reported following the PRISMA-DTA guidelines [11].

Eligibility Criteria

Studies were included if they evaluated the yield and/or sensitivity of EBUS-TBNA for diagnosing centrally located lung tumors adjacent or near the major airways – with the aim of obtaining a tissue sample from the suspected lesion. Various definitions of a centrally located lung tumor exist and we followed those as reported by the authors of the primary studies. Studies were eligible for analysis regardless of whether patients were selected based on the results of previous tests. If studies aimed to obtain a tissue diagnosis from centrally located lung tumors invading the mediastinum or central vessels, they were also included. However, we excluded studies that focused on diagnosing mediastinal tumors, studies that aimed to diagnose lung cancer by sampling mediastinal nodes, liver lesions or left adrenal gland lesions, and studies focusing on lung cancer staging rather than diagnosis. We also excluded studies using a radial instead of a linear EBUS scope, and studies including <10 patients with centrally located lung tumors.

Literature Search Strategy and Selection

We searched for eligible studies in MEDLINE (Ovid), Embase (Ovid), BIOSIS Previews (Ovid), and Web of Science. Searches were developed by a medical information specialist (R.S.). No date or language restrictions were applied. The complete search strategy is provided in online supplementary Appendix (online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000500363). The final search was performed on November 18, 2018. We checked reference lists of all included papers for additional studies.

Two authors (J.C.K. and L.C.C.) independently reviewed the titles and abstracts of all search results for eligibility. If an article was considered potentially eligible, both authors independently examined the full article for inclusion. Disagreements were resolved after discussion with a third author (J.T.A.).

Data Extraction and Synthesis

Data were extracted from included studies by 2 authors (J.C.K. and F.L.). We extracted the first author, year of publication, journal of publication, and country of patient recruitment. We also extracted whether or not patients had received previous tests to obtain a biopsy-based diagnosis of the centrally located tumor. We extracted details about age and gender, availability of rapid on-site cytological evaluation (ROSE), needle type, number of needle passes performed, procedure length, tumor size, the number of patients with endobronchial abnormalities, the reference standard, and any complications induced by EBUS-TBNA.

Furthermore, we extracted the total number of patients in whom EBUS-TBNA was performed with the aim of diagnosing a centrally located lung tumor, the number of patients in whom an adequate tissue sample was obtained by EBUS-TBNA, the number of patients in whom EBUS-TBNA made a correct biopsy-proven diagnosis (malignant or non-malignant), the number of patients in whom EBUS-TBNA diagnosed a malignancy, and the number of patients in whom the targeted intrapulmonary tumor turned out to be malignant, according to the reference standard.

EBUS-TBNA was considered to have reached an inadequate diagnosis if additional diagnostics were needed to obtain a correct diagnosis (e.g., because the tumor could not be visualized or sampled through EBUS-TBNA), or if the reference standard reached a different diagnosis. EBUS-TBNA was considered to have reached a correct diagnosis if the reference standard resulted in the same diagnosis, or if EBUS-TBNA tissue samples contained malignant cells as in such cases a reference standard is rarely performed.

Risk of Bias and Applicability Concerns Assessment

Two authors (J.C.K. and F.L.) independently assessed study quality using the QUADAS-2 tool [12]. Disagreements were resolved by consensus and in difficult cases, 2 other authors (L.C.C.

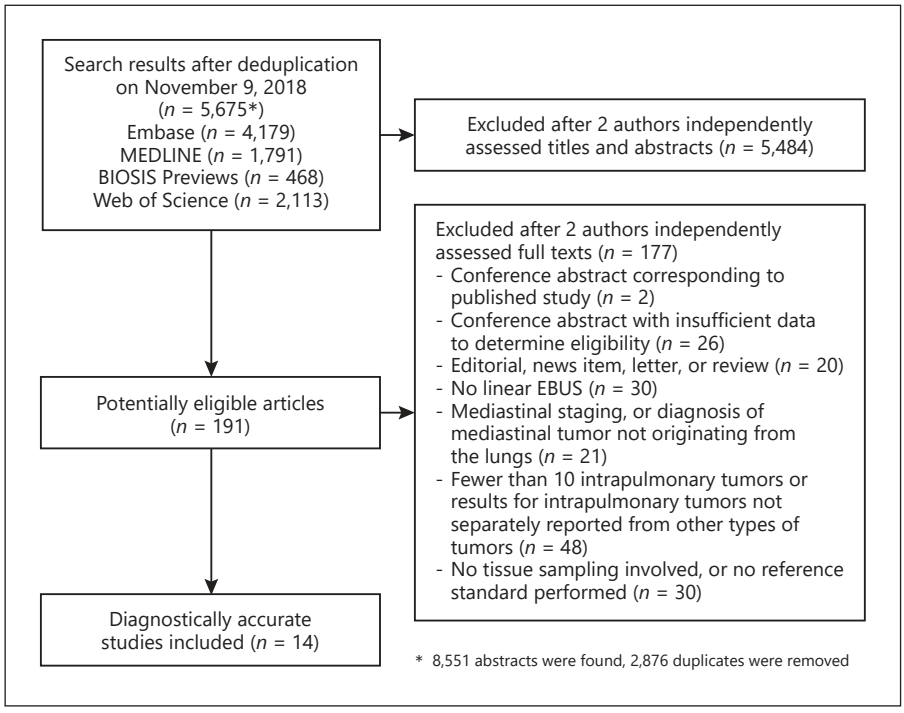

Fig. 1. Flowchart of the selection process of the included studies. EBUS, endobronchial ultrasound.

and D.A.K.) made the final decision. Study designs with a high risk of bias or applicability concerns included: (1) retrospective (nonconsecutive) inclusion of patients; (2) exclusion of patients in whom the intrapulmonary tumor could not be visualized by EBUS; (3) a case-control design; (4) exclusion of patients that did not match the review question; (5) endoscopists that were not blinded to the final diagnosis while performing EBUS; (6) a suboptimal reference standard for patients with a non-diagnostic or non-malignant EBUS-TBNA (e.g., clinical follow-up instead of surgical-pathological verification); (7) partial or (8) differential verification of patients with a non-diagnostic or non-malignant EBUS-TBNA; (9) exclusion of patients with missing reference standard results.

Primary Outcomes

The primary outcomes of this review were: (1) the yield of EBUS-TBNA for diagnosing centrally located lung tumors and (2) the sensitivity of EBUS-TBNA for diagnosing malignant centrally located lung tumors.

Yield was defined as the number of patients in whom EBUS-TBNA made a correct tissue diagnosis, relative to the total number of patients in whom EBUS was performed with the aim of diagnosing a centrally located lung tumor.

Sensitivity was defined as the number of patients in whom EBUS-TBNA made a correct tissue diagnosis of any malignancy, relative to the total number of patients in whom the targeted centrally located lung tumor turned out to be malignant.

Analysis

We calculated estimates of yield and sensitivity of the included studies with 95% CIs, using the normal approximation. We then performed a univariate random effects meta-analysis according to DerSimonian-Laird [13]. Data analyses were performed in the "meta" package in R version 3.0.

Results

Study Selection and Study Characteristics

The searches identified 5,675 results. After screening titles and abstracts, 191 potentially eligible articles remained, of which 14 studies were included in the final analysis [9, 14–26]. Of these, 3 were conference abstracts. Figure 1 provides the details of the study selection and the reasons for excluding studies.

Across included studies various definitions for the targeted lung tumors were used, ranging from "central lung parenchymal lesions" [16] to "an intrapulmonary mass with the medial margin located within the inner third of the hemi-thorax based on chest CT-scan imaging" [14]. Table 1 summarizes the different definitions used for centrally located lung tumors across the included studies.

Table 2 shows detailed characteristics of the 14 included studies. The first article was published in 2008 and the last in 2018. Nine studies reported the proportion of patients that underwent a previous non-diagnos-

Table 1. Definitions of targeted intrapulmonary lesions

Study [ref.], year	Targeted intrapulmonary tumors were defined as
Nakajima et al. [9], 2008	Pulmonary masses whose drainage bronchus is difficult to be reached such as mediastinal type lung cancer adjacent to the trachea, lesions adjacent to the main bronchus or the segmental bronchus
Tournoy et al. [14], 2009	The centrally located lung lesions were defined as an intrapulmonary mass with the medial margin located within the inner third of the hemi-thorax based on chest CT-scan imaging
Khan et al. [16], 2012	Central lung parenchymal lesions
Bhatti et al. [17], 2013	Centrally located peribronchial lung lesions
Verma et al. [18], 2013	Centrally located lung lesions were defined as an intrapulmonary nodule or mass located adjacent to the tracheobronchial tree as visualized on chest CT scan
Yang et al. [19], 2013	Parabrachial or parabronchial intrapulmonary lesions proved by CT scan
Zhao et al. [20], 2013	Intrapulmonary lesions located near the central airway
Evison et al. [21], 2013	Intra-parenchymal lung lesions
Argento et al. [22], 2016	Centrally located intraparenchymal lesions Lesions completely surrounded by lung parenchyma were included
Chen et al. [23], 2017	Peribronchial lung lesions

tic conventional bronchoscopy, ranging from 33 to 100%; information on previous bronchoscopy was not reported in the remaining 5 studies. The mean/median age of the patients ranged from 56 to 69 year, and the ratio of male patients ranged from 31 to 83%. ROSE was available in 6 studies, not available in 4 studies, and 4 studies did not report on the availability of ROSE. The type of needle that was used was a 22 Gauge needle in 11 studies, both 21- or 22-Gauge needles in 1 study, and not reported in 2 studies. Six studies reported on the number of needle aspirates, which varied from 2 to 6. Three studies reported on the mean/median procedure length: 21, 46, and 56 min. The mean/median tumor size ranged from 25 to 53 mm. Seven studies (542 patients in total) explicitly excluded patients with endobronchial abnormalities or did not encounter such patients, and 3 studies explicitly included patients with endobronchial abnormalities (27 patients with endobronchial abnormalities in total). The remaining 4 studies made no comments regarding the presence of patients with endobronchial abnormalities.

Risk of Bias and Applicability Concerns

Detailed results of the quality assessment of included studies are available in the online supplementary appendix (online suppl. Table S2). All studies had at least one item with a high risk of bias and/or applicability concerns. The most common source of bias was the retrospective inclusion of patients, which was the case in 12 of 14 included studies. It was unclear for 11 studies whether inappropriate exclusions were avoided, which we considered the case if patients in whom the tumor could not be visualized by EBUS were excluded. The quality of the reference standard, in the absence of a specific diagnosis following EBUS, was variable ranging from surgical-pathological verification to clinical follow-up.

Diagnostic Yield and Sensitivity

Table 3 shows the estimates of yield and sensitivity for the individual studies. The total number of patients included in this review is 1,175; the number of patients included in the individual studies ranged from 32 to 290. The proportion of patients with a final diagnosis of ma-

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Table 2. Characteristics of the included studies in which patients underwent EBUS procedure for the diagnosis of a centrally located lung lesion

Study details, *Journal* [ref.]	Previous tests to obtain a tissue diagnosis prior to EBUS-TBNA	Age, years, mean/median (range)	Male, %	ROSE	Needle type	Number of needle aspirates	Procedure length, min	Tumor size, mm	Reference standard in patients with a non-diagnostic or non-malignant EBUS-TBNA	EBUS-TBNA induced complications
Nakajima et al. [9], 2008, *J Thorac Oncol,* Japan	Non-diagnostic conventional bronchoscopy in 74% of patients	63 (37–86)	83	Available	22G	NR	NR	Mean: 30 (range: 10–70)	Surgical-pathological verification	None
Tournoy et al. [14], 2009, *Lung Cancer,* Belgium	Non-diagnostic conventional bronchoscopy in 82% of patients	65 (43–82)	60	Available	22G	NR	Mean: 21, (range: 10–60)	Mean: 25 (range: 10–70)	Surgical-pathological verification CT-guided biopsy	Patient intolerance with procedure being abandoned *n* = 2 (3.3%) Self-limiting atrial fibrillation *n* = 1 (1.7%)
Eckardt et al. [15], 2010, *World J Surg,* Denmark	Non-diagnostic conventional bronchoscopy in all (100%) patients	67 (29–86)	56	Not available	22G	2	NR	NR	Surgical-pathological verification Bronchoscopy CT-guided biopsy Clinical follow-up	None
Khan et al. [16], 2012[a], *Thorax,* UK	Non-diagnostic conventional bronchoscopy in all (100%) patients	68 (NR)	47	NR	NR	NR	NR	NR	Surgical-pathological verification CT-guided biopsy CT-scan follow-up	NR
Bhatti et al. [17], 2013, *Journal of Bronchology Interv Pulmonol,* USA	NR	69 (NR)	50	NR	22G	NR	Mean: 56, (SD 23)	Mean: 53 (SD 24)	Surgical-pathological verification CT-guided biopsy	Moderate bleeding *n* = 3 (9.4%) Tachycardia *n* = 1 (3.1%)
Verma et al. [18], 2013, *Yonsei Med J,* South Korea	Non-diagnostic conventional bronchoscopy in 40% of patients	63 (40–81)	68	Not available	22G	2	NR	Mean (short axis): 27.5 (range: 8–82)	Surgical-pathological verification CT-guided biopsy Clinical follow-up (>6 months)	Pneumothorax *n* = 1 (2.7%) Self-limiting moderate bleeding *n* = 1 (2.7%)
Yang, et al. [19], 2013, *Zhonghua Jie He He Hu Xi Za Zhi,* China	NR	NR	NR	Not available	22G	NR	NR	NR	NR	Moderate bleeding *n* = 1 (1.3%)
Zhao et al. [20], 2013, *Chin Med J,* China	Non-diagnostic conventional bronchoscopy in all (100%) patients	56 (33–78)	64	Available	22G	3–6	NR	Mean (short axis): 34 (range: 20–100)	Surgical-pathological verification	None
Evison et al. [21], 2013, *Lung Cancer,* UK	Non-diagnostic conventional bronchoscopy in 33% of patients	NR	NR	NR	NR	NR	NR	NR	NR	NR
Argento et al. [22], 2016, *Respir Med,* USA	NR	66 (44–91)	31	Not available	22G	3	NR	Mean: 25.6 (range: 13.2–61.6)	Surgical-pathological verification CT-guided biopsy CT-scan follow-up Transbronchial biopsy EUS-FNA	None
Chen et al. [23], 2017[c], *Chin Med J (Engl),* China	NR	64 (19–83)	68	NR	21G 22G	NR	NR	NR	Surgical-pathological verification CT-guided biopsy CT-scan follow-up Transbronchial biopsy	None

Table 2 (continued)

Study details, *Journal* [ref.]	Previous tests to obtain a tissue diagnosis prior to EBUS-TBNA	Age, years, mean/median (range)	Male, %	ROSE	Needle type	Number of needle aspirates	Procedure length, min	Tumor size, mm	Reference standard in patients with a non-diagnostic or non-malignant EBUS-TBNA	EBUS-TBNA induced complications
Almeida et al. [24], 2018, *J Bronchology Interv Pulmonol*, USA	Non-diagnostic conventional bronchoscopy in all (100%) patients	NR	NR	Available	22G	≥5	NR	Mean: 43, (range: 9–131)	Diagnosis by any other technique Clinical follow-up (>3 months)	Minor (not specified) $n = 4$ (3.7%) Major bleed $n = 1$ (0.9%) Pneumothorax $n = 1$ (0.9%)
Guarize et al. [25], 2018[d], *Can Resp J*, Canada	NR	65 (20–92)[c]	63	Available	22G	NR	NR	NR	NR	NR
Chaiyakul et al. [26], 2018, *J Med Assoc Thailand*, Thailand	Non-diagnostic conventional bronchoscopy in all (100%) patients	59 (19–87)	75	Available	22G	Mean: 5	Mean: 45, (range: 20–60)	Mean: 49, (range 22–109)	Surgical-pathological confirmation Microbiology confirmation Transbronchial biopsy CT-guided biopsy Clinical follow-up (>3 months)	Minor bleeding n = 12 (6.9%) Desaturation $n = 14$ (8.0%)

[a] Age and gender data apply to the complete cohort of 119 patients; however, 5 of these were excluded from this review because of the lack of a final diagnosis.
[b] Age and gender data apply to the complete cohort of 308 patients; however, only 82 of these had an intrapulmonary tumor.
[c] Age and gender data apply to the complete cohort of 72 patients; however, 6 of these were excluded from this review because of the lack of a final diagnosis.
[d] Age and gender data apply to the complete cohort of 1,891 patients, however, only 290 of these had an intrapulmonary tumor.
NR, not reported; EBUS-TBNA, endobronchial ultrasound-guided transbronchial-needle aspiration; CT, computed tomography; ROSE, rapid on-site cytological evaluation.

lignancy varied from 62 to 100%. Final diagnosis of malignancy included non-small cell lung cancer in 620 patients, SCLC in 126 patients and another malignant diagnosis in 61 among 12 studies reporting this information. Detailed information about the final diagnosis is available on the online supplementary appendix (online suppl. Table S3).

The yield of EBUS-TBNA for diagnosing intrapulmonary lesions ranged from 0.72 to 0.96 across the included studies; 1 study did not report sufficient information to calculate yield. The average yield after meta-analysis was 0.89 (95% CI 0.84–0.92; Fig. 2). The sensitivity of EBUS-TBNA for diagnosing malignant intrapulmonary tumors ranged from 0.77 to 0.97 across included studies; 1 study did not report sufficient data to calculate sensitivity. The average sensitivity after meta-analysis was 0.91 (95% CI 0.88–0.94; Fig. 3).

Complications

In 5 studies (281 patients) there were no complications due to EBUS-TBNA, and in 3 studies (453 patients) this information was not reported. In the remaining 6 studies (490 patients), a total of 42 complications were reported: major bleed ($n = 1$), moderate/self-limiting bleeding ($n = 17$), atrial fibrillation ($n = 1$), tachycardia ($n = 1$), intolerance with the procedure ($n = 2$), pneumothorax ($n = 2$), desaturation ($n = 14$), and a minor complication that was not specified ($n = 4$). Overall, among studies reporting this information, the complication rate was 5.4% (42/721), although many of these can be considered as minor.

Discussion

In this systematic review, we found that EBUS-TBNA has a high yield and sensitivity for diagnosing centrally located lung tumors. The findings of this study are clinically relevant as tissue acquisition of centrally located lung tumors without endobronchial abnormalities is a large clinical problem. The current analysis seems to imply that under the condition that the tumor is located adjacent to the major airways, a diagnosis can be obtained through EBUS-TBNA in approximately 9 out of 10 patients with low risk of complications.

Some limitations should be discussed regarding the studies under consideration. All studies included in this systematic review had a high risk of bias or applicability concerns when assessed by QUADAS-2 [12]. Especially the fact that almost no prospective studies on the topic have been performed is surprising. Because of this, yield

Table 3. Yield and sensitivity for EBUS-TBNA for the diagnosis of centrally located intrapulmonary lesions

Study [Ref.], years	Total EBUS performed, *n*	Total with any malignancy, *n* (%)	Adequate tissue sample by EBUS-TBNA, *n* (%)	Correct diagnosis by EBUS-TBNA, *n*	Correct diagnosis of any malignancy by EBUS-TBNA, *n*	Yield for correct diagnosis[a], (95% CI)	Sensitivity for malignancy[b] (95% CI)
Nakajima et al. [9], 2008	35	34 (97)	35 (100)	33	32	0.94 (0.80–0.99)	0.94 (0.79–0.99)
Tournoy et al. [14], 2009	60	58 (97)	46 (77)	46	46	0.77 (0.64–0.86)	0.79 (0.67–0.88)
Eckardt et al. [15], 2010	82	51 (62%)	79 (96)	59	48	0.72 (0.61–0.81)	0.94 (0.83–0.98)
Khan et al. [16], 2012	114	111 (95)	113 (99)	110	108	0.96 (0.91–0.99)	0.97 (0.92–0.99)
Bhatti et al. [17], 2013	32	32 (100)	NR	30	30	0.94 (0.78–0.98)	0.94 (0.78–0.98)
Verma et al. [18], 2013	37	33 (89)	NR	32	32	0.86 (0.71–0.94)	0.97 (0.81–1.00)
Yang et al. [19], 2013	78	65 (83)	NR	75	62	0.96 (0.89–0.99)	0.95 (0.87–0.99)
Zhao et al. [20], 2013	66	63 (95)	66 (100)	59	59	0.89 (0.79–0.95)	0.94 (0.84–0.98)
Evison et al. [21], 2013	49	47 (95)	NR	NR	38	–	0.81 (0.67–0.90)
Argento et al. [22], 2016	32	30 (94)	NR	27	26	0.84 (0.68–0.93)	0.87 (0.69–0.95)
Chen et al. [23], 2017	66	56 (85)	NR	56	48	0.85 (0.74–0.92)	0.86 (0.74–0.93)
Almeida et al. [24], 2018	108	93 (86%)	NR	94	88	0.87 (0.79–0.92)	0.95 (0.88–0.98)
Guarize et al. [25], 2018	290	NR	NR	266	241	0.92 (0.88–0.94)	–
Chaiyakul et al. [26], 2018	175	147 (84%)	NR	158	135	0.90 (0.85–0.94)	0.92 (0.86–0.95)

[a] Yield was calculated as the number of patients in whom EBUS-TBNA made a correct tissue diagnosis (non-malignant or malignant) divided by the total number of patients in whom EBUS was performed with the aim of diagnosing an intrapulmonary tumor.
[b] Sensitivity was calculated as the number of patients in whom EBUS-TBNA made a correct tissue diagnosis of malignancy divided by the total number of patients in whom the targeted intrapulmonary tumor turned out to be malignant.
NR, not reported; EBUS, endobronchial ultrasound; EBUS-TBNA, endobronchial ultrasound-guided transbronchial-needle aspiration.

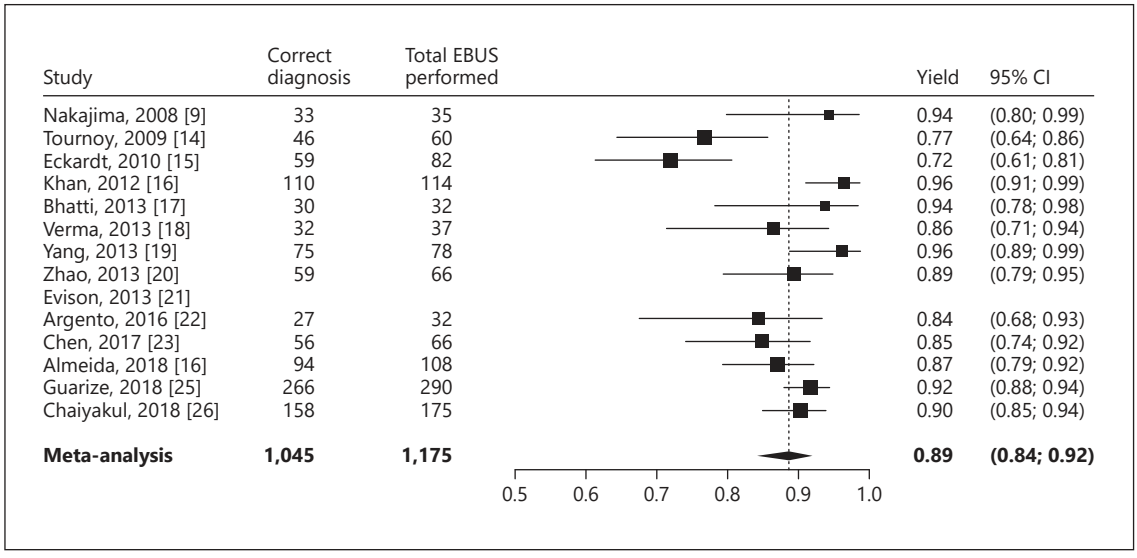

Fig. 2. Yield of EBUS-TBNA for diagnosing centrally located intrapulmonary lesions. EBUS, endobronchial ultrasound.

and sensitivity may have been overestimated. In addition, several different definitions of a centrally located lung tumor were used in the included studies, ranging from the inner one third (American College of Chest Physicians guidelines) [8] to the inner two thirds (European Society of Thoracic Surgery guidelines and National Comprehensive Cancer Network) [7, 27] of the hemi-thorax.

Variations operator's experience, lesion size, localization in relation to the major airways, and the availability of ROSE are key factors that may affect the performance of EBUS-TBNA [28]. Such heterogeneity could lead to major variation in yield and sensitivity across clinical settings, but the limited number of eligible studies and incomplete reporting in some of them, did not allow us to perform sensitivity analyses. However, average estimates of yield and sensitivity were relatively consistent across individual studies, suggesting that EBUS-TBNA may be useful in different clinical settings.

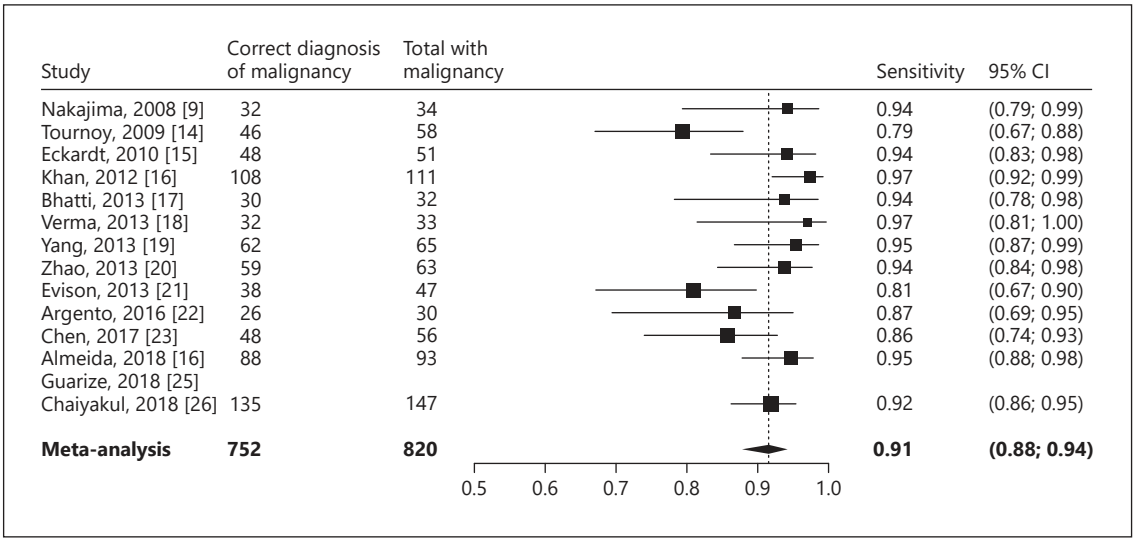

Fig. 3. Sensitivity of EBUS-TBNA for diagnosing malignant centrally located intrapulmonary tumors.

Seven studies explicitly excluded or did not encounter patients with endobronchial abnormalities and 3 studies explicitly reported to have included several patients with such abnormalities. Among these 10 studies, only 27 of 660 (4%) patients showed endobronchial abnormalities. Therefore, it is unlikely that the presence of endobronchial lesions has overestimated the yield and sensitivity of EBUS-TBNA in diagnosing centrally located lung tumors in our review.

We found a high proportion of patients with malignancy across the included studies. This may, again, be related to the retrospective nature of most studies; some may have only selected patients with a high likelihood of malignancy. The prevalence of malignant tumors is likely to be lower in practice.

Complications occurred in only 5.8% of patients, with just 2 serious adverse events (a major bleed which needed an intervention and one pneumothorax). These numbers are comparable with those reported in previous studies on EBUS-TBNA related complications in sampling nodes and mediastinal masses [29]. The most common complication was self-limiting bleeding, and only 2 patients had a pneumothorax due to EBUS-TBNA, thus suggesting that a routine chest X-ray after EBUS-FNA of intrapulmonary tumors may not be indicated.

EBUS-TBNA is a cost-effective lung cancer staging procedure that can be performed in outpatients under moderate sedation [30]. Moreover, it provides the advantage that it can combine lung tumor diagnosis and loco regional mediastinal and hilar staging in a single procedure. Endosonography is very operator-dependent and should be learned and performed in a systematic way [4, 28]. There is a need for learning and certification programs in endosonography such as the "ERS comprehensive training program" to train qualified doctors to be able to independently and competently perform EBUS [31]. Besides nodal assessment, diagnosing intrapulmonary tumors should be part of training programs.

A substantial number of studies have evaluated the performance of EBUS-TBNA in diagnosing mediastinal tumors and in mediastinal nodal staging in patients with lung cancer [32], and this application is now recommended in most clinical guidelines [7, 8]. However, the number of evaluations on the performance of EBUS-TBNA in diagnosing intrapulmonary tumors is limited and almost all are retrospective [6]. Based on our own experience, for patients with a previous non-diagnostic bronchoscopy, we believe that EBUS-TBNA should be considered for those patients who present with an intrapulmonary tumor located adjacent or near the larger airways, especially in case of the absence of endobronchial lesions or nodal metastases. Future prospective studies with clear definitions of a centrally located lung tumor are advised to confirm the current findings. The definition of the tumor positioned within the inner one third of the hemi-thorax by drawing concentric lines from the midline may qualify best [33].

Despite the parenchymal origin of the lesion, linear EBUS seems more useful then radial EBUS for the analysis of centrally located lung tumors without endobronchial abnormalities. Radial EBUS can be used to detect lung lesions provided an airway reaches the lesion; however, a real-time controlled aspiration is not possible [34–36].

Also conventional TBNA – without EBUS guidance – can also be used for primary lung tumor analysis [2]. The needle can be placed on a widened carina or inserted on a specific location in the airways based on chest CT scan findings. The diagnostic yield of conventional TBNA depends on the size and the location of the lung tumor, and a diagnostic yield of 56% was reported [2]. A comparison study between EBUS guided TBNA and conventional TBNA has not been performed.

A recent meta-analysis of our group reported a high yield and sensitivity of EUS-(B)-FNA for diagnosing centrally located intrapulmonary tumors in case the lung mass is located adjacent the esophagus [37]. Using EUS-(B)-FNA, left sided and lower paraesophageal nodes and tumors can be reached [10]. As such, it is complementary to EBUS-TBNA, which provides access to structures close to the large airways on both sides [38]. A combined approach of EBUS-TBNA and EUS-B-FNA for mediastinal lymph node staging is increasingly performed in clinical practice [3, 8]. Such an approach could also be useful in the diagnosis of centrally located intrapulmonary tumors [39]. A combined EBUS and EUS procedure using just the EBUS scope for both nodal and tumor diagnosis is an elegant minimally invasive diagnostic approach.

In conclusion, the present systematic review and meta-analysis implies that EBUS-TBNA is a safe procedure with a high yield and sensitivity for diagnosing centrally located lung tumors. However, caution should be taken to extrapolate these results into routine real-life practice due to the lack of high-quality studies included. Future prospective studies are indicated to evaluate whether the current findings are reproducible and to further refine the criteria for recommending EBUS-TBNA in this setting.

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