

Transesophageal endoscopic ultrasound-guided tissue acquisition of lung masses: a case series with systematic review and meta-analysis

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Abstract

Background The diagnosis of intraparenchymal lung masses is challenging when lesions are located at sites inaccessible through bronchoscopy or endobronchial ultrasound. Endoscopic ultrasound (EUS)-guided tissue acquisition (TA)—fine-needle aspiration (FNA) or fine-needle biopsy—provides a potentially useful diagnostic tool for lesions located adjacent to the esophagus. This study was conducted to analyze the diagnostic outcome and safety of EUS-guided tissue sampling of lung masses.

Methods Data were retrieved for patients who underwent transesophageal EUS-guided TA between May 2020 and July 2022 at 2 tertiary care centers. A meta-analysis was performed after pooling these data with studies obtained from a comprehensive search of Medline, Embase, and ScienceDirect from January 2000 to May 2022. Pooled event rates across studies were expressed with summative statistics.

Results After screening, 19 studies were identified and, after their data had been combined with those of 14 patients from our centers, a total of 640 patients were included in the analysis. The pooled rate of sample adequacy was 95.4% (95% confidence interval [CI] 93.1-97.8), while the pooled rate of diagnostic accuracy was 93.4% (95%CI 90.7-96.1). The pooled rate of adverse events with transesophageal EUS-guided TA from lung masses was 0.7% (95%CI 0.0-1.6%). There was no significant heterogeneity with respect to various outcomes and results were comparable on sensitivity analysis.

Conclusions EUS-FNA offers a safe and accurate diagnostic modality for the diagnosis of paraesophageal lung masses. Future studies are needed to determine the needle type and techniques for improving outcomes.

Keywords Endoscopic ultrasound, transesophageal endobronchial ultrasound, transesophageal tissue acquisition, lung mass

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Introduction

Fine-needle aspiration (FNA) or fine-needle biopsy (FNB) guided by endoscopic ultrasound (EUS) or endobronchial ultrasound (EBUS) is an accurate, safe and minimally invasive procedure for the evaluation of mediastinal lesions in the subcarinal, paraesophageal area, aortopulmonary window, and para-aortic area. Advances in EUS and EBUS have reduced the dependence on more invasive procedures, such as video-assisted thoracoscopic surgery and mediastinoscopy, for tissue sampling in the mediastinum [1]. Worldwide, lung cancer is one of the leading causes of mortality and morbidity [2]. Tissue acquisition (TA) of lung tumors using EUS or EBUS is an emerging procedure. It can be done by EBUS-guided transbronchial needle aspiration (TBNA) via the trachea, or by EUS-FNA. The utilization of combined endobronchial and esophageal endosonography is recommended by European guidelines for diagnosing and staging lung cancer [3]. For the lesions immediately adjacent to the esophagus, TA can be

achieved using FNA guided by EBUS with the scope in the esophagus (EUS-B-FNA), or directly by EUS FNA or FNB [4].

Data on the use of transesophageal EUS-guided TA from lung lesions is limited. Moreover, large comparative studies analyzing the difference in outcome using EUS-FNA and EUS-B-FNA are lacking. In this study, we report our experience of the diagnostic utility of EUS-guided sampling for lung masses, along with a systematic review and meta-analysis to obtain a summary estimate of the diagnostic yield and accuracy of EUS-guided TA from lung lesions.

Patients and methods

Present series

This is a retrospective analysis of a prospectively maintained database from 2 tertiary care centers in India from May 2020 to July 2022. The data on patients undergoing EUS-FNA/FNB of a parenchymal lung mass adjacent to the esophagus were collected and analyzed. This study was performed in accordance with the Declaration of Helsinki.

Technique

EUS-guided sampling from lung masses was planned after a multidisciplinary team discussion consisting of thoracic surgeons, pulmonologists, endoscopists and radiologists, based on location and possible approach to increase yield. After informed consent had been obtained, EUS procedures were performed by experienced endosonographers who had performed at least 500 independent EUS procedures. The procedures were performed under total intravenous or general anesthesia using linear echoendoscopes (Olympus GF-UCT 180, Tokyo, Japan). An EUS-FNA/FNB needle of 22-G (Expect needle/Acquire needle, Boston Scientific Ltd., USA) with slow stylet pull through and fanning technique was used. A minimum of 2 passes with at least 10 actuations per pass were used for all procedures. Rapid on-site evaluation (ROSE) could not be performed because in-house pathologists were not available. Macroscopic on-site evaluation was performed for all patients, and the sample was deemed adequate with at least one whitish core of tissue of 4 mm in length. For macroscopic visualization of the sample, it was placed on a glass slide after each pass. The observed tissue fragment was transferred immediately to a 10% formalin fixative for histopathological evaluation. In the case of drop-like material, it was smeared between 2 glass slides. Half of the slides were air-dried, half fixed with absolute alcohol, and all were sent for cytological examination.

Outcomes

The study's primary outcome was diagnostic accuracy, defined as the summary of true positives + true negatives

in the total number of patients. Surgery or clinical follow up for a minimum of 6 months was considered the gold standard for diagnosis. Secondary outcomes included sample adequacy, defined as the proportion of samples defined as adequate for diagnosis and the adverse events (AE) related to the procedures, reported as per the standard ASGE Lexicon [5].

Systematic review and meta-analysis

A meta-analysis was conducted according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1) [6]. This SMA has been registered with PROSPERO (CRD42022337946).

Database search

The MEDLINE, Embase and ScienceDirect electronic databases were searched from January 2000 to May 2022 for titles and abstracts using the keywords: (EUS OR "Endoscopic ultrasound") AND (Lung OR Pulmonary). There was no bar on language as long as study outcomes were mentioned in the text. Two independent reviewers screened the titles and abstracts of the retrieved studies and assessed the full texts for eligibility before including them. The bibliography of the included studies was also searched for any relevant studies. A third reviewer resolved any disagreement.

Study inclusion

Studies included in this analysis were prospective and retrospective studies fulfilling the following criteria: (a) Study population – patients with lung mass; (b) intervention – EUS-guided transesophageal FNA or FNB; (c) outcomes – diagnostic efficacy and safety. Case reports, case series with fewer than 5 patients, studies of pediatric patients, review articles, correspondence, and editorials were excluded. Studies without relevant clinical data or incomplete data were also excluded.

Data extraction and quality assessment

Data were collected in a structured extraction form by 2 reviewers. The record contained the following parameters of each study: title, first author, year of publication, country, number of patients, age, sex, tumor location, details of EUS needle, adequacy, accuracy, and AEs. Two independent reviewers assessed the quality of the included studies using a scale modified from the Newcastle-Ottawa scale for cohort studies [7]. A third independent individual was consulted in case of any discrepancy.

Data analysis

The pooled proportions were computed using a random-effects inverse-variance model with a DerSimonian-Laird estimate of τ^2 [8]. Prior to statistical analysis, a continuity correction of 0.5 was applied when the incidence of an outcome was zero in a study. The heterogeneity was assessed by I^2 and the P-value of heterogeneity. A P-value <0.10 was taken as statistically significant while I^2 values of 25%, 50%, and 75% were considered cutoffs for low, moderate, and considerable heterogeneity, respectively [9]. A sensitivity analysis was performed based on the study design and the use of EUS or EBUS. "Leave-one-out" meta-analysis was performed to investigate each study's influence on the overall effect-size estimate and to identify influential studies. Meta-regression was used to determine the source of heterogeneity by analyzing the linear relationship between study-level covariates and the effect size. The assessment of publication bias was done by evaluating funnel plot asymmetry and quantified using Egger's test. The meta-analysis was performed using Stata 17.0 software package (Stata Corp LP, College Station, TX, USA).

Results

Present series

The analysis included 14 patients (9 male; median age 60.5, range 31-76 years). All patients had prior bronchoscopic

or EBUS-guided biopsy attempts that had failed because the lesion was in a difficult location. Additional samples were taken from involved mediastinal nodes in 7 (50%) patients. Table 1 shows the patients' details along with the lesion locations and procedural details. Fig. 1 shows the details of one of the cases included in this study.

The median size of the tumor in the longest axis was 49 (range 31-71) mm. The median number of passes was 3 (range 2-3). The EUS-FNA from lung mass was diagnostic in 13 (92.8%) patients. In one patient, the FNA sample from a lung lesion was suspicious for malignancy, and the associated subcarinal node FNA showed squamous cell carcinoma, confirming the diagnosis without requiring additional procedures. There were no reported early or late AEs following the EUS-FNA. Adenocarcinoma was the most common diagnosis (5/14), followed by squamous cell carcinoma (4/14) and small-cell carcinoma (2/14).

Systematic review and meta-analysis

Literature search and study characteristics

The search criteria yielded 2166 studies, of which 19 [10-28] were included in the meta-analysis. Fig. 2 shows the PRISMA flow diagram for study selection and inclusion. Table 2 shows the characteristics of the studies included in the meta-analysis. Among the included studies, 17 were full-text articles [10-17,20-28], while 2 were conference abstracts [18,19]. Based on the study design, 6 studies were

Table 1 Details of the patient and lung lesions included in the study

Case	Age, in years	Sex	ECOG	Location of lesion	Size of lesion, in mm	Mediastinal nodes	No. of passes	Sample adequacy	Final diagnosis	Adverse events
Case 1	66	Female	0	LLL	45×41	Subcarinal	2	Yes	Squamous cell carcinoma	None
Case 2	57	Male	1	RLL	54×47	No	3	Yes	Adenocarcinoma	None
Case 3	60	Female	1	RML	58×40	Subcarinal	3	Yes	Squamous cell carcinoma	None
Case 4	64	Male	0	RLL	47×34	Subcarinal	2	No	Small cell carcinoma	None
Case 5	67	Female	1	RLL	43×35	Subcarinal	3	Yes	Adenocarcinoma	None
Case 6	69	Male	1	LLL	51×42	No	2	Yes	High-grade NET	None
Case 7	48	Male	0	RUL	44×32	Subcarinal	2	Yes	Squamous cell carcinoma	None
Case 8	62	Male	1	RML	55×38	Subcarinal	3	Yes	Small cell carcinoma	None
Case 9	49	Female	0	RLL	50×42	No	2	Yes	Adenocarcinoma	None
Case 10	56	Male	1	RML	48×39	Subcarinal	3	Yes	Squamous cell carcinoma	None
Case 11	61	Female	1	LLL	60×43	No	2	Yes	Adenocarcinoma	None
Case 12	76	Male	1	LUL	31×24	No	2	Yes	Anthraxis	None
Case 13	36	Male	0	RML	71×68	No	3	Yes	Schwannoma	None
Case 14	31	Male	0	RLL	45×36	No	3	Yes	Adenocarcinoma	None

ECOG, Eastern Cooperative Oncology Group; NET, neuroendocrine tumor; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LLL, left lower lobe; LUL, left upper lobe

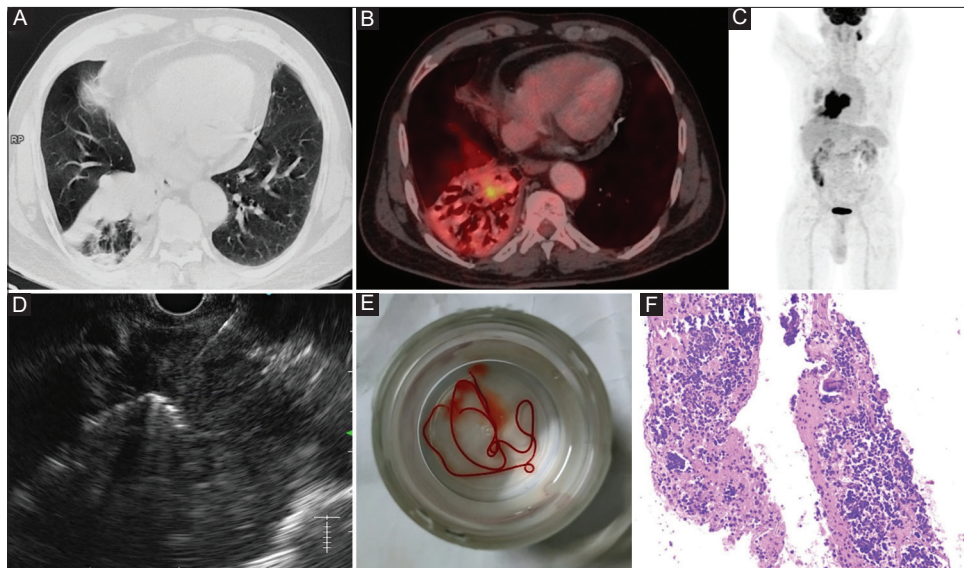


Figure 1 (A) High-resolution computed tomography showing a mass in right lower lobe; (B, C) 18F-FDG PET/CT showing FDG-avid right lower lobe mass without any metastasis; (D) Hypoechoic lung mass on endoscopic ultrasound with 22-G FNA needle in-situ; (E) Core biopsy specimen; (F) Microscopic findings suggestive of high-grade neuroendocrine carcinoma
18F-FDG PET/CT, fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; FNA, fine-needle aspiration

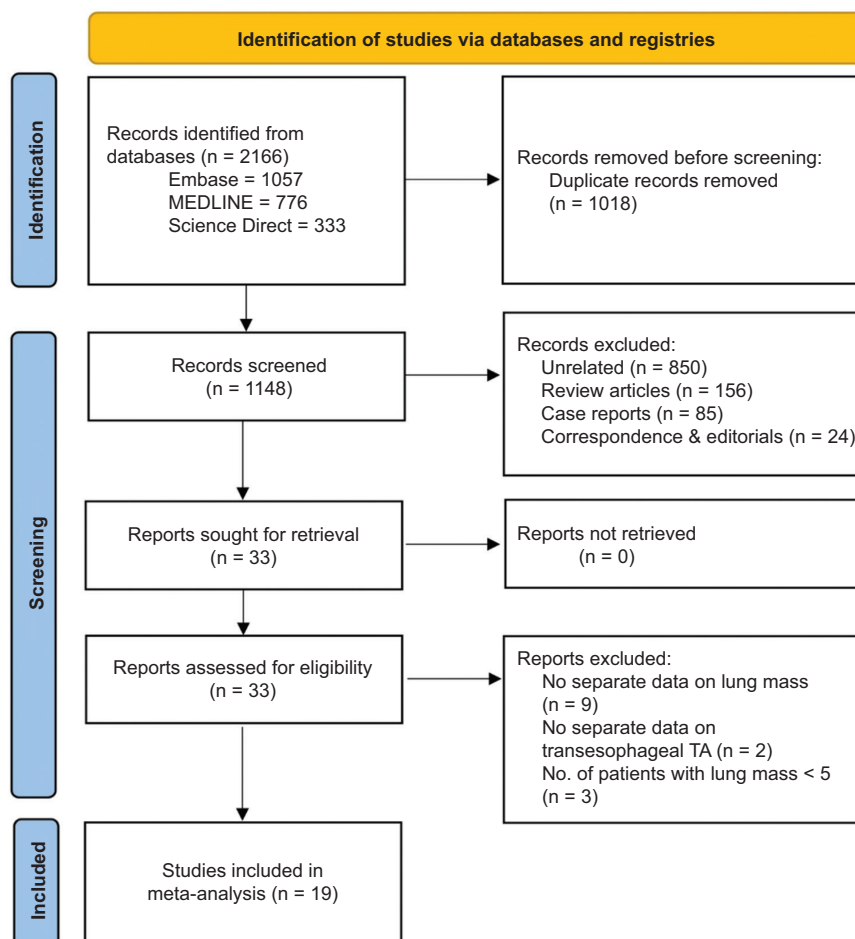


Figure 2 PRISMA flowchart for study identification and selection process
TA, tissue acquisition

Table 2 Characteristics of studies included in the meta-analysis

Authors, year [ref.]	Country	Study design	No. of patients	Age	M/F	Tumor size, in mm	Type of test	Needle type, ROSE	No. of passes	Reference standard
Varadarajulu, 2004 [10]	USA	Retrospective	18	63* (41-77)	11/7	46* (24-85)	EUS	22-G, yes	2* (1-6)	All diagnosed with FNA
Annema, 2005 [11]	The Netherlands	Prospective	32	62* (43-81)	20/12	45* (15-90)	EUS	22-G, yes	2* (1-6)	Surgical pathology
Paquin, 2005 [12]	Canada	Retrospective	15	63* (20-80)	12/3	20×24 to 45×47	EUS	22-G, yes	4* (1-5)	NR
Sawhney, 2006 [13]	USA	Prospective	19	67* (43-82)	NR	40*	EUS	NR, yes	5* (3-8)	Surgical pathology, clinical follow up, CT-guided biopsy
Anand, 2007 [14]	USA	Retrospective	7	NR	NR	NR	EUS	22-G, yes	NR	NR
Hernandez, 2007 [15]	USA	Retrospective	17	66 (48-81)	8/9	50×40*	EUS	22- or 25-G, yes	3* (2-4)	All diagnosed with FNA
von Bartheld, 2009 [16]	The Netherlands	Retrospective	9	60* (49-77)	7/2	25* (13-46)	EUS	22-G, yes	NR	Surgical pathology
Nguyen, 2011 [17]	Australia	Retrospective	24	64 (27-85)	NR	NR	EUS	19- or 22-G, NR	NR	Surgical pathology, clinical follow up
Songur, 2011 [18]	Turkey	Prospective	22	58 (32-78)	NR	35* (28-47)	EUS	19- or 22-G, NR	3.3* (3-5)	Surgical pathology, clinical follow up
Assisi, 2013 [19]	Italy	Retrospective	11	NR	NR	NR	EUS	NR, NR	NR	All diagnosed with FNA
Sequeiros, 2013 [20]	Spain	Retrospective	62	68 (61-82)	48/14	26* (12-65)	EUS	25-G, yes	1* (1-3)	Surgical pathology, clinical follow up, mediastinoscopy, thoracoscopy, percutaneous biopsy, autopsy
Nasir, 2014 [21]	Canada	Retrospective	55	63 (39-83)	24/31	49* (8-110)	EUS	22-G, no	2-4	Surgical pathology
Steinfort, 2016 [22]	Australia	Retrospective	27	NR	NR	36±16	EUS-B	22-G, yes	NR	Surgical pathology
Christiansen, 2018 [23]	Denmark	Retrospective	58	78 (41-90)	24/34	55* (7-120)	EUS-B	21- or 22-G, no	2	Surgical pathology, clinical follow up, CT-guided biopsy
Pais, 2018 [24]	USA	Prospective	20	29-89	9/11	12-109	EUS	22-G, yes	2-4	NR
Chira, 2019 [25]	Romania	Retrospective	19	65.1 (45-80)	15/4	6.7* (3.1-11)	EUS	22-G, no	2.1* (1-3)	NR

(Contd...)

Table 2 (Continued)

Authors, year [ref.]	Country	Study design	No. of patients	Age	M/F	Tumor size, in mm	Type of test	Needle type, ROSE	No. of passes	Reference standard
Christiansen, 2021 [26]	Denmark	Prospective	46	68±9.3	25/21	52±28	EUS-B	22-G, no	2	Clinical follow up, CT-guided biopsy
Mondoni, 2021 [27]	Italy	Prospective	107	69 (60-70)	60/47	42.2* (32-59)	EUS-B	19-,21-,22-,25-G, yes	4.6±0.9	Surgical pathology, clinical follow up, mediastinoscopy, thoracoscopy, percutaneous biopsy, autopsy
Mangiavillano, 2022 [28]	Italy	Retrospective	47	64.47 ±9.05	36/11	38±15	EUS	19- or 22-G, no	3±0.5	Surgical pathology, clinical follow up

M, male; F, female; FNA, fine-needle aspiration; NR, not reported; CT, computed tomography; ROSE, rapid on-site evaluation; EUS, endoscopic ultrasound; EUS-B, transesophageal endobronchial ultrasound

prospective [11,13,18,24,26,27], and the remaining 13 were retrospective [10,12,14-17,19-23,25,28]. The diagnostic test was EUS-FNA/FNB in 15 studies [10-21,24,25,28] and EUS-B-FNA [22,23,26,27] in 4 studies. Ten studies used only a 22-G needle [10-12,14,16,21,22,24-26], 7 studies used a variety of needle sizes ranging from 19-25-G [15,17,18,20,23,27,28], and 2 studies did not report the type of needle used [13,19]. Supplementary Table 2 shows the details of the study quality analysis. Study quality assessment showed that 2 were of high quality [11,27], 10 were of medium quality [10,13,15,16,20-24,28], and 7 were of low quality [12,14,17-19,25,26].

Sample adequacy

The adequacy of the sample was reported by all 19 studies [10-28]. The pooled rate of sample adequacy was 95.4% (95% confidence interval [CI] 93.1-97.8; $I^2=43.0\%$), with low heterogeneity among the studies (Supplementary Fig. 1). On subgroup analysis, based on the type of sampling procedure, both EUS-FNA (95.4%, 95%CI 92.5-98.4; $I^2=42.3\%$) and EUS-B-FNA were found to have comparable diagnostic adequacy (95.2%, 95%CI 90.8-99.6; $I^2=58.9\%$; $P=0.925$).

Diagnostic accuracy

All 19 studies [10-28] reported diagnostic accuracy. The pooled diagnostic accuracy rate was 93.4% (95%CI 90.7-96.1; $I^2=46.0\%$), with low heterogeneity among the studies (Fig. 3). On subgroup analysis based on the type of sampling procedure, both EUS-FNA (93.6%, 95%CI 90.1-97.1; $I^2=50.3\%$) and EUS-B-FNA were found to have comparable diagnostic accuracy (92.6%, 95%CI 88.5-96.7; $I^2=30.5\%$; $P=0.716$).

AEs

AEs directly related to the procedure were reported in 16 studies [10-17,20-25,27,28]. The reported AEs included self-limited severe chest pain, hemoptysis, para-aortic hematoma, and pneumothorax. The pooled rate of AEs with transesophageal EUS-guided TA from lung masses was 0.7% (95%CI 0.0-1.6%; $I^2=0.0\%$), without any heterogeneity among the studies (Supplementary Fig. 2).

Publication bias, sensitivity analysis, and meta-regression

Visual inspection of the funnel plot showed the presence of publication bias for diagnostic accuracy, but not diagnostic adequacy or AEs (Supplementary Fig. 3). Table 3 shows the sensitivity analysis based on the study design, type of echoendoscope used, needle size and study quality. On "leave-one-out" meta-analysis, there was no difference in the effect size of pooled diagnostic yield or pooled diagnostic accuracy. Meta-regression was not conducted as there was no significant heterogeneity regarding various outcomes.

Discussion

Tissue diagnosis is essential for managing lung mass detected on cross-sectional imaging. EUS is conventionally used in staging lung cancer, but there are no recommended guidelines on EUS-guided TA for diagnosing lung masses. In this study, we reviewed our own experience of TA from lung masses and also performed a systematic review in order to carry out a critical appraisal of the available evidence on this topic. In the present analysis, the pooled sample adequacy and

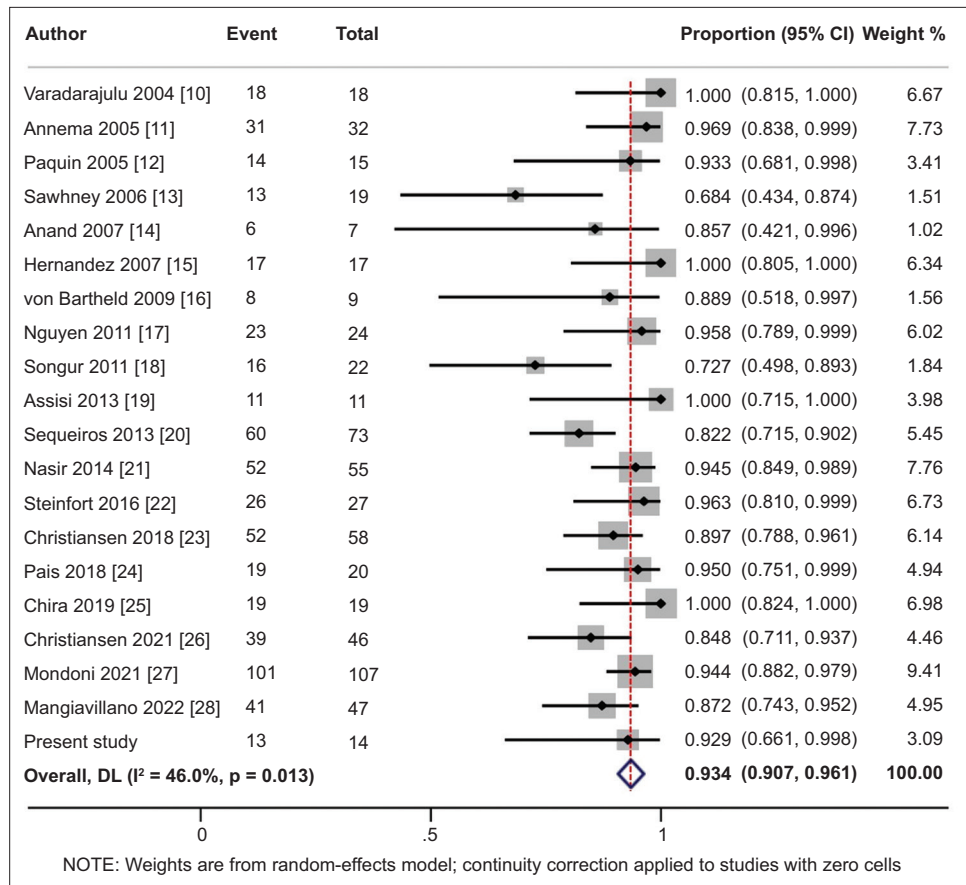


Figure 3 Forest plot for pooled diagnostic accuracy with endoscopic ultrasound-guided transesophageal tissue acquisition of lung mass
CI, confidence interval

Table 3 Summary table with sensitivity analysis

Studies	Sample adequacy		Diagnostic accuracy		Adverse events	
	Pooled rate (95%CI)	I^2	Pooled rate (95%CI)	I^2	Pooled rate (95%CI)	I^2
Overall	95.4% (93.1-97.8)	43.0%	93.4% (90.7-96.1)	46.0%	0.7% (0.0-1.6)	0.0%
Prospective studies	92.2% (87.4-97.0)	45.9%	89.8% (83.5-96.2)	65.3%	0.5% (0.0-1.6)	0.0%
Retrospective studies	96.6% (93.9-99.3)	38.8%	94.5% (91.5-97.5)	35.0%	1.0% (0.0-2.7)	0.0%
Studies with EUS	95.4% (92.5-98.4)	42.3%	93.6% (90.1-97.1)	50.3%	0.6% (0.0-1.9)	0.0%
Studies with EUS-B	95.2% (90.8-99.6)	58.9%	92.6% (88.5-96.7)	30.5%	0.7% (0.0-2.1)	0.0%
Studies using only 22-G needle	97.2% (94.8-99.6)	4.6%	95.8% (93.2-98.4)	0.0%	0.5% (0.0-2.2)	0.0%
Medium-to-high quality studies	95.0% (92.4-97.6)	37.8%	93.4% (90.3-96.5)	46.7%	0.7% (0.0-1.7)	0.0%

CI, confidence interval; EUS, endoscopic ultrasound; EUS-B, transesophageal endobronchial ultrasound

diagnostic accuracy were 95.4% (95%CI 93.1-97.8) and 93.4% (95%CI 90.7-96.1), respectively. Further, both EUS-FNA and

EUS-B-FNA were found to have comparable adequacy and diagnostic accuracy. The present case series shows a diagnostic

accuracy of 92.6%, comparable to the pooled diagnostic accuracy rate of 93.4% obtained from the meta-analysis. There were no AEs associated with EUS-FNA in the present case series, a finding consistent with the low pooled AE rate of 0.7% (95%CI 0.0-1.6%) in the meta-analysis.

For lung masses that are in peripheral locations, computed tomography (CT)-guided transthoracic needle biopsy has been found to have a higher diagnostic yield (odds ratio [OR] 0.23, 95%CI 0.13-0.42; $P<0.001$) and accuracy (OR 0.43, 95%CI 0.25-0.74; $P=0.002$), at the cost of a higher risk of complications (OR 7.27, 95%CI 5.61-9.43; $P<0.001$) than EBUS-TBNA [29]. For centrally located tumor masses, CT-guided biopsy has a high false-negative rate [30], apart from a greater incidence of complications such as pneumothorax needing chest tube placement [31]. EUS-guided transesophageal TA is particularly useful for centrally placed pulmonary masses, especially when the tumor invades or is adjacent to the mediastinal compartment [32]. In addition to obtaining biopsies from pulmonary mass, EUS further helps acquire additional biopsies from the mediastinum and upper abdomen simultaneously for staging purposes.

EUS-B-FNA has advantages compared to EBUS-TBNA in that it minimizes patient discomfort as the airway is not compromised [33]. However, there are other drawbacks associated with the use of the EBUS scope. The EBUS scope is shorter than the EUS scope, leading to suboptimal visualization of the left adrenal gland. The lack of a channel for air insufflation poses problems. Further, image quality is suboptimal in the EBUS scope, and the sonographic angle is narrow. Because of its narrow caliber, EBUS has lesser stability in the esophagus, and the lack of an elevator mechanism means that the needle angle cannot be altered. So, theoretically, the EUS scope fares better than EBUS in the complete staging of pulmonary masses and tissue sampling. However, on subgroup analysis based on the type of sampling procedure, our meta-analyses showed that EUS-FNA (93.6%, 95%CI 90.1-97.1) and EUS-B-FNA (92.6%, 95%CI 88.5-96.7) have comparable diagnostic accuracy ($P=0.716$). Combined EUS and EBUS are complementary methods for staging lung cancer [4].

The mean size of the lesion in the included studies varied from 27-68 mm, and the lesion was not a determinant of heterogeneity for either sample adequacy or diagnostic accuracy. In the study by Mangiovillano *et al* [28], nodule size at the cutoff of 15 mm was reported as a significant predictor of higher diagnostic accuracy. Peripherally located lesions may represent an impediment to the sample using EUS-FNA/B, which may have to be sampled using the traditional EBUS or CT-guided approach. However, EUS-FNA/B represents a potentially efficacious and safe alternative for centrally located tumors, even small-sized lesions. In a previous study of patients with centrally located lung tumors and a non-diagnostic bronchoscopy, EUS-FNA diagnosed lung cancer in 31 of 32 patients (97%) without complications [11].

The rate of AEs in the present series and meta-analysis was very low. In a systematic review by Von Bartheld *et al*, the complication rate for TA through endosonography for mediastinal lesions was low, at 0.14% [34]. Most of these were infectious complications in the form of mediastinitis and

mediastinal abscess formation, which can be life-threatening. Necrosis in the mediastinal lymph nodes was a risk factor for infectious complications. However, during TA of lung masses, such complications are rarely encountered, as was observed in a meta-analysis of esophageal endosonography for the diagnosis of intrapulmonary tumors. Esophageal perforation, although theoretically reported, is very rare [35].

For TA, FNA needles are commonly used. In an algorithm proposed by Bang *et al* for needle selection, 19 G, 22 G, and 25 G needles are used for transesophageal FNA [36]. In a randomized controlled crossover trial, EUS-FNB had a superior diagnostic yield for non-pancreatic masses compared to EUS-FNA (88.2% vs. 54.5%, $P=0.006$), with EUS-FNB being cost-effective compared to EUS-FNA [37]. However, in that study EUS-FNB was performed using 2 passes without on-site cytopathology evaluation. In EUS-FNA, the number of passes was dictated by on-site cytopathology evaluation. On-site cytopathology evaluation is not routinely practiced in Asian countries, apart from US-based centers [38]. However, newer-generation FNB needles have superseded the utility of FNA needles, which are rarely used. A recent network meta-analysis by Gkolfakis *et al* showed that end-cutting FNB needles had the best performance while sampling solid pancreatic masses compared to side-cutting and FNA needles [39]. No previous studies have assessed different needles in solid lung masses, and EUS-FNB for lung mass biopsy has only been reported in one study. The most recent multicentric, retrospective study from 8 Italian centers evaluated the feasibility, accuracy, and safety of transesophageal EUS-FNA/FNB for sampling lung nodules [28]. The reported overall diagnostic accuracy was 88.9% (76.3-96.2). EUS-FNB was associated with a higher sensitivity (100% vs. 78.73%, $P=0.05$), diagnostic accuracy (100% vs. 78.57%, $P=0.05$) and sample adequacy (100% vs. 78.5%, $P=0.05$), compared to EUS-FNA. On multivariate analysis, nodule size >15 mm (OR 2.29, 95%CI 1.04-5.5; $P=0.05$) and the use of an FNB needle (OR 4.33, 95%CI 1.05-6.31; $P=0.05$) were significant predictors of higher diagnostic accuracy. Thus, FNB may also be the procedure of choice over FNA for solid lung lesions.

Contrast-enhanced harmonic EUS (CH-EUS) can help identify the target for EUS-FNA, with easier avoidance of anechoic areas and vessels inside the tumor. Arteries supplying lung carcinoma show late onset and a variable degree of contrast enhancement (due to their bronchial origin). This allows improved targeting of enhancing tissue compared to non-enhancing necrotic zones, which should be avoided at biopsy [40]. A recent meta-analysis reported superior sample adequacy and diagnostic accuracy of CH-EUS-FNA over standard EUS-FNA for the diagnosis of pancreatic lesions [41]. However, the lack of relevant studies prevented us evaluating the role of contrast-enhanced fine-needle aspiration (CH-EUS-FNA) for TA from lung masses, and this remains an area of future research.

There are multiple limitations to the present meta-analysis. As most studies included in the meta-analyses were retrospective, it is possible that only masses comfortably accessible by the transesophageal route had been selected. Properly conducted prospective studies on lung masses are

likely to eliminate this selection bias. No data were available for direct comparison of EUS and EBUS-guided TA. The ideal suction technique also remains a topic for future studies.

To conclude, EUS-FNA/B from lung masses is a safe and effective alternative to EBUS-FNA and can be considered for centrally placed masses. EUS-FNA/B is additionally useful in sampling mediastinal lymph nodes and may help in the optimal staging of lung tumors. There is a need for future prospective studies to determine whether these findings are reproducible and to refine the criteria for recommending EUS-FNA in this setting.

Summary Box

What is already known:

- Endoscopic ultrasound (EUS) has an established role in tissue acquisition (TA) from mediastinal lymph nodes
- However, the diagnosis of intraparenchymal lung masses is challenging in the absence of an associated mediastinal node, or when lesions are located at sites inaccessible through bronchoscopy or endobronchial ultrasound
- Transesophageal EUS-guided TA provides a useful diagnostic modality for paraesophageal lung lesions, but with limited data

What the new findings are:

- The pooled sample adequacy and diagnostic accuracy rates were >90% with transesophageal EUS-guided TA
- Simultaneous sampling of lung lesions and associated mediastinal lymph nodes increases diagnostic accuracy
- Transesophageal EUS-guided TA is a safe technique with a pooled adverse event rate of less than 1%

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Supplementary material

Supplementary Table 1 PRISMA checklist for systematic review and meta-analysis

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	3
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	8
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	8
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	8

(Contd...)

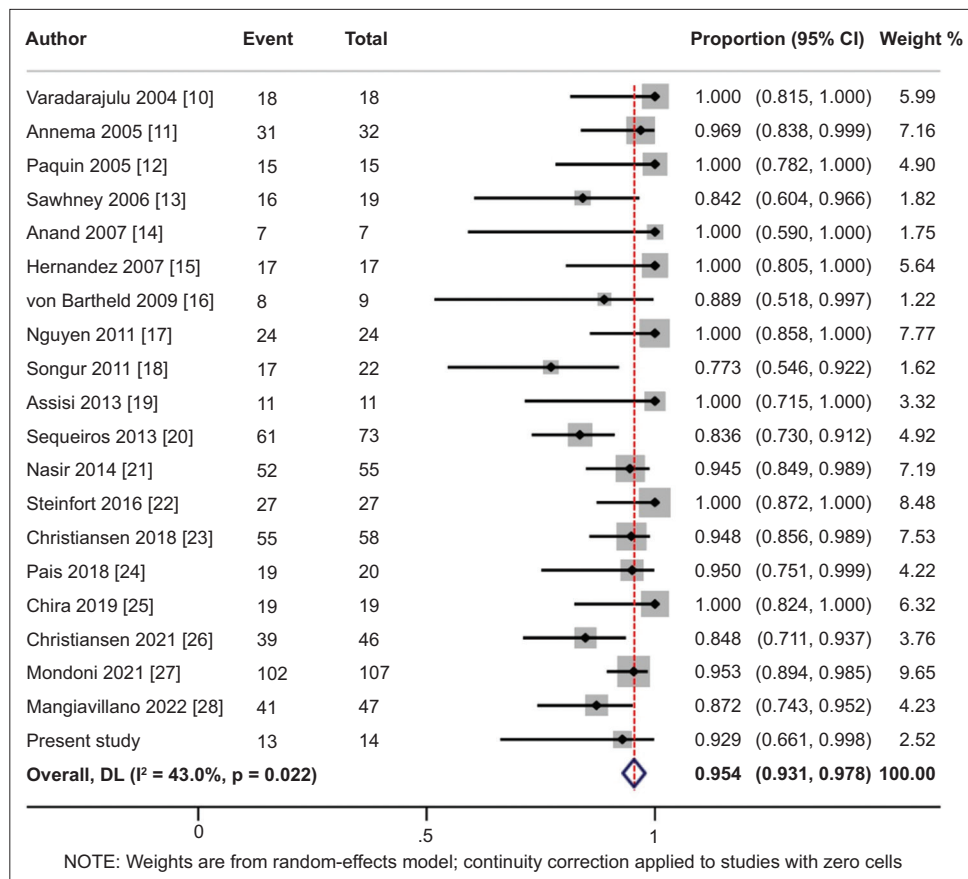
Supplementary Table 1 (Continued)

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment Certainty assessment	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8
	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8
RESULTS			
Study selection	16	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	10
Study characteristics	17	Cite each included study and present its characteristics.	Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	11
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12
	23b	Discuss any limitations of the evidence included in the review.	14
	23c	Discuss any limitations of the review processes used.	14
	23d	Discuss implications of the results for practice, policy, and future research.	14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	3
Competing interests	26	Declare any competing interests of review authors.	3
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

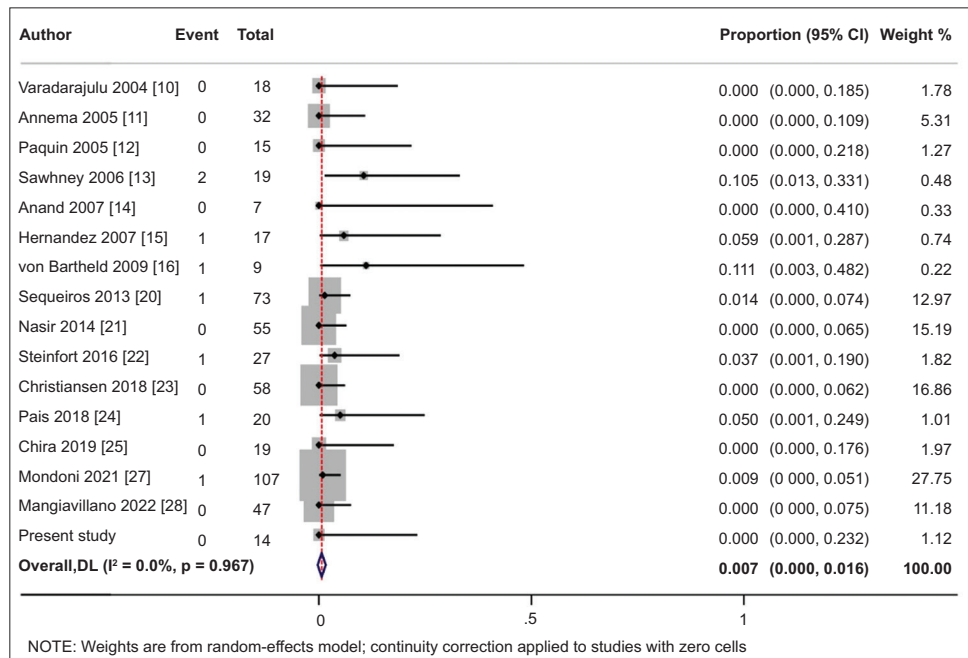
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Supplementary Table 2 Assessment of study quality using modified Newcastle-Ottawa scale

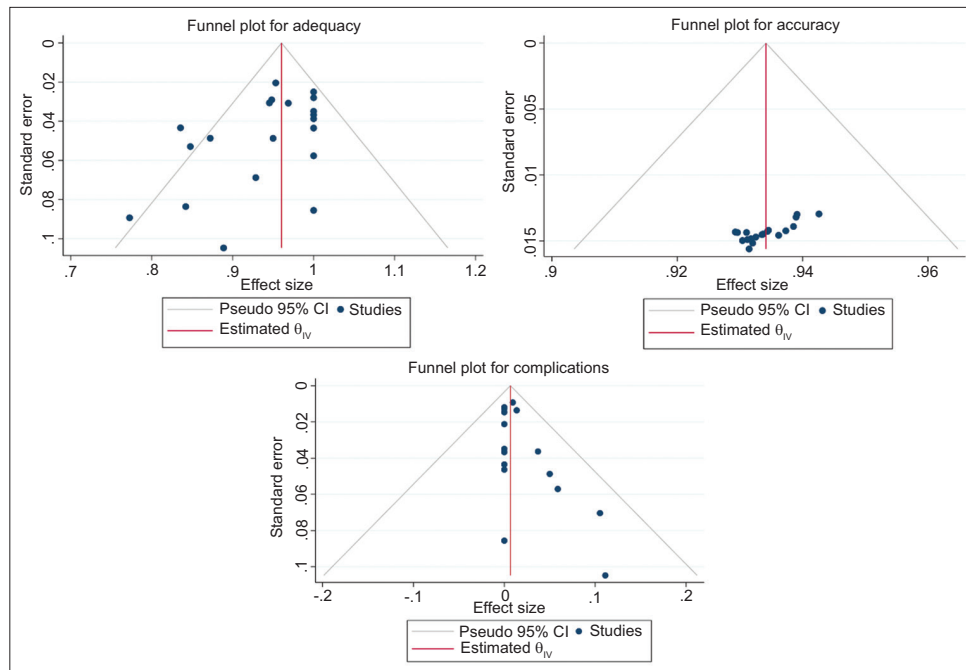
Study, year [ref.]	Representative of the average adult in the community	Cohort size	Type of study	Definite information on technical and clinical success	Information reported on adverse events	Reference standard	Length and adequacy of follow-up	Total
	1-point, multicenter study (different country); 0.5-point, multicenter study (same country); 0-point, single-center study	1-point, > 30 patients; 0.5-point, 30-15 patients; 0-point, < 15 patients	1-point, Prospective; 0.5-point, Ambispective; 0-point, Retrospective	1-point, reported with clarity; 0.5-point if value had to be derived; 0-point, not reported	1-point, adequate information reported; 0-point, not reported	1-point, surgical pathology only; 0.5-point, others; 0-point, not reported	1-point, adequate; 0-point, inadequate or not reported	Maximum, 7; high, >6; medium 4-6; low, <4
Varadarajulu, 2004 [10]	0	0.5	0	1	1	0.5	1	4 = medium
Annema, 2005 [11]	0	1	1	1	1	1	1	6 = high
Paquin, 2005 [12]	0	0.5	0	1	1	0	1	3.5 = low
Sawhney, 2006 [13]	0	0.5	1	1	1	0.5	1	5 = medium
Anand, 2007 [14]	0	0	0	1	1	0	1	3 = low
Hernandez, 2007 [15]	0	0.5	0	1	1	0.5	1	4 = medium
von Bartheld, 2009 [16]	0	0	0	1	1	1	1	4 = medium
Nguyen, 2011 [17]	0	0.5	0	1	1	0.5	0	3 = low
Songur, 2011 [18]	0	0.5	1	1	0	0.5	0	3 = low
Assisi, 2013 [19]	0	0.5	0	1	0	0.5	0	2 = low
Sequeiros, 2013 [20]	1	1	0	1	1	0.5	1	5.5 = medium
Nasir, 2014 [21]	0	1	0	1	1	1	1	5 = medium
Steinfort, 2016 [22]	0.5	0.5	0	1	1	1	1	5 = medium
Christiansen, 2018 [23]	0.5	1	0	1	1	0.5	1	5 = medium
Pais, 2018 [24]	0	0.5	1	1	1	0	1	4.5 = medium
Chira, 2019 [25]	0	0.5	0	1	1	0	1	3.5 = low
Christiansen, 2021 [26]	0.5	1	1	1	0	0.5	0	3.5 = low
Mondoni, 2021 [27]	0.5	1	1	1	1	0.5	1	6 = high
Mangiavillano, 2022 [28]	0.5	1	0	1	1	0.5	1	5 = medium



Supplementary Figure 1 Forest plot for pooled sample adequacy rate with transesophageal endoscopic ultrasound-guided tissue acquisition
CI, confidence interval



Supplementary Figure 2 Forest plot for pooled incidence of adverse events with transesophageal endoscopic ultrasound-guided tissue acquisition
CI, confidence interval



Supplementary Figure 3 Funnel plot for publication bias with respect to various outcomes
CI, confidence interval