*Annals of Gastroenterology* (2023) **36,** 185-194

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

**Suprabhat Giri[a], Sumaswi Angadi[a], Shivaraj Afzalpurkar[b], Sunil Kumar Nanjegowda[a], Sukanya Bhrugumalla[a], Sridhar Sundaram[c]**

Nizam's Institute of Medical Sciences, Hyderabad; Apollo Multispecialty Hospital, Kolkata; Tata Memorial Hospital, Mumbai, India

## 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

*Ann Gastroenterol 2023; 36 (2): 185-194*

[a]Department of Gastroenterology, Nizam's Institute of Medical Sciences, Hyderabad (Suprabhat Giri, Sumaswi Angadi, Sunil Kumar Nanjegowda, Sukanya Bhrugumalla); [b]Institute of Gastrosciences and Liver, Apollo Multispecialty Hospital, Kolkata (Shivaraj Afzalpurkar); [c]Department of Digestive Disease and Clinical Nutrition, Tata Memorial Hospital, Mumbai (Sridhar Sundaram), India

Conflict of Interest: None

Correspondence to: Dr. Sridhar Sundaram, MD, DM, FISG, Associate Professor, Department of Digestive Diseases and Clinical Nutrition, Tata Memorial Hospital, Homi Bhabha National Institute, Dr. E Borges Road, Parel, Mumbai, 400012, India, e-mail: drsridharsundaram@gmail.com

Received 6 August 2022; accepted 2 January 2023; published online 2 February 2023

DOI: https://doi.org/10.20524/aog.2023.0778





## 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 tau$^2$ [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 | Anthracosis | 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*

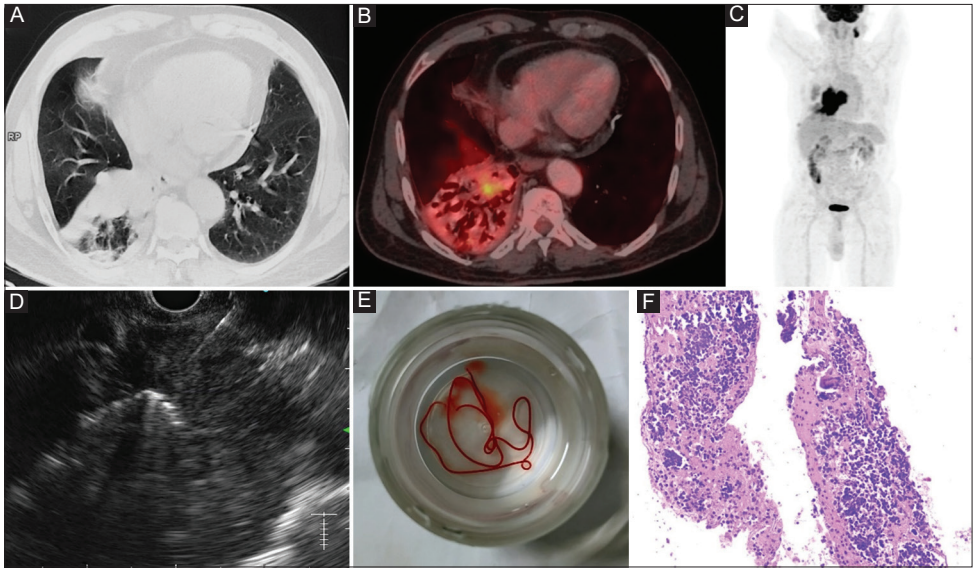



**Figure 1** (A) High-resolution computed tomography showing a mass in right lower lobe; (B, C) 18F-FDG PET/CT showing FDG-avid right lower lobe mass without any metastasis; (D) Hypoechoic lung mass on endoscopic ultrasound with 22-G FNA needle in-situ; (E) Core biopsy specimen; (F) Microscopic findings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

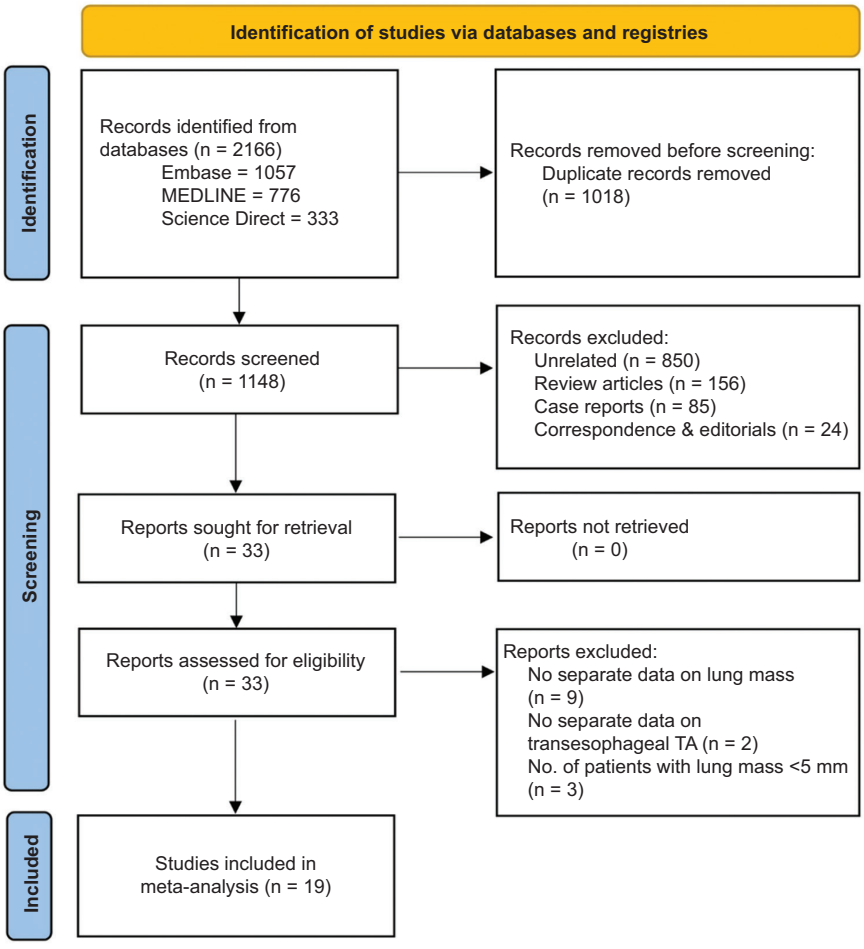



**Figure 2** PRISMA flowchart for study identification and selection process
*TA, tissue acquisition*

**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** *(Conutined)*

| 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

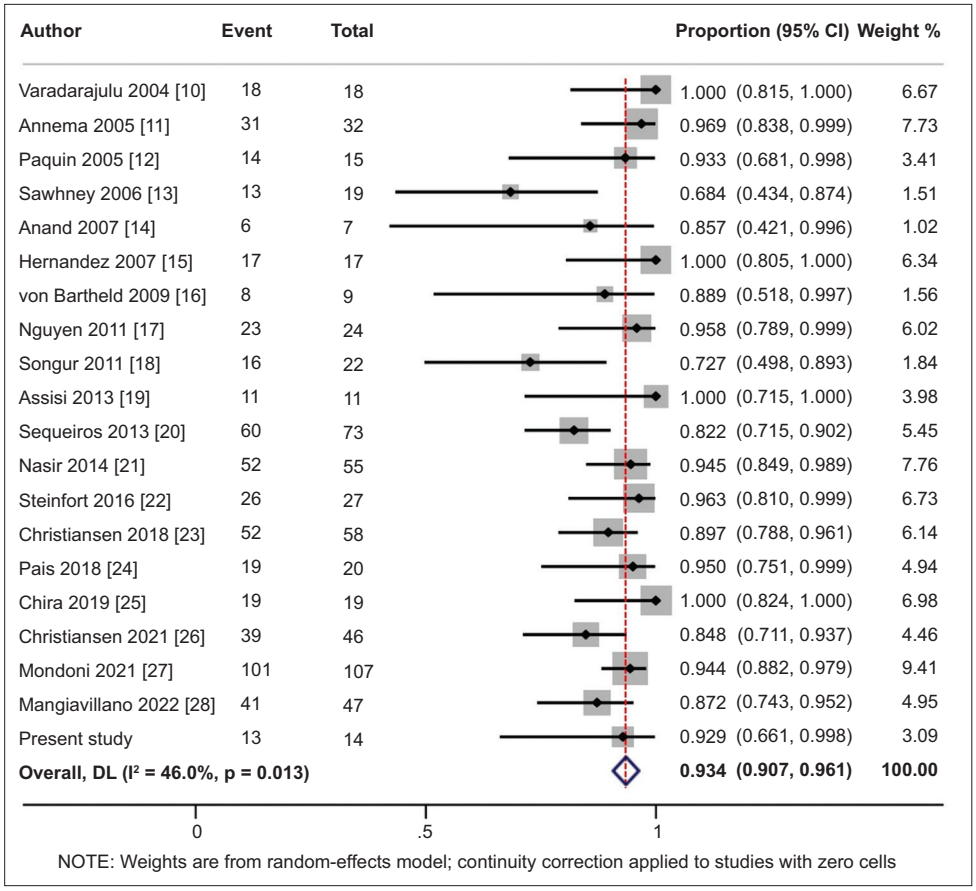



**Figure 3** Forest plot for pooled diagnostic accuracy with endoscopic ultrasound-guided transesophageal tissue acquisition of lung mass
*CI, confidence interval*

**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%

## References


1. Navani N, Nankivell M, Lawrence DR, et al; Lung-BOOST trial investigators. Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: an open-label, pragmatic, randomised controlled trial. *Lancet Respir Med* 2015;**3**:282-289.
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;**71**:209-249.
3. Vilmann P, Clementsen PF, Colella S, et al. Combined endobronchial and oesophageal endosonography for the diagnosis and staging of lung cancer. European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). *Eur Respir J* 2015;**46**:40-60.
4. Vilmann P, Clementsen PF. Combined EUS and EBUS are complementary methods in lung cancer staging: do not forget the esophagus. *Endosc Int Open* 2015;**3**:E300-E301.
5. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc* 2010;**71**:446-454.
6. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71.
7. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;**25**:603-605.
8. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177-188.
9. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-560.
10. Varadarajulu S, Hoffman BJ, Hawes RH, Eloubeidi MA. EUS-guided FNA of lung masses adjacent to or abutting the esophagus after unrevealing CT-guided biopsy or bronchoscopy. *Gastrointest Endosc* 2004;**60**:293-297.
11. Annema JT, Veseliç M, Rabe KF. EUS-guided FNA of centrally located lung tumours following a non-diagnostic bronchoscopy. *Lung Cancer* 2005;**48**:357-361.
12. Paquin SC, Hoffmann BJ, Hawes RH, Chong AK, Faias SR, Hoda RS. Utility of on-site cytologic assessment of transesophageal endoscopic ultrasound-guided fine needle aspiration of lung masses. *Gastrointest Endosc* 2005;**61**:PAB296.
13. Sawhney MS, Kratzke RA, Lederle FA, Holmstrom AM, Nelson DB, Kelly RF. EUS-guided FNA for the diagnosis of advanced lung cancer. *Gastrointest Endosc* 2006;**63**:959-965.
14. Anand D, Barroeta JE, Gupta PK, Kochman M, Baloch ZW. Endoscopic ultrasound guided fine needle aspiration of non-pancreatic lesions: an institutional experience. *J Clin Pathol* 2007;**60**:1254-1262.
15. Hernandez A, Kahaleh M, Olazagasti J, et al. EUS-FNA as the initial diagnostic modality in centrally located primary lung cancers. *J Clin Gastroenterol* 2007;**41**:657-660.
16. von Bartheld MB, Rabe KF, Annema JT. Transaortic EUS-guided FNA in the diagnosis of lung tumors and lymph nodes. *Gastrointest Endosc* 2009;**69**:345-349.
17. Nguyen TQ, Kalade A, Prasad S, et al. Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) of mediastinal lesions. *ANZ J Surg* 2011;**81**:75-78.
18. Songür N, Songür Y, Bırcan S, Kapucuoğlu N. Comparison of 19- and 22-gauge needles in EUS-guided fine needle aspiration in patients with mediastinal masses and lymph nodes. *Turk J Gastroenterol* 2011;**22**:472-478.
19. Vazquez-Sequeiros E, Levy MJ, Van Domselaar M, et al. Diagnostic yield and safety of endoscopic ultrasound guided fine needle aspiration of central mediastinal lung masses. *Diagn Ther Endosc* 2013;**2013**:150492.
20. Assisi D, Visca P, Monteferrante I, Federici T, Anti M, Filippetti M. Role of EUS FNA in diagnosis and staging of lung cancer: an institutional series. *Dig Liv Dis* 2014;**46S:**S62.
21. Nasir BS, Edwards M, Tiffault V, et al. Transesophageal pulmonary nodule biopsy using endoscopic ultrasonography. *J Thorac Cardiovasc Surg* 2014;**148**:850-855.
22. Steinfort DP, Farmer MW, Irving LB, Jennings BR. Pulmonologist-performed per-esophageal needle aspiration of parenchymal lung lesions using an EBUS bronchoscope: diagnostic utility and safety. *J Bronchology Interv Pulmonol* 2017;**24**:117-124.
23. Skovgaard Christiansen I, Kuijvenhoven JC, Bodtger U, et al. Endoscopic ultrasound with bronchoscope-guided fine needle aspiration for the diagnosis of paraesophageally located lung lesions. *Respiration* 2019;**97**:277-283.

24. Pais FM, Shah RA, Vempilly JJ, et al. Transesophageal approach to lung, adrenal biopsy and fiducial placement using endoscopic ultrasonography (EUS): An interventional pulmonology experience. Initial experience of the UCSF-FRETOC (fresno tracheobronchial & oesophageal center) study group. *Respir Med* 2018;**141**:52-55.
25. Chira RI, Chira A, Ichim VA, et al. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) of paraesophageal lung tumors - diagnostic yield and added value. *Med Ultrason* 2019;**21**:377-381.
26. Christiansen IS, Svendsen MBS, Bodtger U, et al. Characterization of lung tumors that the pulmonologist can biopsy from the esophagus with endosonography (EUS-B-FNA). *Respiration* 2021;**100**:135-144.
27. Mondoni M, Gasparini S, Varone F, et al. Accuracy and predictors of success of EUS-B-FNA in the diagnosis of pulmonary malignant lesions: a prospective multicenter Italian study. *Respiration* 2022;**101**:775-783.
28. Mangiavillano B, Spatola F, Facciorusso A, et al. Transesophageal endoscopic ultrasound in the diagnosis of the lung masses: a multicenter experience with fine-needle aspiration and fine-needle biopsy needles. *Eur J Gastroenterol Hepatol* 2022;**34**:757-762.
29. Fu YF, Zhang JH, Wang T, Shi YB. Endobronchial ultrasound-guided versus computed tomography-guided biopsy for peripheral pulmonary lesions: A meta-analysis. *Clin Respir J* 2021;**15**:3-10.
30. Yung RC. Tissue diagnosis of suspected lung cancer: selecting between bronchoscopy, transthoracic needle aspiration, and resectional biopsy. *Respir Care Clin N Am* 2003;**9**:51-76.
31. Kazerooni EA, Lim FT, Mikhail A, Martinez FJ. Risk of pneumothorax in CT-guided transthoracic needle aspiration biopsy of the lung. *Radiology* 1996;**198**:371-375.
32. Varadarajulu S, Schmulewitz N, Wildi SM, et al. Accuracy of EUS in staging of T4 lung cancer. *Gastrointest Endosc* 2004;**59**:345-348.
33. Dhooria S, Aggarwal AN, Singh N, et al. Endoscopic ultrasound-guided fine-needle aspiration with an echobronchoscope in undiagnosed mediastinal lymphadenopathy: first experience from India. *Lung India* 2015;**32**:6-10.
34. von Bartheld MB, van Breda A, Annema JT. Complication rate of endosonography (endobronchial and endoscopic ultrasound): a systematic review. *Respiration* 2014;**87**:343-351.
35. Korevaar DA, Colella S, Spijker R, et al. Esophageal endosonography for the diagnosis of intrapulmonary tumors: a systematic review and meta-analysis. *Respiration* 2017;**93**:126-137.
36. Bang JY, Ramesh J, Trevino J, Eloubeidi MA, Varadarajulu S. Objective assessment of an algorithmic approach to EUS-guided FNA and interventions. *Gastrointest Endosc* 2013;**77**:739-744.
37. Aadam AA, Wani S, Amick A, et al. A randomized controlled cross-over trial and cost analysis comparing endoscopic ultrasound fine needle aspiration and fine needle biopsy. *Endosc Int Open* 2016;**4**:E497-E505.
38. van Riet PA, Cahen DL, Poley JW, Bruno MJ. Mapping international practice patterns in EUS-guided tissue sampling: outcome of a global survey. *Endosc Int Open* 2016;**4**:E360-E370.
39. Gkolfakis P, Crinò SF, Tziatzios G, et al. Comparative diagnostic performance of end-cutting fine-needle biopsy needles for EUS tissue sampling of solid pancreatic masses: a network meta-analysis. *Gastrointest Endosc* 2022;**95**:1067-1077.
40. Dietrich CF. Contrast-enhanced endobronchial ultrasound: potential value of a new method. *Endosc Ultrasound* 2017;**6**:43-48.
41. Facciorusso A, Mohan BP, Crinò SF, et al. Contrast-enhanced harmonic endoscopic ultrasound-guided fine-needle aspiration versus standard fine-needle aspiration in pancreatic masses: a meta-analysis. *Expert Rev Gastroenterol Hepatol* 2021;**15**:821-828.

## Supplementary material

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

| Section and Topic | Item # | Checklist item | Page No. |
|---|---|---|---|
| | | 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...)*

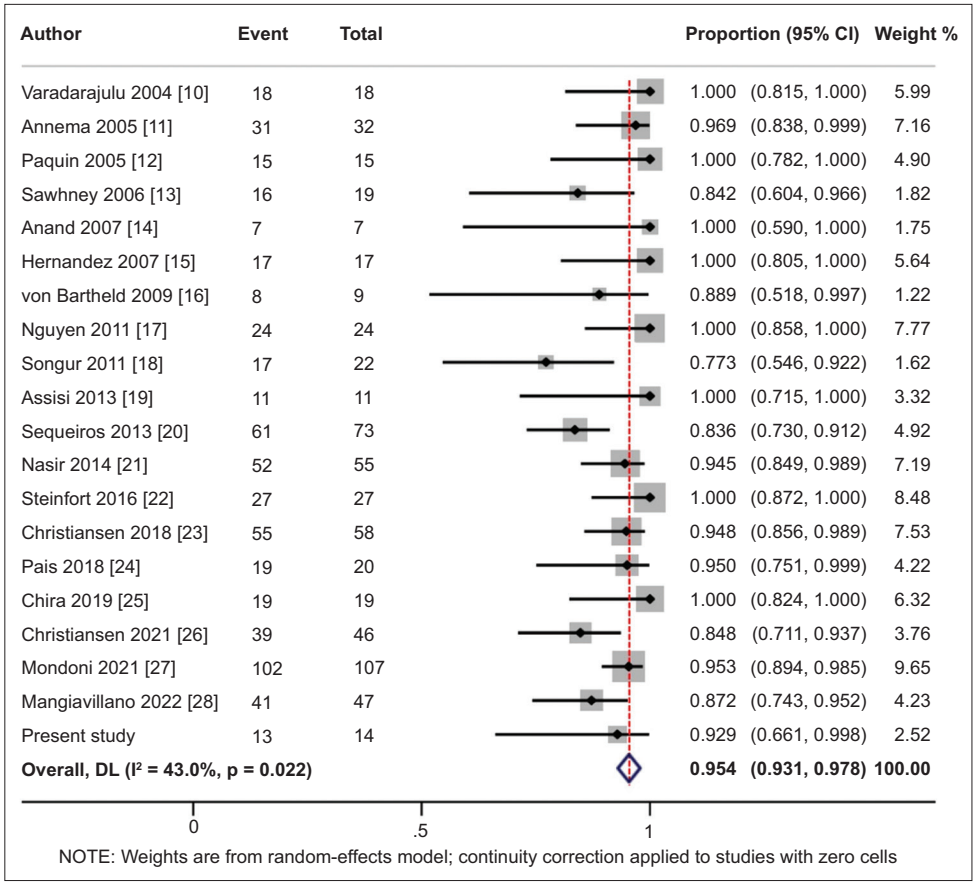
**Supplementary Table 1** *(Continued)*

| Section and Topic | Item # | Checklist item | Page No. |
|---|---|---|---|
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | 8 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 8 |
| Certainty assessment | 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 |

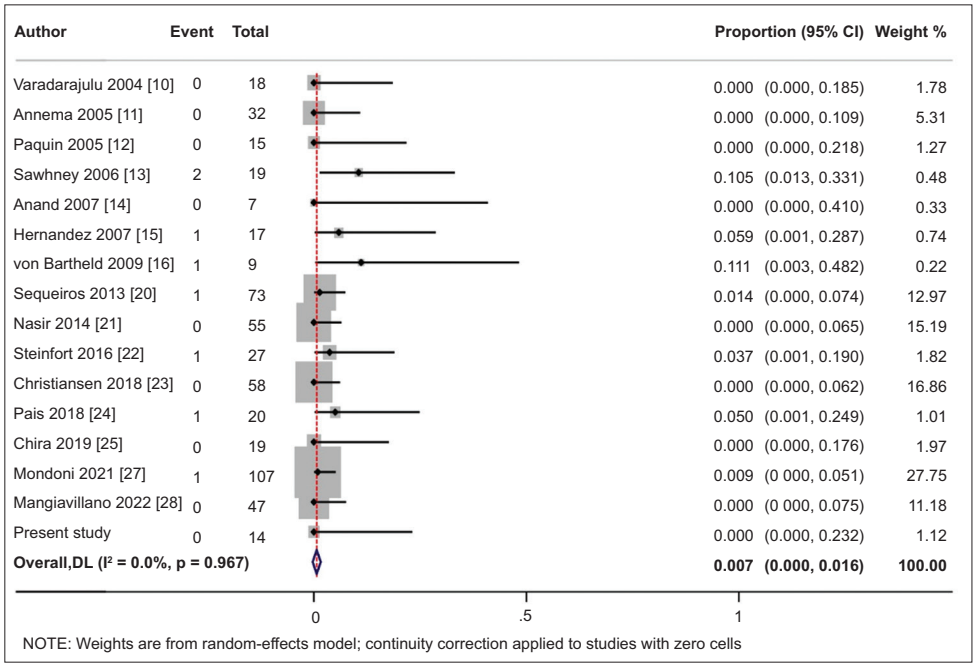
*N/A, not available*

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

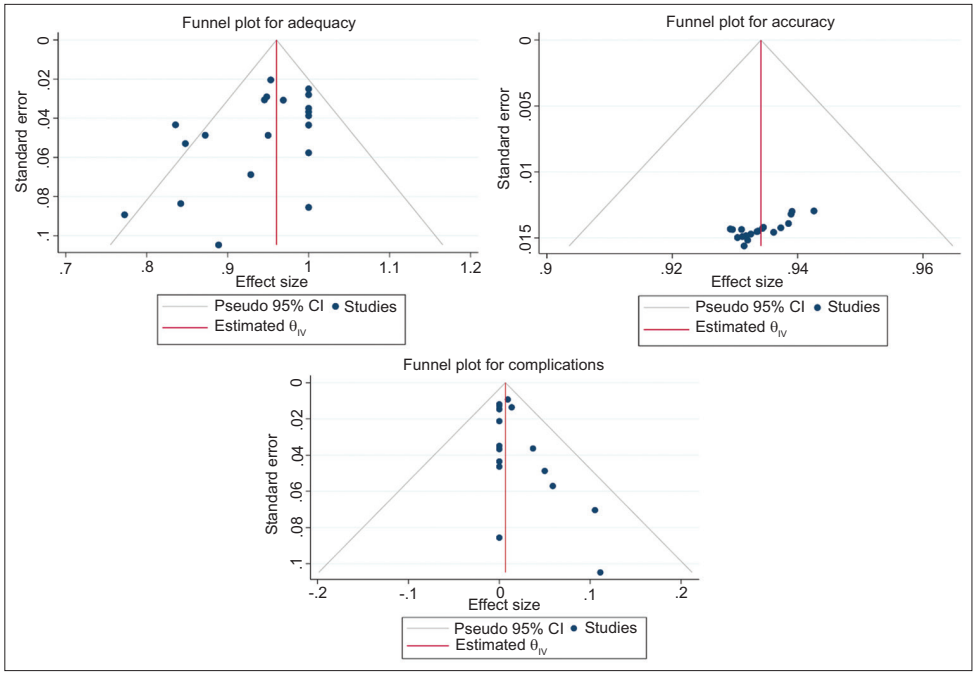
| Study, year [ref.] | Representative of the average adult in the community | Cohort size | Type of study | Definite information on technical and clinical success | Information reported on adverse events | Reference standard | Length and adequacy of follow-up | Total |
|---|---|---|---|---|---|---|---|---|
| | 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*