EBUS-TBNA versus surgical mediastinoscopy for mediastinal lymph node staging in potentially operable non-small cell lung cancer: a systematic review and meta-analysis

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Submitted: 24 July 2019.
Accepted: 1 May 2020.

Study carried out at the Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, and at the Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: Lung cancer (LC) is one of the leading causes of death worldwide. Accurate mediastinal staging is mandatory in order to assess prognosis and to select patients for surgical treatment. EBUS-TBNA is a minimally invasive procedure that allows sampling of mediastinal lymph nodes (LNs). Some studies have suggested that EBUS-TBNA is preferable to surgical mediastinoscopy for mediastinal staging of LC. The objective of this systematic review and meta-analysis was to compare EBUS-TBNA and mediastinoscopy in terms of their effectiveness for mediastinal LN staging in potentially operable non-small cell lung cancer (NSCLC). **Methods:** This was a systematic review and meta-analysis, in which we searched various databases. We included studies comparing the accuracy of EBUS-TBNA with that of mediastinoscopy for mediastinal LN staging in patients with NSCLC. In the meta-analysis, we calculated sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios. We also analyzed the risk difference for the reported complications associated with each procedure. **Results:** The search identified 4,201 articles, 5 of which (with a combined total of 532 patients) were selected for inclusion in the meta-analysis. There were no statistically significant differences between EBUS-TBNA and mediastinoscopy in terms of the sensitivity (81% vs. 75%), specificity (100% for both), positive likelihood ratio (101.03 vs. 95.70), or negative likelihood ratio (0.21 vs. 0.23). The area under the summary ROC curve was 0.9881 and 0.9895 for EBUS-TBNA and mediastinoscopy, respectively. Although the number of complications was higher for mediastinoscopy, the difference was not significant (risk difference: −0.03; 95% CI: −0.07 to 0.01; I^2 = 76%). **Conclusions:** EBUS-TBNA and mediastinoscopy produced similar results for mediastinal staging of NSCLC. EBUS-TBNA can be the procedure of first choice for LN staging in patients with NSCLC.

Keywords: Lung neoplasms/diagnosis; Neoplasm staging; Mediastinal neoplasms/diagnosis; Endoscopic ultrasound-guided fine needle aspiration; Mediastinoscopy.

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide.[1] For patients diagnosed with lung cancer, the five-year survival rate is 17.7%, and 50% of such patients present with mediastinal metastasis at diagnosis.[2,3]

In patients with non-small cell lung cancer (NSCLC) and no distant metastases, the most important prognostic information is neoplastic involvement of the mediastinal lymph nodes (LNs). Therefore, accurate mediastinal staging is mandatory in order to assess prognosis and enable treatment planning. Patients with mediastinal LN metastasis (N2/N3 disease) should be considered candidates for multimodal treatment, which might or might not include surgery.[3,4]

The use of CT and PET/CT has improved radiological staging of the mediastinum. However, both have limited sensitivity and specificity.[3-5] Invasive mediastinal staging is recommended for all patients with potentially resectable NSCLC, except for those with bulky disease and no metastases, as well as those with a peripheral clinical stage IA tumor (with no LN involvement on CT or PET/CT), the radiological staging of which is usually sufficient.[6]

Among the methods for surgical staging of NSCLC, surgical mediastinal staging by mediastinoscopy was the gold standard until a few years ago.[7] Although mediastinoscopy provides accurate staging, the costs and risks inherent to the method make it less than ideal.[8-11]

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Financial support: None.

The introduction of endoscopy-based techniques, such as EBUS-TBNA and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), revolutionized the approach to lung cancer staging, and these techniques are recommended as the first choice for invasive staging.[6] Numerous LN stations that are important in the setting of lung cancer staging can be accessed with EBUS-TBNA and EUS-FNA.[12]

Most of the systematic reviews available have compared the combined use of endoscopic methods (EBUS-TBNA and EUS-FNA) with that of mediastinoscopy, and few of those reviews have distinguished between the data collected by each endoscopic method.[13,14]

With EBUS-TBNA, real-time biopsy samples can be obtained from mediastinal, hilar, and interlobar LNs, which are relevant stations in lung cancer staging, whereas EUS-FNA is unable to access all of the relevant LN stations on the right side. However, unlike EBUS-TBNA, EUS-FNA enables access to lower paraesophageal, infradiaphragmatic, and retroperitoneal LNs, the latter two having a lesser clinical impact on the therapeutic strategy.[15]

Dong et al.,[16] in a meta-analysis, evaluated the efficacy of EBUS-TBNA for staging mediastinal LNs in cases of NSCLC. However, none of the studies selected compared EBUS-TBNA with mediastinoscopy. In most of the selected studies, mediastinoscopy was not employed in the LN staging.

A meta-analysis conducted by Gu et al.[17] evaluated the efficacy of EBUS-TBNA in LN staging. Eleven studies were selected, of which 5 (45%) also included the diagnostic investigation of lymphadenopathy and 4 (35%) did not compare EBUS-TBNA with mediastinoscopy. In addition, some studies that carried out that comparison provided no information about how many patients underwent mediastinoscopy.

Other studies compared patients who underwent EBUS-TBNA with those who underwent mediastinoscopy. In a meta-analysis, Ge et al.[18] selected studies that used EBUS-TBNA or mediastinoscopy for NSCLC staging. Of the 17 studies selected, only 3 actually compared the two methods in their sample of patients.

Because most of the available studies and meta-analyses have shown that the accuracy of the combined use of EBUS-TBNA and EUS-FNA for mediastinal staging in patients with potentially operable NSCLC is equivalent to that of the use of mediastinoscopy,[19,20] the question that remains is whether EBUS-TBNA alone would have a similar diagnostic yield.

METHODS

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations[21] and was registered with the International Prospective Register of Systematic Reviews (Registration no. CRD42016046522).

Eligibility criteria

The studies selected consisted of prospective randomized and nonrandomized clinical trials evaluating the diagnostic efficacy of EBUS-TBNA and that of mediastinoscopy for mediastinal LN staging in patients with potentially operable NSCLC. This meta-analysis included only studies that directly or indirectly provided all the data necessary to calculate the sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR−). Studies that evaluated the combined use of EUS-FNA and EBUS-TBNA, providing no separate data for EBUS-TBNA, were excluded. We imposed no restrictions regarding the language or year of publication.

The studies selected included patients diagnosed with potentially resectable NSCLC, as defined by radiological criteria, without distant metastasis, and without evidence of bulky disease. There were no limitations regarding patient characteristics such as gender, age, and presence of comorbidities.

The types of interventions studied were EBUS-TBNA and mediastinoscopy. The standard for comparing the two methods was the result of tumor resection surgery, based on systematic mediastinal LN sampling or dissection.

The outcome measures were the sensitivity, specificity, LR+, and LR− for mediastinal LN staging. In addition, the complication rate for each procedure was analyzed.

Information sources and search strategy

Systematic searches were conducted in the MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, Elton Bryson Stephens Company (EBSCO), LILACS, Brazilian Virtual Library of Health, and Scopus databases, the date ranges being set to from the inception of the indices through February 12, 2018. We also performed gray literature searches, which included references in the articles selected and in those within the collection of the library of the University of São Paulo. Specific search strategies were used for each database: MEDLINE—("Pulmonary Neoplasms" OR "Neoplasms, Lung" OR "Lung Neoplasm" OR "Neoplasm Lung" OR "Neoplasms Pulmonary" OR "Neoplasm, Pulmonary" OR "Pulmonary Neoplasm" OR "Lung Cancer" OR "Cancer Lung" OR "Cancers Lung" OR "Lung Cancers" OR "Pulmonary Cancer" OR "Cancer Pulmonary" OR "Cancers Pulmonary" OR "Pulmonary Cancers" OR "Cancer of the Lung" OR "Cancer of Lung" OR "Non small cell cancer" OR "Non small cell carcinoma") AND ("EBUS-TBNA" OR "Endobronchial Ultrasound" OR "Endobronchial ultrasound-guided transbronchial needle aspiration") AND ("Mediastinoscopies" OR "Mediastinoscopic Surgical Procedures" OR "Mediastinoscopic Surgical Procedure" OR "Procedure, Mediastinoscopic Surgical" OR "Procedures, Mediastinoscopic Surgical" OR "Surgical Procedure, Mediastinoscopic" OR "Surgery, Mediastinoscopic" OR "Surgical Procedures, Mediastinoscopic" OR "Mediastinoscopic Surgery"

OR "Mediastinoscopic Surgeries" OR "Surgeries, Mediastinoscopic" OR "Surgery"); and Cochrane Central Register of Controlled Trials, EMBASE, EBSCO, LILACS, Brazilian Virtual Library of Health, and Scopus—("Lung Cancer" OR "Pulmonary Neoplasms" OR "Lung Neoplasm" OR "Cancer Lung" OR "Pulmonary Cancer") AND ("EBUS-TBNA" OR "Endobronchial Ultrasound" OR "Endobronchial ultrasound-guided transbronchial needle aspiration") AND ("Mediastinoscopy" OR "Surgery").

Study selection

Studies were selected in a standardized way by two independent specialists. The articles were initially selected by title and abstract. For the meta-analysis, each study was then included or excluded on the basis of a full-text evaluation. Abstract-only and retrospective studies were not included in the systematic review.

Data collection and data items

Absolute numbers were collected directly from the text and separated into true positives, true negatives, false positives, and false negatives. Only studies containing all the necessary data and meeting the criteria applied in the meta-analysis were included. Only published data were considered. The same positivity criteria for the methods used in the selected studies were considered. The interventions compared were EBUS-TBNA and mediastinoscopy, both followed by surgical resection and systematic LN sampling or dissection. The total number of complications reported was also considered in the analysis.

Risk of bias

Two independent reviewers analyzed the quality of the studies using predefined criteria. We used the revised version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) to assess the risk of bias and applicability concerns in patient selection, as well as to assess the risk of bias in the flow and timing of tests.[22] Homogeneous prospective randomized studies were considered eligible. The risk of bias and applicability concerns was considered high when the selected patients were not under suspicion of having NSCLC or had a confirmed diagnosis of NSCLC. Crossover studies in which EBUS-TBNA was followed by mediastinoscopy were considered eligible. In addition, if the interval between tests was short, the risk of bias was assumed to be low.

Synthesis of results and analysis

Quantitative analyses were conducted with the software Review Manager, version 5.3 (RevMan 5; Cochrane Collaboration, Oxford, England). The meta-analysis was carried out using the Meta-Disc program, version 1.4 (Unit of Clinical Biostatistics, Ramon y Cajal Hospital, Madrid, Spain).[23] The sensitivity, specificity, LR+, and LR− are presented in forest plots. Summary ROC (sROC) curves were constructed, and the areas under the curves were estimated. All of the variables were analyzed by patient. Heterogeneity was assessed by calculating the I^2 coefficient. The Mantel-Haenszel fixed-effect model was used in the meta-analysis. The DerSimonian-Laird random-effects model was used for calculation in cases of high heterogeneity between studies (I^2 > 50%). The Moses-Littenberg linear model was used in the construction of the sROC curves.

Complications were classified as major or minor adverse intraprocedural events. Major complications were death; lidocaine intoxication requiring special intervention; respiratory failure requiring interventions other than oxygen administration; tracheal, nerve, or vessel injury; parenchymal lesions adjacent to major airways; pneumonia; mediastinitis; pericarditis; other infectious complications; fever lasting longer than 24 h; pneumothorax requiring bed rest or thoracic drainage; prolonged bronchospasm; hemorrhage not responsive to the topical application of adrenaline or cold saline, thus requiring further intervention; and vocal cord paralysis. Minor complications were hemorrhage other than that described above; temporary laryngospasm; bronchospasm; desaturations during the procedure; and fever lasting up to 24 h.[24,25]

The total numbers of complications associated with each procedure were considered for analysis as dichotomous data in a forest plot. The risk difference was determined using the Mantel-Haenszel fixed-effects model. In the case of high heterogeneity, a sensitivity analysis was performed in order to identify outlier studies.

Primary and secondary outcomes

The primary outcome of the present systematic review and meta-analysis was to determine the accuracy of EBUS-TBNA for mediastinal LN staging in patients with potentially operable NSCLC. The secondary outcomes were used in order to compare the effectiveness of EBUS-TBNA with that of mediastinoscopy.

RESULTS

The searches of the literature resulted in 1,423 records in MEDLINE and 2,778 in the other databases. Therefore, a total of 4,201 records were eligible for inclusion in this systematic review. After an initial selection, 30 articles were included for full-text evaluation. Eight comparative prospective studies were selected for the systematic review.[26-33] One clinical trial was included despite the combined use of EBUS and EUS, because it provided separate data on EBUS for the analysis.[31] Two randomized controlled clinical trials were excluded because it was impossible to obtain separate data on EBUS-TBNA for the analysis.[29,33] Another clinical trial was excluded because it was not clear whether the study design was retrospective or prospective.[32] One clinical trial reported all data in a per-lesion analysis form, thus rendering it unfeasible to calculate separate values for true positives, false positives, true negatives, and false negatives, as would

be possible in a per-patient analysis.[30] For the purpose of the meta-analysis, 5 studies were considered for the analysis of complications,[26-28,30,31] although only 4 included diagnostic outcomes (Figure 1).[26-28,31]

Among the studies selected for data extraction and analysis, there were 5 prospective sequential clinical studies, all of which were included in the meta-analysis. Those 5 studies included patients diagnosed with potentially resectable NSCLC, as defined by radiological criteria, without distant metastasis, and without evidence of bulky disease. In 4 of the studies included, sensitivity and specificity were presented as fractions. The characteristics of the studies are presented in Table 1.

Risk of bias

We evaluated the studies by qualitative analysis in accordance with the QUADAS-2 criteria (Table 2). The majority of the articles were considered to have a low risk of bias in all domains.

Results in individual studies

Four studies used per-patient analysis. The sensitivity of EBUS-TBNA and mediastinoscopy was 81% (95% CI: 75-86%, I^2 = 46.5%) and 75% (95% CI: 69-81%; I^2 = 84.7%), respectively (Figure 2). The specificity of EBUS-TBNA and mediastinoscopy was 100% for both (95% CI: 99-100%; I^2 = 0.0%). The LR+ for EBUS-TBNA and mediastinoscopy was 101.03 (95% CI: 25.71-397.04; I^2 = 0.0%) and 95.70 (95% CI: 23.94-382.58; I^2 = 0.0%), respectively. The LR− for EBUS-TBNA and mediastinoscopy was 0.21 (95% CI: 0.16-0.28; I^2 = 44.5%) and 0.23 (95% CI: 0.11-0.47; I^2 = 83.5%), respectively (Figure 3). No statistically significant differences were found between the methods regarding the sensitivity, specificity, LR+, or LR−. The area under the sROC curve was 0.9881 for EBUS-TBNA (Figure 4) and 0.9895 for mediastinoscopy (Figure 5).

The total number of complications was higher in the mediastinoscopy group. Nevertheless, no significant difference was found in the meta-analysis (risk difference: −0.03, 95% CI: −0.07 to 0.01; I^2 = 76%; Figure 6). A random-effects model was used because of the high heterogeneity, which persisted even after the exclusion of outliers.

DISCUSSION

Accurate staging of potentially operable NSCLC is mandatory to determine the prognosis and define

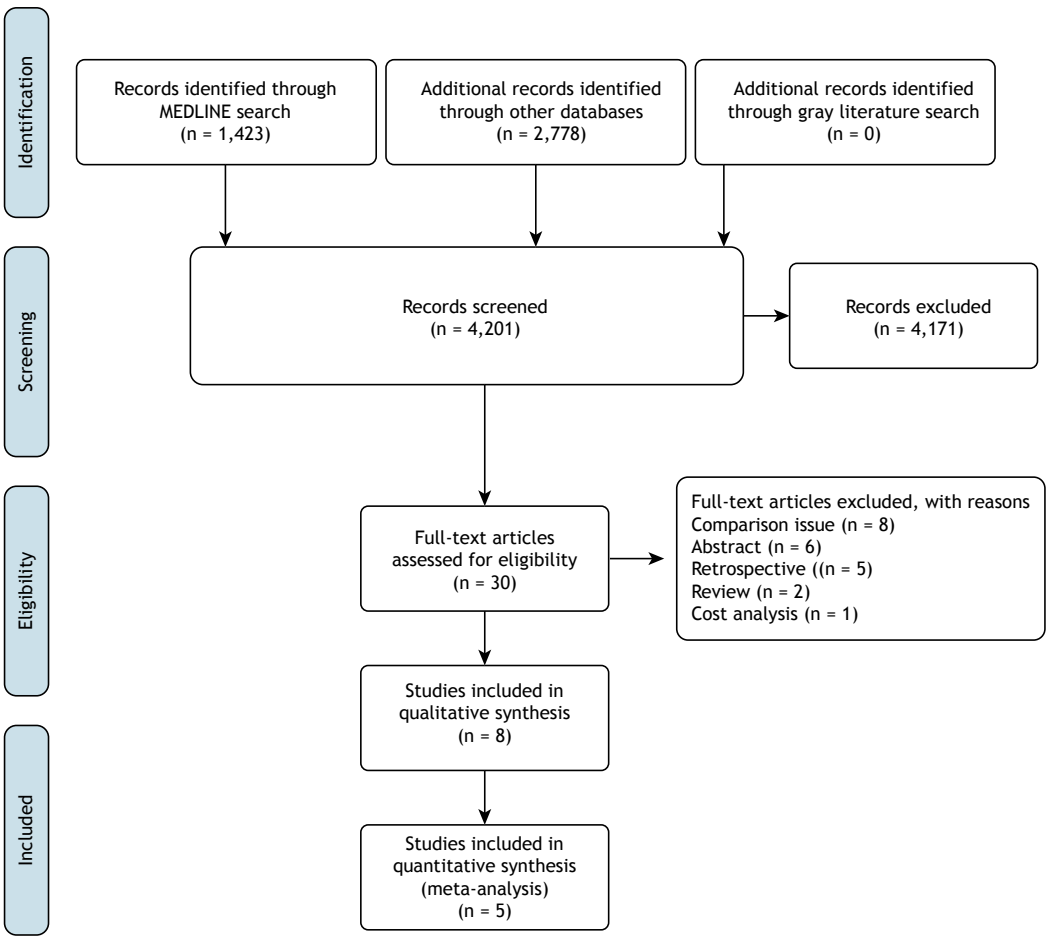

Figure 1. Flow chart of the article selection process.

Table 1. Characteristics of the studies selected that were included or excluded in the meta-analysis.

Study	Patient (n)	Gold standard	Interval	Study design	Inclusion criteria	Test method
Included						
Ernst et al.[30]	60	Surgical staging	Sequential approach or tests performed within a 1-week interval	Prospective crossover	Suspected NSCLC, potentially resectable	EBUS-TBNA vs. cervical mediastinoscopy
Yasufuku et al.[28]	153	Surgical staging	Sequential approach	Prospective crossover	Confirmed or suspected NSCLC	EBUS-TBNA vs. cervical mediastinoscopy
Zhang et al.[27]	26	Surgical staging and mediastinoscopy	Sequential approach	Prospective crossover	Confirmed or suspected NSCLC	EBUS + TBNA vs. transcervical video-assisted mediastinoscopy
Liberman et al.[31]	166	Surgical staging and mediastinoscopy	Sequential approach	Prospective crossover	Potentially resectable NSCLC	EBUS vs. EUS vs. EBUS + EUS vs. SMS (cervical mediastinoscopy and anterior mediastinostomy if necessary)
Um et al.[26]	127	Surgical staging and mediastinoscopy	Tests performed within a 3-week interval	Prospective crossover	Potentially resectable NSCLC	EBUS-TBNA vs. mediastinoscopy (cervical and VAM)
Excluded						
Annema et al.[29]	241	Surgical staging	Unclear	RCT	Potentially resectable NSCLC	Surgical staging vs. endosonography (combined EBUS-TBNA and EUS-FNA) and surgical staging
Sharples et al.[33]	241	Surgical staging	Unclear	RCT	Confirmed or suspected NSCLC, potentially resectable	Surgical staging vs. endosonography (combined EBUS-TBNA and EUS-FNA) and surgical staging
Dziedzic et al.[32]	1,841	Surgical staging	Sequential approach or unclear	Retrospective chart review	Suspected or proven NSCLC	EBUS-TBNA vs. cervical mediastinoscopy

NSCLC: non-small cell lung cancer; EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound with fine needle aspiration; SMS: surgical mediastinal staging (by mediastinoscopy); VAM: video-assisted mediastinoscopy; and RCT: randomized clinical trial.

Table 2. Risk of bias in individual studies.

Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ernst et al.[30]	Low	Low	Low	Low	Low	Low	Low
Yasufuku et al.[28]	Low	Low	Low	Low	Low	Low	Low
Zhang et al.[27]	Low	Low	Low	Low	Low	Low	Low
Liberman et al.[31]	Low	Low	Low	Low	Low	Low	Low
Um et al.[26]	Low	Low	Low	High	Low	Low	Low

the appropriate treatment. Although CT and PET/CT are frequently used for primary screening, these methods cannot establish the presence of malignancy and definitive tissue diagnosis with EBUS-TBNA or mediastinoscopy is required in order to confirm the results.[6,7]

Yasufuku et al.[28] reported no significant differences between EBUS-TBNA and mediastinoscopy in the

staging of mediastinal LNs in NSCLC. When performed by experienced specialists, EBUS-TBNA can replace mediastinoscopy for accurate mediastinal staging of potentially resectable lung cancer.

A few meta-analyses have been carried out over the last decade to determine the effectiveness of EBUS-TBNA in the staging of LNs in NSCLC. In a meta-analysis, Ge et al.[18] compared video-assisted mediastinoscopy (VAM) and EBUS-TBNA for mediastinal staging and included two different groups. The first group included 10 studies with a collective total of 999 patients who underwent EBUS-TBNA, although only 2 of the studies compared EBUS-TBNA with mediastinoscopy. The second group included 7 studies with a collective total of 915 patients who underwent VAM (without EBUS-TBNA). The pooled sensitivities of VAM and EBUS-TBNA were not significantly different. However, a greater number of procedural complications and fewer false negatives were found in the VAM group than in the EBUS-TBNA group. The two techniques exhibited equally high diagnostic accuracy for the mediastinal staging of lung cancer.[18]

The present meta-analysis selected only studies in which patients underwent EBUS-TBNA followed by mediastinoscopy and in which, if there was no evidence of N2 or N3 disease, patients underwent surgical resection of the tumor and systematic nodal sampling or dissection.[26-28,31] In most of the studies, patients underwent the two procedures sequentially.[27,28,31] In one clinical trial, patients underwent the two procedures within a one-week interval.[28] In another study, patients underwent the two procedures within a three-week interval, which constituted a flow and timing bias.[26]

The European Society of Gastrointestinal Endoscopy, in cooperation with the European Respiratory Society and the European Society of Thoracic Surgeons, published a guideline[34] suggesting that the combined use of EBUS-TBNA and EUS-FNA is preferred over the use of either procedure alone (grade C recommendation). However, if combining EBUS-TBNA and EUS-FNA is not an option, EBUS-TBNA alone is acceptable (also a grade C recommendation).

Various meta-analyses have reported on the performance of EBUS-TBNA/EUS-FNA in the mediastinal staging of lung cancer. Sehgal et al.[20] compared endosonography (EBUS-TBNA and EUS-FNA) with mediastinoscopy for lung cancer staging. Of the 5 studies selected, only 2 showed separate results for EBUS-TBNA. The ability of endoscopic ultrasound (EBUS-TBNA and EUS-FNA) to sample multiple stations with a sensitivity and negative predictive value higher than that of mediastinoscopy makes it the first choice for invasive staging.[20] The present meta-analysis selected studies that compared EBUS-TBNA with mediastinoscopy.[26-28] There was only 1 study that evaluated the combined use of EBUS and EUS, although that study provided separate data for EBUS.[31]

The paraesophageal and infradiaphragmatic LNs (stations 8 and 9), which are inaccessible by EBUS-TBNA, can be accessed with EUS-FNA. To analyze the impact of these stations on LN staging, a multicenter study evaluated data from 1,421 surgical resections in patients with NSCLC. In the sample as a whole, 736

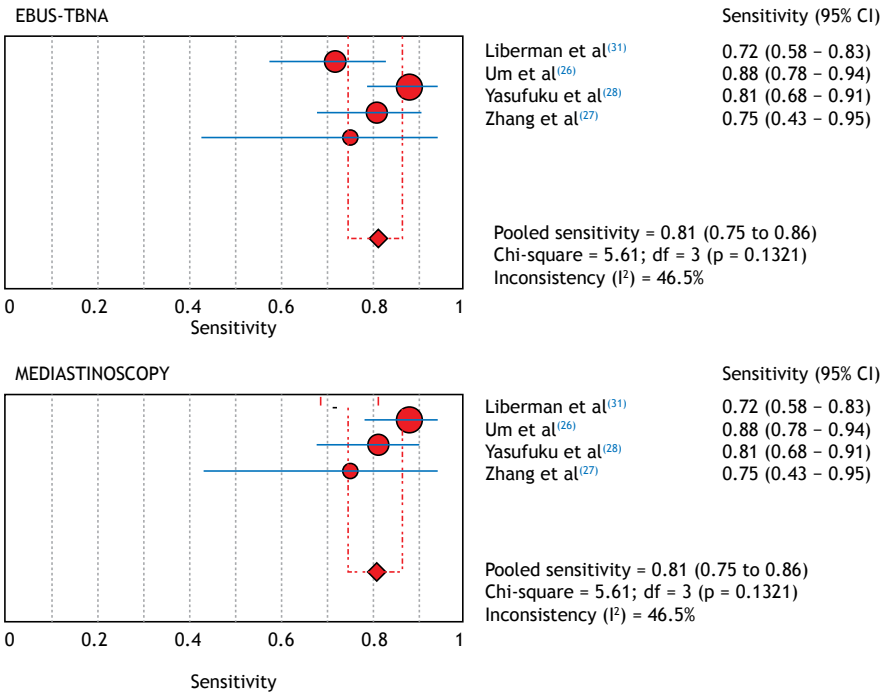

Figure 2. Sensitivity of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy. df: degree(s) of freedom.

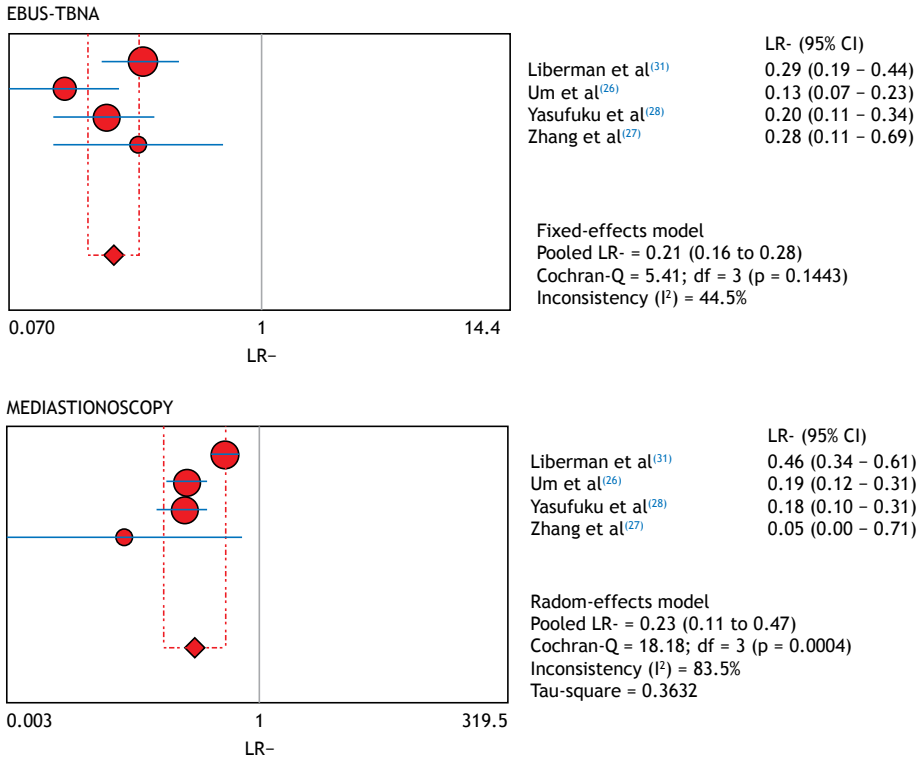

Figure 3. Negative likelihood ratio (LR−) of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy. df: degree(s) of freedom.

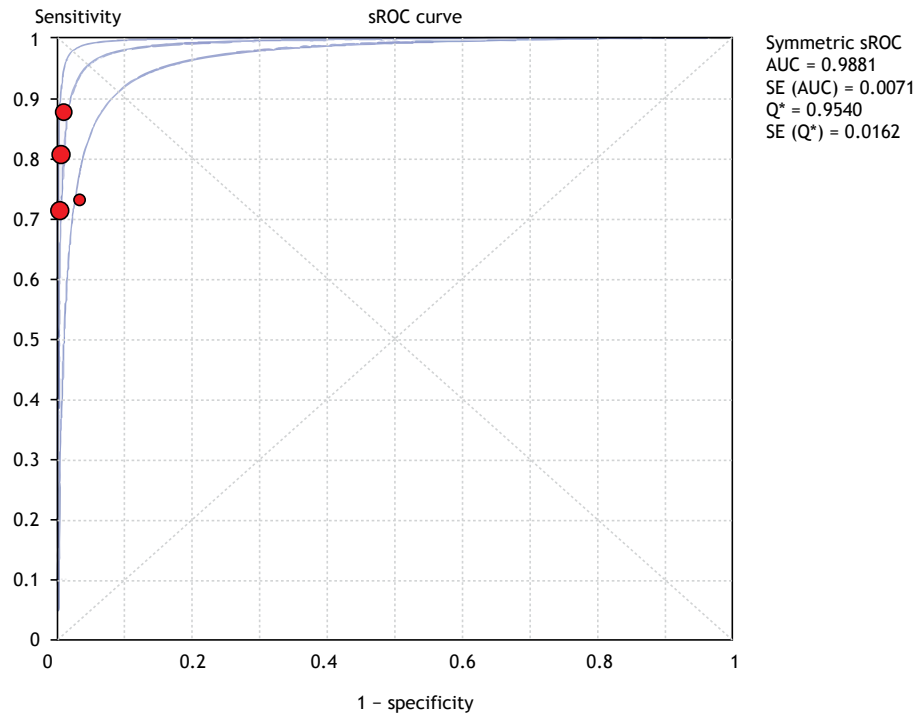

Figure 4. Summary ROC (sROC) curve for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). AUC: area under the curve; and Q*: the point at which sensitivity and specificity are equal, which is the point on the curve closest to the upper left corner.

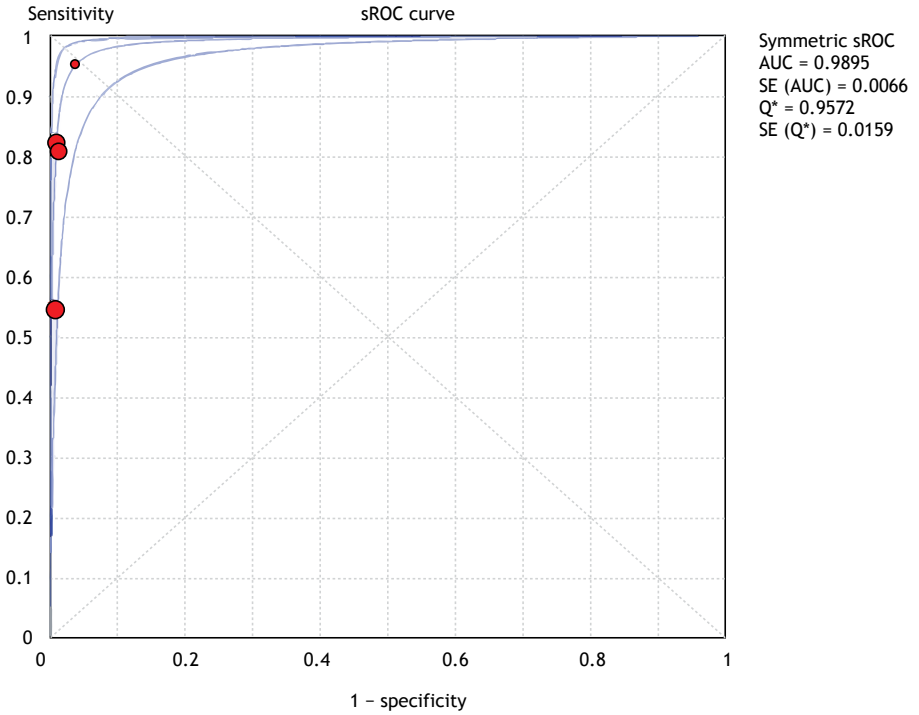

Figure 5. Summary ROC (sROC) curve for mediastinoscopy. AUC: area under the curve; and Q*: the point at which sensitivity and specificity are equal, which is the point on the curve closest to the upper left corner.

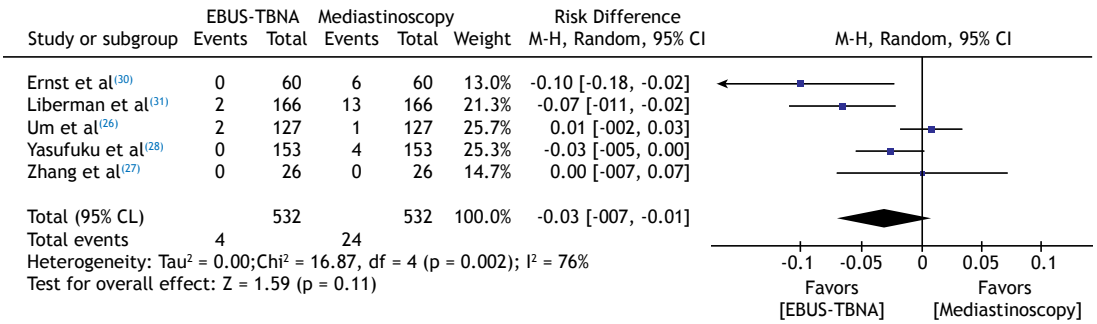

Figure 6. Adverse events (complications) during endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and during mediastinoscopy. M-H: Mantel-Haenszel; and df: degree(s) of freedom.

patients (52%) underwent sampling of LN stations 8 and 9, and only 12 (1.6%) of those patients had metastatic LNs only in these stations, no statistically significant difference in survival being found between those 12 patients and the other 724.[15] In the present systematic review, we sought evidence that EBUS-TBNA is the only procedure capable of effectively performing mediastinal LN staging in patients with NSCLC.

Our results showed no significant differences in sensitivity or specificity between EBUS-TBNA and mediastinoscopy. However, in 1 of the studies selected, it was concluded that EBUS-TBNA could replace mediastinoscopy, given the similarity of the results obtained with the two procedures (91%; $\kappa = 0.8$),[28] whereas the authors of another clinical trial concluded that the results obtained with EBUS-TBNA were superior to those obtained with mediastinoscopy.[31]

EBUS-TBNA cannot replace mediastinoscopy in all scenarios. Czarnecka-Kujawa et al.,[35] in a cost-effectiveness study, compared various modalities of mediastinal staging for NSCLC and found that invasive mediastinal staging is unlikely to be cost-effective in clinical N0 patients if the probability of N2 is smaller than 2.5%. However, EBUS-TBNA is the only staging modality that is cost-effective in patients with a probability of mediastinal metastasis ranging between 2.5% and 57%. In patients with negative EBUS-TBNA results and a probability of N2 > 57%, confirmatory mediastinoscopy should be considered.[35]

Mediastinoscopy has long been considered to be the gold standard for NSCLC staging. It has a sensitivity of 83% and a negative predictive value of 90%.[6] The drawback of mediastinoscopy is its complication rate, which ranges from 1.7% to 2.5%.[12]

The current literature supports the idea that EBUS-TBNA is a safe, minimally invasive procedure. Asano et al.,[36] investigating 7,345 patients who underwent EBUS-TBNA at 210 centers, reported a complication rate of 1.23% (95% CI: 0.97-1.48%). The most frequent complications were hemorrhage, in 50 patients (0.68%); infectious complications, in 14 (0.19%); and pneumothorax, in 2 (0.03%).

Verdial et al.[25] investigated 30,570 patients—15,097 (49%) underwent EBUS-TBNA, and 15,473 (51%) underwent mediastinoscopy. The authors reported that severe adverse events, such as pneumothorax, hemothorax, airway/vascular injuries, and death, were rare and were similar in the EBUS-TBNA and mediastinoscopy groups (0.3% vs. 0.4%; p = 0.189). However, the rate of major vessel injuries was lower in the EBUS-TBNA group than in the mediastinoscopy group (1.4% vs. 2.2%; p < 0.001), as was the rate of vocal cord paralysis (0.02% vs. 0.1%; p = 0.003). EBUS-TBNA was associated with a lower adjusted risk of severe adverse events (OR = 0.42; 95% CI: 0.32-0.55) and of vocal cord paralysis (OR = 0.57; 95% CI: 0.54-0.60).[25]

In the present systematic review, the complication rate for EBUS-TBNA was lower than was that for mediastinoscopy, although the difference was not statistically significant. Adverse events associated with EBUS-TBNA and with the surgical procedure were analyzed in 5 studies.[27-31] No deaths or major adverse events were associated with EBUS-TBNA or mediastinoscopy. The most common adverse events were minor bleeding, in 16 patients; postoperative wound infection, in 3; and left-sided recurrent nerve injury, in 3.

One study,[31] involving 166 patients, showed a greater number of major and minor intraprocedural adverse events associated with EBUS-TBNA and mediastinoscopy. Major adverse events during mediastinoscopy occurred in 2.4% of the patients (tracheal injury requiring muscle flap coverage, external jugular vein injury requiring vessel ligation, left-sided recurrent nerve injury resulting in vocal cord paralysis, and left-sided vocal cord paresis that lasted four months), whereas major adverse events during EBUS-TBNA occurred in 1.2% of the patients (left mainstem bronchus laceration requiring surgical repair and massive hemoptysis controlled with endoscopic interventions). No minor adverse events occurred during EBUS-TBNA, whereas, during mediastinoscopy, there was minor bleeding, in 7 patients; bradycardia, in 1; and arrhythmia, in 1.

Some differences among the selected studies came to light during our analysis. An important factor that might have contributed to higher heterogeneity of complications associated with mediastinoscopy is the fact that 1 study[27] had a sample size that was small in comparison with those of the other studies included (26 patients vs. > 100 patients). In addition, the study with the largest patient sample showed the highest number of complications.[31] A significant difference might have been detected if we had included more studies or studies with larger sample sizes, which could have reduced the degree of heterogeneity. Another issue is the variability among the various centers regarding technical aspects, patient selection, and follow-up periods. For instance, Zhang et al.[27] reported no complications, although the duration of the follow-up period was unclear. However, Liberman et al.[31] provided a very precise description of the follow-up period and of the strategy to detect complications after patient discharge, which contributed to the detection of a greater number of complications. Those authors performed a secondary fixed-effects analysis considering only major complications , which showed low heterogeneity (I^2 = 24%) and no significant differences (risk difference = −0.01; 95% CI: −0.02 to 0.00).

High heterogeneity in EBUS-TBNA results was present in some of the analyses and might be due to the individual experience of the examiner, the number of needle passes, and the expertise of the pathologist. Other aspects not addressed in the present systematic review were the combined use of EBUS-TBNA and EUS-FNA for LN staging, rapid on-site evaluation, and the use of elastography.

One of the advantages of EBUS-TBNA over mediastinoscopy is its ability to provide concomitant accurate lung cancer diagnosis and mediastinal staging during the same procedure if the lesion is central or if mediastinal or hilar LN involvement is suspected. Cytology specimens obtained by EBUS-TBNA are also sufficient to provide accurate histopathological diagnosis, allowing molecular testing (diagnostic yield of 95%) and staging of lung cancer. Therefore, EBUS-TBNA reduces the time to treatment decision when compared with other conventional diagnostic and staging techniques.[37]

In the present systematic review, the complication rate associated with EBUS-TBNA was lower than was that associated with mediastinoscopy, although there was no statistically significant difference. The strength of this systematic review includes the broad search for prospective studies. The limitation is the small number of articles included. Nevertheless, the studies included were of satisfactory quality, and the risk of bias can be considered low. The features of the studies and the sample sizes resulted in a certain degree of heterogeneity. It would be interesting to have more randomized trials comparing these interventions in the future.

In conclusion, EBUS-TBNA and mediastinoscopy achieved similar results for the mediastinal staging of lung cancer. EBUS-TBNA showed a performance and a safety profile that are good enough to replace mediastinoscopy altogether in the mediastinal staging for patients with potentially resectable NSCLC.

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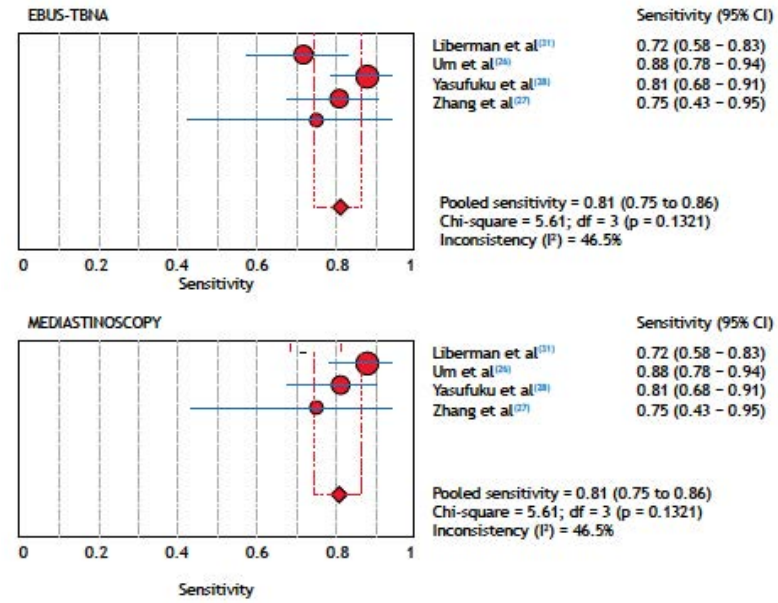
Artigo: EBUS-TBNA versus surgical mediastinoscopy for mediastinal lymph node staging in potentially operable non-small cell lung cancer: a systematic review and meta-analysis

Publicação: J Bras Pneumol. 2020;46(6):e20190221

DOI: https://doi.org/10.36416/1806-3713/e20190221

On page 6 of the original publication, in Figure 2, where is written



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