

Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis and staging of mediastinal lymphadenopathy: initial experience in Brazil*

Punção aspirativa guiada por ultrassom endobrônquico no diagnóstico e estadiamento de linfadenopatia mediastinal: experiência inicial no Brasil

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Abstract

Objective: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a new method for the diagnosis and staging of mediastinal lymph nodes. The objective of this study was to evaluate the preliminary results obtained with EBUS-TBNA in the diagnosis of lesions and mediastinal lymph node staging. **Methods:** We evaluated patients with tumors or mediastinal adenopathy, diagnosed with or suspected of having lung cancer. The procedures were performed with the patients under sedation or under general anesthesia. Material was collected by EBUS-TBNA, after which it was prepared on slides, fixed in either absolute alcohol (for cytology) or formalin (for cell-block analysis). **Results:** We included 50 patients (30 males). The mean age was 58.3 ± 13.5 years. We performed 201 biopsies of 81 lymph nodes or mediastinal masses (mean of 2.5 punctures/biopsy). The quantity of material was considered appropriate for cytology in 37 patients (74%), 21 (57%) of whom were thus diagnosed with malignancy. Of the remaining 16 patients, 1 was diagnosed with tuberculosis, 6 entered clinical follow-up, and 9 underwent further investigation (2 diagnosed with neoplasm—false-negative results). The yield was higher when the procedure was performed for diagnostic purposes, as well as being higher in patients with lesions in multiple stations and in biopsies involving the subcarinal lymph node station. One patient had endobronchial bleeding, which was resolved with local measures. There were no deaths among the patients evaluated. **Conclusions:** This preliminary experience shows that EBUS-TBNA is a safe procedure. Our diagnostic yield, although lower than that reported in the literature, was consistent with the learning curve for the method.

Keywords: Ultrasonography, interventional; Biopsy, fine-needle; Neoplasm staging; Lung neoplasms; Bronchoscopy.

Resumo

Objetivo: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA, punção aspirativa por agulha guiada por ultrassom endobrônquico) é um método novo em diagnóstico e estadiamento linfonodal mediastinal. O objetivo do estudo foi avaliar os resultados preliminares obtidos com EBUS-TBNA no diagnóstico de lesões e no estadiamento linfonodal mediastinal. **Métodos:** Foram avaliados pacientes com tumores ou adenopatias mediastinais e com diagnóstico ou suspeita de câncer de pulmão. Os procedimentos foram realizados com os pacientes sob sedação ou anestesia geral. O material coletado foi preparado em lâminas fixadas em álcool absoluto para citologia e em formol para bloco de células. **Resultados:** Foram incluídos 50 pacientes (30 do sexo masculino), com média de idade de $58,3 \pm 13,5$ anos. Foram realizadas 201 punções em 81 linfonodos ou massas mediastinais (média de 2,5 punções). O material obtido foi considerado adequado para análise citológica em 37 pacientes (74%), dos quais 21 (57%) foram diagnosticados com malignidade. Nos 16 pacientes remanescentes, 1 teve diagnóstico de tuberculose, 6 tiveram seguimento clínico, e 9 foram submetidos a investigação adicional (2 diagnosticados com neoplasia — resultados falso-negativos). O rendimento do exame foi maior nos procedimentos com objetivo diagnóstico, em pacientes com lesões em múltiplas estações, e nas punções da estação linfonodal subcarinal. Um paciente apresentou sangramento endobrônquico resolvido com medidas locais. Não houve mortalidade na série. **Conclusões:** Esta experiência preliminar confirmou que o EBUS-TBNA é procedimento seguro, e que o nosso rendimento diagnóstico, inferior ao da literatura, foi compatível com a curva de aprendizado do método.

Descritores: Ultrassonografia de intervenção; Biópsia por agulha fina; Estadiamento de neoplasias; Neoplasias pulmonares; Broncoscopia.

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Introduction

Invasive diagnosis of mediastinal lesions is fundamental, particularly in the presence of mediastinal lymphadenopathy or in the staging of lung cancer. Despite the advances in imaging methods, tissue samples are essential for diagnostic confirmation and treatment planning. Mediastinoscopy is considered the standard invasive method for the evaluation of mediastinal masses and lymph nodes.⁽¹⁾

Recently, less invasive methods have emerged as an alternative for collecting material for cytology. Among these methods, endobronchial ultrasound (EBUS), which was developed in the past decade, stands out as an outpatient method and allows access not only to paratracheal stations but also to hilar stations, being able to detect and collect material from lymph nodes smaller than 1 cm.⁽²⁾

Internationally, EBUS with transbronchial needle aspiration (TBNA) has been routinely used in the staging of lung cancer. Studies have shown that EBUS-TBNA has a sensitivity of approximately 93%, a specificity of 100%, and a negative predictive value of 96% in the evaluation of mediastinal and hilar lymph nodes in the staging of lung cancer.^(3,4)

The objective of the present study was to describe the first Brazilian experience with EBUS-TBNA, the results obtained, and the learning curve for the method in the diagnosis of masses and adenopathies, as well as in the mediastinal staging of lung cancer.

Methods

This was a prospective cohort study conducted at the Heart Institute of the University of São Paulo School of Medicine *Hospital das Clínicas* and at the São Paulo Cancer Institute, both located in the city of São Paulo, Brazil, between February of 2010 and February of 2011. We included patients treated at the thoracic surgery and pulmonology outpatient clinics who had lung cancer and (mediastinal or hilar) lymph node enlargement (greater than 10 mm) or (mediastinal or hilar) masses requiring confirmation by CT findings. We excluded patients who were deemed clinically unfit for respiratory endoscopy, patients with endobronchial lesions, and those who did not give written informed consent. The study was approved by the medical ethics committees of the two institutions (*Comissão de Ética para a*

Análise de Projeto de Pesquisa—CAPPesq, Ethics Committee for the Analysis of Research Projects—Protocol no. 0923/08).

Conventional bronchoscopy was performed previously, and patients with endobronchial lesions were excluded from the study. The EBUS-TBNA procedure was performed with the patient under sedation or under general anesthesia, together with noninvasive monitoring of cardiac function and blood pressure, as well as oximetry. The EBUS device (model BF-UC180F; Olympus Corp., Tokyo, Japan) was introduced orally, through a laryngeal mask or an intubation tube.

After ultrasound identification of the lymph nodes or masses, an aspiration needle (model NA-201SX-402; Olympus Corp.) was introduced into the working channel of the device. Real-time ultrasound-guided TBNA was performed through the tracheobronchial wall. The material collected was prepared on slides, fixed in either absolute alcohol (for cytology smear testing) or formalin (for paraffin-embedded cell-block analysis). The material was separated on the basis of the lymph node station punctured (2R, 2L, 4R, 4L, 7, 10R, 10L, 11R, and 11L). Tissue fragments that might have been collected were fixed in formaldehyde. In some cases, immunohistochemical analysis was performed to complement the study.

The cytological specimens obtained were classified as “appropriate” material when there were lymphocytes or pathological cells, or both, on the slide. An excess of red blood cells on the slide, as well as technical errors in sampling or processing the material, can generate samples considered “inappropriate” for cytology.

In the cancer cases, the presence of malignant cells defined the diagnosis as “positive”. The sample that was appropriate and normal, or benign, was classified as “negative” diagnosis. If the diagnostic EBUS-TBNA sample was normal, but it was classified as malignant after the confirmatory procedure, the result was classified as “false-negative”. If the EBUS-TBNA sample was malignant, but it was considered normal after the confirmatory procedure, the result was defined as “false-positive”.

Possible adverse events were recorded. Confirmatory procedures, such as mediastinoscopic biopsy or video-assisted thoracoscopic biopsy, were performed as needed for further investigation.

Table 1 – Characteristics of the population studied.^a

Characteristic	Result
	n = 50
Gender, M/F	30/20
Age, years ^b	58.3 ± 13.5
Previous diagnosis of neoplasm ^c	25 (50)
Pulmonary	12
Purpose of the procedure	
Diagnosis	29
Staging	12
Diagnosis and staging	9
Location of the lesion ^d	
Hilum	10
Mediastinum (single station)	13
Multiple stations	21

^aValues expressed as n, except where otherwise indicated.

^bValue expressed as mean ± SD. ^cValue expressed as n (%).

^dThe location of the lesion was not accurately determined in 6 patients.

Numerical variables are expressed as means and standard deviations, and categorical variables are expressed as frequencies and proportions.

Results

In the present study, we included 50 patients submitted to EBUS-TBNA. The characteristics of the population studied are described in Table 1.

In 1 patient, there was bleeding requiring the discontinuation of the procedure, and the bleeding was controlled with cold saline and with adrenaline solution. The patient's course was satisfactory, without hematomas or other complications.

We performed 201 biopsies of 81 lymph nodes, totaling 2.5 punctures/biopsies per lymph node. Figure 1 summarizes the results obtained. The samples considered inappropriate for cytology had a large proportion of red blood cells or a sparse representation of lymphoid cells, or both.

As can be seen in Figure 1, among the patients in whom the material was considered appropriate for cytology, 21 had neoplastic disease and 16 had benign disease. The cytological diagnoses were as follows: adenocarcinoma, in 10 cases; epidermoid carcinoma, in 5; small cell cancer, in 3; undifferentiated neoplasm, in 2; and lymphoma, in 1. With regard to benign disease, the diagnoses were reactive lymphadenitis, in 15 cases, and granulomatous lymphadenitis, in 1.

Among the patients diagnosed with benign disease, 1 was diagnosed with tuberculosis and 9 underwent further investigation, which identified malignant disease (lymphoma and lung cancer) in 2, thereby constituting false-negative results of the method. The remaining 6 patients did not undergo additional procedures and remained under clinical follow-up.

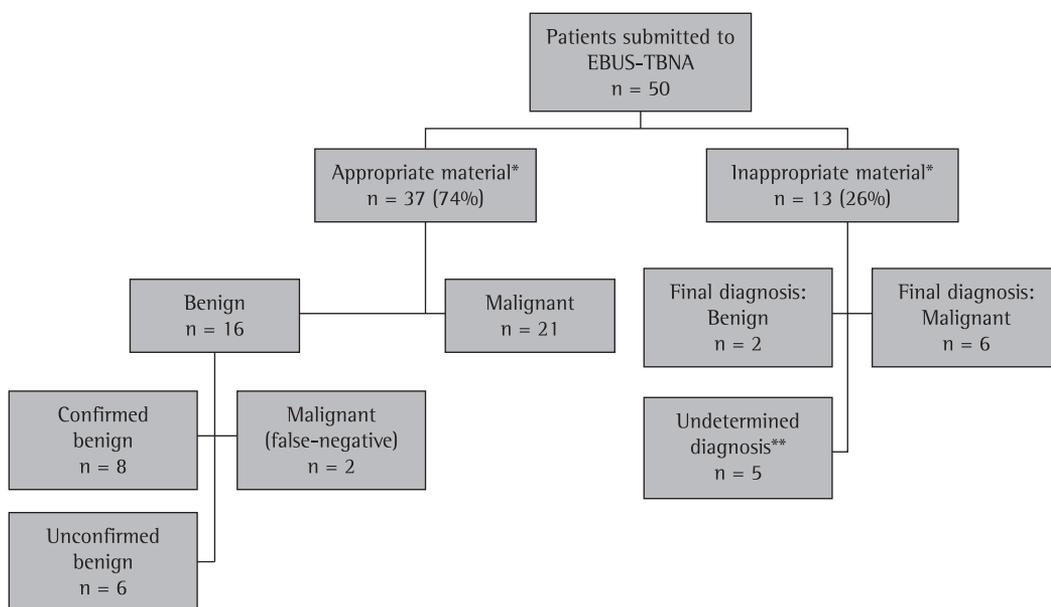


Figure 1 – Results for the patients submitted to endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA). *For cytology. **The suspicious lymph nodes were not addressed, and the final diagnosis was established otherwise.

Table 2 – Results by purpose of the procedure for each patient.^a

Purpose of the procedure ^b	Patients in whom the material was considered appropriate	Result	
		Malignant disease	False-negative
Diagnosis (n = 29)	24 (69.6)	12 (50)	2 (16.6)
Staging (n = 12)	5 (41.6)	2 (40)	0 (0.0)
Diagnosis and staging (n = 9)	8 (88.8)	7 (87.5)	0 (0.0)

^aValues expressed as n (%). ^bDiagnosis: cases with mediastinal lesions with no previous diagnosis; staging: cases with an established diagnosis of lung cancer requiring mediastinal staging; and diagnosis and staging: cases of radiologically suspected lung cancer with no previous diagnosis.

Tables 2 and 3 show, by purpose of the procedure and by location of the suspicious lesion, the proportion of cases whose samples contained appropriate material for analysis. The yield seemed to be higher when the procedure was performed for diagnostic purposes than when it was performed for cancer staging. The yield was also higher in patients with lesions in multiple stations. Supporting this hypothesis is the fact that, in all 7 patients with mediastinal disease in multiple stations and with radiological suspicion of lung cancer, all of whom underwent the procedure for diagnostic and staging purposes, the definitive diagnosis was established by EBUS-TBNA. In contrast, only 1 patient diagnosed with ovarian cancer and presenting with a suspicious hilar lesion underwent EBUS-TBNA for staging purposes, and, in this patient, the sample was considered inappropriate for cytology.

Of the 81 lymph nodes punctured, most were located in the paratracheal stations, as shown in Table 4. The analysis of the yield of the punctures/biopsies in relation to the location of the lymph nodes punctured revealed that the subcarinal station exhibited the highest yield, whereas the hilar stations exhibited the lowest yield.

Discussion

A review of the first studies on EBUS showed that a few centers were responsible for much of that scientific output. Even after encouraging initial results were published by those groups, the high costs of the equipment and accessories and the need for training limited the rapid dissemination

of the method. In Brazil, EBUS only became available in 2010.

The discussion of our results, in comparison with literature data, which are generally produced by long-established centers, shows significant differences. In order to explain the reasons for these differences, we chose to perform an analysis by topic areas. This discussion reveals the difficulties faced during the development of the study, which corresponded to the period of implementation of the procedure, since it was a new technique, which, to our knowledge, had not been used in Brazil before.

The initial reports on the use of EBUS indicated that the procedure should be performed with the patient under general anesthesia. Although, in some of our cases, the procedure was performed with the patient under sedation, in most of them, we used general anesthesia, which allows the examining physician to perform a more accurate staging, especially when there is no evidence of mediastinal lymph node enlargement on CT, or when one begins to use the method. However, this is not the rule. Many centers in the world perform the procedure with the patient under sedation in order to reduce costs. One group of authors evaluated, with the use of questionnaires, the degree of satisfaction of 41 patients submitted to EBUS under sedation. The authors concluded that EBUS can be performed safely under conscious sedation, with a high degree of patient satisfaction.⁽⁵⁾

One difficulty in implementing the procedure is related to working together with the surgical

Table 3 – Results by location of the lesion for each patient.^a

Location of the lesion	Patients in whom the material was considered appropriate	Result	
		Malignant disease	False-negative
Hilum (n = 10)	5 (50.0)	3 (60.0)	0 (0.0)
Mediastinum (single station; n = 13)	10 (76.9)	5 (50.0)	1 (20.0)
Mediastinum (multiple stations; n = 21)	18 (85.7)	11 (61.1)	0 (0.0)

^aValues expressed as n (%).

Table 4 – Frequency and proportion of patients in whom the material was considered appropriate by lymph node station evaluated.^a

Lymph node station	Patients in whom the material was considered appropriate
Paratracheal (n = 36)	22 (61.1)
Subcarinal (n = 26)	17 (65.3)
Hilar (n = 19)	8 (42.1)

^aValues expressed as n (%).

pathology section. Although there is the possibility of occasionally collecting (core) fragments of the lesion, the method is essentially cytological rather than histological. Unless the fellow pathologists are used to cytological methods, which is not always current practice in Brazil, this requires a period of adaptation or even a learning curve.

Another factor involves the diagnostic criteria. The presence of lymphocytes on the slides from mediastinal aspirates is an essential criterion for determining whether a specimen is appropriate. One group of authors demonstrated that the predictive value of a negative result was 78% and 36%, respectively, for a “non-malignant” aspirate that contained lymphocytes and for a “non-malignant” aspirate that did not contain lymphocytes ($p \leq 0.005$).⁽⁶⁾

It is recommended that the samples that do not have lymphocytes be classified as “inappropriate”, being thus differentiated from inconclusive samples. The literature shows that the number of nondiagnostic samples ranges from 4% to 23%.^(7,8)

Even experienced centers show relatively high rates of inappropriate samples. One group of authors reported that, of 131 cases of mediastinal lymph node sampling performed at the Johns Hopkins Hospital, 7 (5.3%) had samples that were considered inappropriate.⁽⁹⁾ In the present study, the rate of inappropriate samples was 25%, which is similar to the rates reported in the literature for initial experiences. Contributing to that is the fact that the biopsies involved hilar lymph node stations, which had a higher rate of “inappropriate” samples when compared with the biopsies involving the subcarinal station, which is more easily accessed.

Performing EBUS involves an important point: the preparation of smears on slides. Although there are descriptions, it is recommended that the pathologist responsible for reading the

slides determine how the preparation should be performed.

Considering that the samples collected at each biopsy/puncture should be distributed on four or more slides, which should be rapidly placed in 70% alcohol to avoid artifacts, it is clear that there is need for trained and qualified in-room personnel to perform the procedures.⁽¹⁰⁾ Inappropriate slide preparation, which certainly occurred at the beginning of our experience, probably contributed to the large number of tests whose results were classified as “inappropriate sample” or inconclusive.

Studies in the literature suggest that a pathologist should be present in the room where EBUS is being performed, in an attempt to minimize the number of inconclusive tests. The international literature refers to this working structure as rapid on site cytology.⁽¹¹⁾ Although the advantages of this scheme are indisputable because it facilitates rapid clinical decision-making, few centers can afford to maintain an in-room pathologist who has time to wait for the test. This scheme is justifiable in a scenario where cases with nondiagnostic EBUS results are further investigated via mediastinoscopy or video-assisted thoracoscopy.

Considering that passing the needle, puncturing the lymph nodes, and preparing the slides are time-consuming procedures, it is clear that the number of aspirations per lymph node exponentially increases the duration of the procedure.

To determine the optimal number of aspirations per lymph node needed to obtain a higher diagnostic yield, one group of authors reported having performed four aspirations on each of the 163 lymph nodes studied in 102 patients with lung cancer. Those authors obtained 90.1% of appropriate samples in the first aspiration, reaching 100% in the third aspiration. Their conclusion was that maximum diagnostic values were achieved in three aspirations.⁽¹²⁾ In the present study, we performed 2.5 punctures/biopsies per lymph node. Our impression is that, in the learning curve, the number of punctures/biopsies per lymph node should have been higher in order to increase the diagnostic yield of the method. The technical difficulty in accessing the lymph nodes, which was a result of our learning curve, explains the fact that, in some situations, fewer than 3 aspirations were performed.

In the case of a patient with a highly vascularized peribronchial mass, it was necessary to discontinue the procedure due to bleeding. Complications resulting from EBUS-TBNA are rare. Contributing to that is the fact that the biopsies/punctures are performed with a fine needle (22G). In addition, the EBUS device is equipped with a Doppler mode, which allows the identification of vascular structures, minimizing the risk of bleeding. The literature reports more than one thousand EBUS procedures without the occurrence of significant complications.^(13,14)

There are aspects related to the published literature on EBUS that should be highlighted. Because the method is relatively new and the equipment is sophisticated and costly, until recently, only a few centers around the world were responsible for most of the published literature. Therefore, it is possible that the excellent results were obtained in centers with the best-trained professionals and the best equipment.

In most published studies on the use of EBUS-TBNA in the staging of lung cancer, there was no standard for monitoring false-negative results. In those studies, negative EBUS results for malignancy were confirmed by mediastinoscopy, video-assisted thoracoscopy, or thoracoscopy in some cases. However, there were cases in which the presumed confirmation of the result was based only on patient clinical follow-up, a method that is hardly appropriate for this confirmation.⁽¹⁵⁾

In the present study, we had 6 cases in which, for various reasons, it was not possible to perform ancillary procedures, and those patients remained under clinical follow-up as a way to confirm the EBUS results obtained. This type of situation, which is independent of the will of the investigator, might distort the result, especially in cases of false-negative results. One group of authors used a methodology that minimized the possibility of false-negative results in a study involving 226 lung cancer patients who underwent EBUS for mediastinal staging. Of those 226 patients, 97 had negative EBUS results and were referred for mediastinal dissection by Transcervical Extended Mediastinal Lymphadenectomy, which revealed 16 patients (7.1% of those 226) with lymph nodes positive for malignancy. All patients whose lymph nodes tested negative were then submitted to thoracotomy and mediastinal lymph node dissection, which revealed no residual lymph

nodes. The authors reported that EBUS had a sensitivity of 89%, a specificity of 100%, an accuracy of 92.9%, a positive predictive value of 100%, and a negative predictive value of 83.5%. In our view, those authors provided the most accurate figures for EBUS-TBNA in the literature.⁽¹⁶⁾

Another point to be considered is the role of mediastinoscopy, which has long been considered the gold standard in mediastinal staging. Consequently, there is a tendency to compare mediastinoscopy results with EBUS results. The advantage of using EBUS over mediastinoscopy is that the former allows access to a larger number of mediastinal lymph node stations than does the latter, as reported in one study (a diagnostic rate of 87.5% in stations 10 and 11).⁽¹⁷⁾ However, we must consider that, although these stations are relevant for obtaining a more accurate staging, they have no impact on the decision-making process regarding surgical treatment.⁽¹⁷⁾ Another argument that has been made in favor of EBUS is that it is less invasive than is mediastinoscopy, which, despite a complication rate of less than 1%, can cause severe complications.^(18,19)

It has also been emphasized that, in cases of reassessment of the mediastinum after previous mediastinoscopy, surgical lymph node drainage, or neoadjuvant therapy, EBUS is safer than a second mediastinoscopy because of the fibrosis following mediastinoscopy. However, no studies have assessed the accuracy and safety of EBUS in such cases.

Another potential advantage of EBUS is the possibility of sampling mediastinal lymph nodes without the need for general anesthesia, because it has been demonstrated that the diagnostic accuracy of EBUS with or without the use of general anesthesia is similar.⁽¹³⁾

A recent study evaluated whether EBUS-TBNA is as accurate as mediastinoscopy in the staging of lung cancer cases. The authors of the study⁽²⁰⁾ stated that, with larger lymph nodes, the sensitivity of EBUS was similar to that of mediastinoscopy, although, with normal-sized lymph nodes, the former was lower than the latter. The rate of false-negative EBUS results seemed higher than that of false-negative mediastinoscopy results, and, therefore, the non-malignant results obtained by EBUS could be unreliable. Those authors also cited two studies, considered somewhat inconsistent, that examined costs and identified that EBUS

had a low cost-benefit ratio. Although there are scenarios in which EBUS is preferable to mediastinoscopy, such as in routine staging of the upper mediastinum in lung cancer cases, the potential benefits of EBUS over mediastinoscopy have yet to be proven.⁽²⁰⁾

These data published in the literature make most authors suggest that the sensitivity and accuracy of EBUS is comparable with that of mediastinoscopy, although formal studies are needed to validate this conclusion.^(18,19,21,22)

Our experience demonstrates that, to obtain a high diagnostic yield with the use of EBUS, it is essential to promote the interaction among the various specialties involved in the use of the method.

The results achieved in the initial phase of our experience confirm that the method is safe, although our results are below those reported by long-established centers—for instance, a study of 502 patients with mediastinal or hilar lymphadenopathy reported a sensitivity and diagnostic accuracy of 94%,⁽¹³⁾ whereas a study of 108 patients diagnosed with or suspected of having lung cancer reported a sensitivity of 92.3% and a diagnostic accuracy of 98%.⁽²³⁾ In contrast, when we compare our results with the initial results of other groups, we can conclude that the difficulties we faced are common. One group of authors chose to exclude the results of the first 10 patients from their data, on the grounds that this would be the number of procedures required for completion of the learning curve.⁽¹⁷⁾

A final point worth commenting upon is the role of TBNA. A study comparing TBNA with EBUS-TBNA in the staging of lung cancer concluded that, except for the subcarinal station 7, the diagnostic yield of EBUS-TBNA was higher than that of TBNA in the other mediastinal lymph node stations.⁽²⁴⁾ However, the analysis of that study shows that, in addition to the existence of a bias in the methodology, the figures obtained do not support the authors' conclusion.⁽²⁵⁾ Therefore, the actual role of TBNA compared with EBUS-TBNA has yet to be determined.

These data lead us to conclude that it is possible to obtain acceptable sensitivity and acceptable diagnostic accuracy in the assessment of mediastinal lymph nodes after a relatively small number of EBUS procedures. This finding is in agreement with other literature reports in

which the authors describe their initial experience with the method.

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