ORIGINAL ARTICLE

Learning curve and advantages of endobronchial ultrasound-guided transbronchial needle aspiration as a first-line diagnostic and staging procedure

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Abstract

Background: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is now the standard for mediastinal lymph node staging of lung cancer. Training and maintenance of technical skills is very important in order to apply new techniques in clinical use.

Methods: A retrospective chart review was performed of patients who underwent EBUS-TBNA from November 2009 to December 2015. We assessed the learning curve, accuracy (%), and whether this procedure shortened the duration of lung cancer staging.

Results: The EBUS-TBNA learning curve continued to improve beyond 120 procedures. Diagnostic accuracy was similar between benign and malignant populations. There was no difference in the learning curve between the groups. Non-small cell lung cancer patients who underwent EBUS-TBNA as the first investigative procedure underwent fewer subsequent investigative procedures (1.47 vs. 2.05; $P < 0.001$), and had a shorter staging duration (4.52 vs. 11.05 days; $P = 0.006$) compared to those who underwent other procedures for the first investigation.

Conclusion: EBUS-TBNA should be one of the preferred options for lung cancer diagnosis and staging because it reduces the staging duration compared to the use of other invasive procedures in initial investigation.

Introduction

The prognosis for lung cancer is extremely poor, with a five-year survival rate of less than 15%.[1] Accurate diagnosis of mediastinal and hilar lymph nodes is not only essential to evaluate prognosis but also to devise an appropriate treatment plan. Imaging tools, including computed tomography (CT) and positron emission tomography (PET), are widely used to stage lung cancer.[2,3] Because of their relatively low sensitivity and specificity, invasive procedures with direct pathological sampling are still needed.[4]

Conventional transbronchial needle aspiration, mediastinoscopy, video-assisted thoracic surgery, and CT-guided biopsy have been used for mediastinal sampling. Each of these techniques has some limitations or complications. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsies of mediastinal and hilar lesions with real-time images using a convex probe was gradually utilized since the early 2000s.[5] Because EBUS-TBNA is less invasive with a relatively higher yield, conventional procedures have gradually been replaced by this technique.[6,7] EBUS-TBNA is now the standard method for the diagnosis of mediastinal and hilar lymphadenopathy and should be considered in patients who have a high probability of lymph node metastases without systemic involvement.[8] EBUS-TBNA is also recommended as an initial investigation for the diagnosis and staging of patients with suspected lung cancer because the procedure provides a tissue diagnosis and nodal staging in one investigation. Initial diagnosis via EBUS-TBNA can reduce the time from diagnosis to treatment planning.[9]

Endobronchial ultrasound-guided transbronchial needle aspiration has high sensitivity (>90%) and specificity (almost 100%). Few improvements can be made by new techniques.[10,11] However, the accuracy of EBUS-TBNA is quite dependent on experience.[12] High-volume hospitals are associated with high diagnostic yields.[12,13] How to acquire mastery during training is an important question in interventional bronchology.[12] In previous studies, different numbers of procedures were needed to develop and maintain EBUS-TBNA skills.[12,14–16] In this study, we investigated our learning curve and examined how to shorten the duration of staging in lung cancer patients.

Methods

Participants

The National Taiwan University Hospital Institutional Review Board (IRB # 201611077RINC) approved the study. Informed consent was waived as existing data were analyzed in a de-identified manner for this study. A retrospective chart review was created using data of patients who underwent EBUS-TBNA for unselected mediastinal and hilar pathology at the Division of Chest Medicine, National Taiwan University Hospital, from November 2009 to December 2015. Patient age, gender, and the number of punctures in each target site were collected. One EBUS-TBNA procedure represented one examination and the data were recorded successively. Lesion size was defined as the longest length measured on cross-sectional CT images. The locations used during the procedure were chosen according to the International Tumor Node Metastasis Staging System reported by Mountain and Dresler.[17]

In patients with malignancy, the diagnosis was determined on the basis of malignant cytological and/or histological results at EBUS-TBNA or surgical-pathological confirmation. In patients with benign tumors, the diagnosis was confirmed by surgical biopsy or at least six months of radiological and clinical follow-up. In patients with lung cancer, the duration to diagnosis, the duration of staging, and all invasive investigations for diagnosis and staging were recorded. The duration of diagnosis was defined as the day from the initial chest image (chest plain film or CT) on which lung cancer was suspected to definite diagnosis by pathological report. The duration of staging was defined as the number of days from the date of definite diagnosis until complete staging. All patients received brain imaging (CT or magnetic resonance imaging) and bone scans (or PET) after diagnosis by pathology or cytology. PET-CT was routinely used in preoperative screening, but not in patients with metastatic disease found by CT, magnetic resonance imaging, or bone scan. In patients whose diagnosis was not made by EBUS-TBNA, the duration of staging was dependent on the results of EBUS-TBNA and/or surgical procedure, except for stage IV disease.

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)

Endobronchial ultrasound-guided transbronchial needle aspiration was performed in an inpatient setting because of the lack of a recovery room in our bronchoscopy suite. Conscious sedation with intravenous fentanyl and midazolam was administered. All procedures were performed by the attending physician (Dr. Ho). Two or three senior pulmonary fellow doctors were also recruited for each EBUS-TBNA procedure to assist. A real-time ultrasound biopsy bronchoscope (BF-UC260-OL8) and dedicated 22-gauge needle (NA-201SX-4022) were used for TBNA biopsies (Olympus, Tokyo, Japan). A rapid on-site cytology exam (ROSE) was not performed for all patients because of the lack of a cytologist or pathologist in our clinical setting. If more than one target site needs to be approached, a sequential N3-N2-N1 strategy is followed for lymph node staging.

Statistical analysis

For overall diagnosis, we defined true positives as any EBUS-TBNA samples that showed malignant cells. True negatives were defined as any EBUS-TBNA samples containing adequate amounts of lymphocytes without malignant cells, also confirmed by surgical or clinical follow-up. False negatives were defined as any EBUS-TBNA samples containing lymphocytes without malignant cells initially, but discovered later through repeated biopsy or disease progression and confirmed via radiological and clinical follow-up in less than six months. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy rate were calculated via standard definitions. Significance was considered at $P < 0.05$. SPSS version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

Patients

The demographic characteristics of the 252 patients evaluated in this study are summarized in Table 1. There were 154 men and 98 women, with a mean age of 61.29 years (range 17–92). The major proportion of our study population had a final diagnosis of malignancy (169, 67.06%): 133 had lung cancer, 31 had other solid organ malignancy, and 5 had large B-cell lymphoma. The histological types of lung cancers were adenocarcinoma in 74, squamous cell carcinoma in 30, small-cell

Table 1 Patient characteristics

Patient characteristics	N (%)
Patients	252
Age	61.29 (17–91)
Gender (M)	154 (61.11)
Diagnosis	
Malignancy	169 (67.06)
Lung Cancer	133 (52.78)
Squamous	30 (11.90)
Adenocarcinoma	74 (29.37)
Small cell lung cancer	9 (3.57)
Other non-small cell lung cancer	20 (7.94)
Other solid organ malignancy	31 (12.30)
Lymphoma	5 (1.98)
Benign	83 (32.94)
Sarcoidosis	40 (15.87)
Pulmonary tuberculosis	18 (7.14)
Non-tuberculous mycobacterial infection	1 (0.40)
Organizing pneumonia	2 (0.79)
Cryptococcosis	1 (0.40)
Thymic cyst	1 (0.40)
Benign inflammation	20 (7.94)

Table 2 Mediastinal and hilar pathogens characteristics

Lesion characteristics	Lymph node (%)	Mediastinal mass (%)	Total
Number	326	18	344
Size (mm)	15.76 (4–53.3)	34.11 (13.7–81.6)	
Location			
2R	14 (4.07)	1 (0.29)	
2L	1 (0.29)	0	
4R	131 (38.08)	1 (0.29)	
4L	27 (7.85)	2 (0.58)	
3P	0	3 (0.87)	
7	91 (26.45)	8 (2.33)	
10R	15 (4.36)	2 (0.58)	
10L	10 (2.91)	1 (0.29)	
11R	19 (5.52)	0	
11L	18 (5.23)	0	
Number of punctures	2.96	3.39	

lung cancer (SCLC) in 9, and other non-small cell lung cancer (NSCLC) in 20. Eighty-three patients were finally diagnosed with benign processes: 40 sarcoidosis, 18 pulmonary tuberculosis, 1 non-tuberculous mycobacterial infection, 2 organizing pneumonia, 1 pulmonary cryptococcosis, and 1 thyroid cyst. The remaining 20 patients had no specific pathological or microbiological diagnosis and were classified with a benign inflammation.

A total of 344 mediastinal and hilar pathogens are summarized in Table 2. During the study period, 326 lymph nodes and 18 mediastinal masses were aspirated. Regarding lymphadenopathy, 264 were mediastinal lymph nodes (stations 2, 4, and 7) and 62 were hilar lymph nodes (stations 10 and 11). The mean size of punctured lymph nodes was 15.76 mm and the mean number of punctures was 2.96. In the mediastinal masses, the mean size was 34.11 mm and the mean number of punctures was 3.39.

Learning curve and diagnostic performance of EBUS-TBNA

Figure 1a shows the curve of the diagnostic accuracy rate of the consequent procedures. Figure 1b shows the curve of the sensitivity, specificity, PPV, and NPV. The learning curve of diagnostic accuracy presented as an "S" curve pattern. The initial curve rose slowly or even dropped, followed by a steeper ascending phase. The accuracy rate at our institution reached 90% after 120 procedures. The curves of sensitivity and NPV are very similar to the diagnostic accuracy rate curve. After excluding the first 120 procedures for learning, the diagnostic accuracy rate was 94.7% (125/132). The sensitivity, specificity, PPV, and NPV were 92.8%, 100%, 100%, and 83.3%, respectively.

Figure 2 shows the comparisons of diagnostic yield between malignancy and benign disease. There were no significant differences in our study population. During the initial 120 procedures (also called the "pre-mature period"), the diagnostic accuracy rate between malignancy and benign tumors was 76.9% versus 69.1% ($P = 0.338$). After excluding the pre-mature period (also called the "well-trained period"), the diagnostic accuracy rate between malignancy and benign tumors was 96.9% versus 92.5% ($P = 0.264$). We also calculated the overall diagnostic accuracy rate and found no difference between these groups (86.9% vs. 82.0%; $P = 0.279$).

Effect of EBUS-TBNA on lung cancer patients

One hundred and thirty-three patients were diagnosed with lung cancer in our study population. After excluding patients with SCLC (9) and those who underwent EBUS-TBNA for re-biopsy (42), 82 NSCLC patients were enrolled in our subgroup population (Table 3). The subgroup population was divided into two groups: 41 patients who underwent EBUS-TBNA for the first investigative procedure (TBNA group), and 41 patients who underwent other invasive procedures for the first investigation and subsequently underwent EBUS-TBNA for complete staging (OIP group). The histological types of lung cancers and disease staging were similar in the two groups.

In the TBNA group, 20 patients were in the pre-mature period and 21 patients were in the well-trained period. In the OIP group, 19 patients were in the pre-mature period and 22 patients were in the well-trained period (Table 4). In the
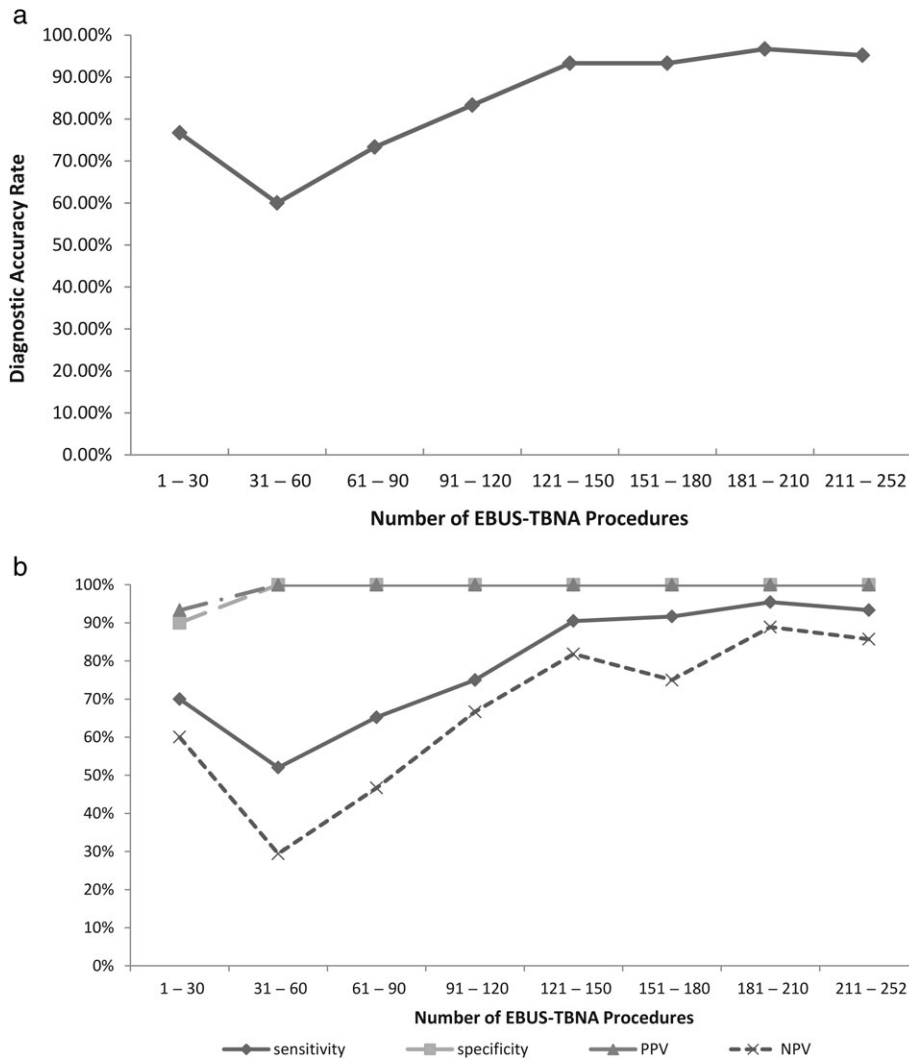
a

b

Figure 1 The curves of the (**a**) diagnostic accuracy rate and (**b**) sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of consequent procedures. EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.
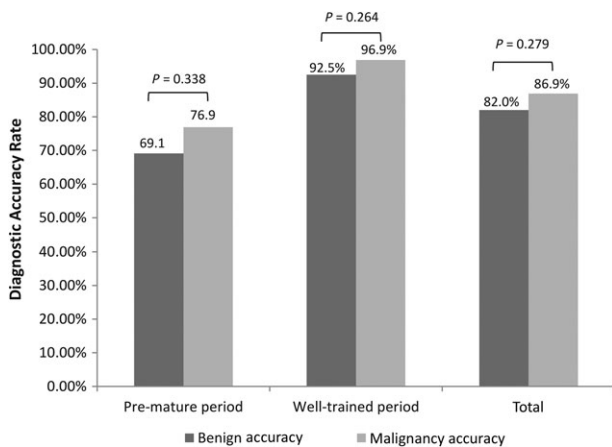

Figure 2 A comparison of the accuracy of endobronchial ultrasound-guided transbronchial needle aspiration between benign and malignant tumors.

pre-mature period, the durations of diagnosis and staging were similar between the groups. After reaching the learning curve, the staging duration was significantly shorter in the TBNA than in the OIP group (4.52 vs. 11.05 days; $P = 0.006$). The TBNA group also required fewer invasive investigations for diagnosis and staging (1.47 vs. 2.05; $P < 0.001$).

Compared to the diagnostic yield of the initial investigation, higher diagnostic yields were noted in the OIP group during the pre-mature period (100% [19/19] vs. 75% [15/20]; $P = 0.019$). After reaching the learning curve, there was no difference between the groups (86.36% [19/22] vs. 100% [21/21]; $P = 0.083$) (Fig 3).

Complications

No patients experienced any major complications related to EBUS-TBNA, with the exception of minimal self-limited wound oozing noted during the procedure.

Table 3 Characteristics of lung cancer patients

Characteristics	TBNA group	OIP group
Patients	41	41
Gender (M)	29 (70.7%)	26 (63.4%)
Age	63.0 (37–84)	65.3 (46–84)
Lung cancer		
Adenocarcinoma	25	24
SqCC	8	16
NSCLC	8	4
Staging		
Ia	1	3
Ib	0	1
IIa	4	1
IIb	0	2
IIIa	9	17
IIIb	12	9
IV	15	8

NSCLC, non-small cell lung cancer; OIP, other invasive procedures; SCLC, small cell lung cancer; SqCC, squamous cell carcinoma; TBNA, transbronchial needle aspiration.

Discussion

In the present study, 120 EBUS-TBNA procedures were needed to reach the learning curve for unselected mediastinal lesion sampling. After reaching the learning curve, the use of EBUS-TBNA as an initial diagnostic tool may shorten the duration of staging and lead to fewer investigations to achieve complete staging.

In early studies of EBUS-TBNA, 10–40 procedures were required to achieve an acceptable diagnostic yield rate;
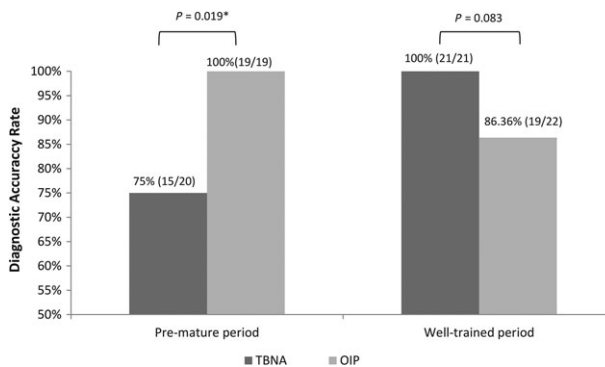

Figure 3 A comparison of the accuracy between endobronchial ultrasound-guided transbronchial needle aspiration (TBNA) and other invasive procedure (OIP) groups at pre-mature and well-trained periods.

however, these studies focused only on cancer patients.[18–20] In our study, patients with both malignancy and benign disease were enrolled. Longer learning curves for EBUS-TBNA were required in recent studies of mixed populations, which reported that diagnostic yield can be improved up to 100 procedures,[21] 140 procedures,[22] or even after 200 procedures.[23] Another study reported that a median of 212 procedures was required for interventional pulmonology fellows to achieve expert-level technical skill in EBUS-TBNA.[16] These findings are consistent with our result, in that more than 100 procedures are recommended to reach the learning curve of EBUS-TBNA.

The longer required EBUS-TBNA learning curve has been attributed to different disease prevalence. Sørhaug

Table 4 Univariate and multivariate analysis of lung cancer patients using different initial investigations

Factors	Initial investigation by EBUS-TBNA	Initial investigation by other methods	Univariate P value	Multivariate P value
Pre-mature period (N)	20	19		
Initial diagnostic tool				
EBUS-TBB		10		
Echo-guided biopsy		6		
CT-guided biopsy		3		
Investigation per patient	1.20	2.09	<0.001*	<0.001*
Duration to diagnosis (days)	20.4 (5–53)	18.19 (2–61)	0.189	0.172
Duration of staging (days)	8.5 (0–44)	10.59 (0–25)	0.720	0.857
Simultaneous diagnosis and staging by EBUS-TBNA (N)	13 (65%)	0 (0%)	<0.001*	<0.001*
Well-trained period (N)	21	22		
Initial diagnostic tool				
EBUS-TBB		7		
Echo-guided biopsy		7		
CT-guided biopsy		8		
Investigation per patient	1.47	2.05	<0.001*	<0.001*
Duration to diagnosis (days)	18.24 (6–49)	13.41 (3–42)	0.171	0.489
Duration of staging (days)	4.52 (0–22)	11.05 (0–35)	0.009*	0.006*
Simultaneously diagnosis and staging by EBUS-TBNA (N)	10 (47.6%)	2 (9.1%)	0.004*	0.013*

CT, computed tomography; EBUS-TBB, endobronchial ultrasound-guided transbronchial biopsy; TBNA, transbronchial needle aspiration.

et al. reported that a benign group has a lower diagnostic yield compared to a malignant group under EBUS-TBNA.[24] A larger proportion of benign tumors may prolong the learning curve. In our study, there was a trend of lower diagnostic accuracy for benign tumors under EBUS-TBNA during the pre-mature and well-trained periods; however, no statistical difference was found between the groups. Varied populations do not impact results but the number of procedures performed is significant.

After the learning curve had been established, using EBUS-TBNA as the first diagnostic method for NSCLC patients shortened the staging duration in our study population from 11.05 to 4.52 days. This result indicates that the use of EBUS-TBNA can reduce the hospitalization course, lower medical costs, and also decrease the duration in which patients are anxious waiting for proper treatment planning. A previous study revealed that using EBUS-TBNA as an initial investigation in NSCLC patients can reduce the time to treatment; however, the population in this study was early stage patients.[9] In our study, a large proportion of late-stage (IIb/IV) NSCLC patients were enrolled (27/41 in the TBNA and 17/41 in the OIP group). The advantage seems to be extended to the NSCLC population with unselected staging status.

Performing EBUS-TBNA can reduce the time taken to make a treatment decision, particularly by reducing the number of outpatient appointments and investigations.[9] The routine use of EBUS-TBNA in our study population led to fewer investigations for each patient (1.47 vs. 2.05; $P < 0.001$). EBUS-TBNA has been reported to provide sufficient diagnosis and staging information. Mohamed *et al.* reported that EBUS-TBNA histological samples are suitable for immunohistochemical analysis.[25] Kang *et al.* reported that EBUS-TBNA specimens are effective to examine EGFR mutation and confirmed that EBUS-TBNA is indeed an effective diagnostic tool for lung cancer.[26] During the well-trained period of our study, around half of the lung cancer patients in the TBNA group (10/21, 47.6%) did not require further invasive procedures as EBUS-TBNA allowed for simultaneous diagnosis and complete staging (Table 4). In addition, a large proportion of patients in the pre-mature period (TBNA group) completed diagnosis and staging at the same time, therefore minimizing the number of investigations. Thus, we advocate that EBUS-TBNA may be a preferred option for lung cancer diagnosis and staging.

The advantage of a shorter duration to staging is negated if the accuracy rate of EBUS-TBNA does not achieve a desired level. In the present study, the staging duration was no different between the TBNA and OIP groups in the pre-mature period, because the diagnostic accuracy of EBUS-TBNA as an initial investigation was statistically lower than other diagnostic tools (100% [19/19] vs. 75% [15/20]). Other procedures are required when diagnosis by EBUS-

TBNA fails. Thus, EBUS-TBNA is not an optimal method until the bronchoscopist acquires the technical skill.

Endobronchial ultrasound-guided transbronchial needle aspiration can be a difficult and time-consuming procedure, thus it is important that the learning curve for this procedure is reduced. Steinfort *et al.* conducted a study in which 66% of the study population was composed of malignancy, which is similar to the proportion in our sample; however only 50 procedures were required to establish the learning curve in their study.[27] The faster skill maturation achieved in Steinfort *et al.*'s study may be the result of two factors. First, ROSE was performed during each procedure in Steinfort *et al.*'s study. To our knowledge, ROSE not only improves the diagnostic yield of EBUS-TBNA, but also offers timely feedback.[28,29] Second, all of the operators were experienced with conventional TBNA. Being more familiar with the process of fine needle aspiration may shorten the maturation time.

Our study has some limitations. First, this is a retrospective study. Many clinical data, such as time to intubation and procedure duration, were not recorded. These are also important assessment methods to achieve learning efficiency. Not all of the invasive procedures were performed in an inpatient setting. Echo-guided biopsy and bronchoscopy-guided transbronchial lung biopsy might have been performed in an outpatient setting, because sedation is not required in our institution. This situation may have influenced the duration to diagnosis. A prospective analysis with a standardized diagnosis and staging protocol is warranted for evaluation. Second, the reason for choosing a diagnostic technique not only depends on the lesion site but also the physician. In our hospital, not all physicians are familiar with EBUS-TBNA. Many physicians still use EBUS-TBNA for nodal staging, although EBUS-TBNA can also provide adequate tissue samples for diagnosis.[9,26] Third, we did not use a surgical criterion standard to define all final pathologies of the patients, although most benign processes were clinically followed for at least six months and characterized via chest CT.

In conclusion, this study showed the diagnostic accuracy and the required learning curve using EBUS-TBNA in an unselected population. Diagnostic performance continues to improve beyond 120 procedures. Because we achieved the same diagnostic accuracy between malignant and benign processes, we posit that the learning curve in different populations will be similar. After achieving a satisfactory level of accuracy, the use of EBUS-TBNA for the initial investigation in NSCLC patients not only decreased the number of invasive procedures but also shortened the staging duration. The procedure is safe and our study population experienced no serious complications. We advocate the use of EBUS-TBNA as one of the preferred options for lung cancer diagnosis and staging.

Acknowledgment

Disclosure

No authors report any conflict of interest.

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