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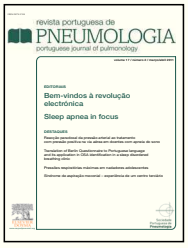

ORIGINAL ARTICLE

Endobronchial ultrasound-guided transbronchial needle aspiration for lung cancer diagnosis and staging in 179 patients

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KEYWORDS
Lung cancer;
Endobronchial ultrasound;
Fine needle aspiration;
Diagnosis;
Staging;
Learning curve

Abstract

Background: Linear endobronchial ultrasound-guided transbronchial needle aspiration (EBUSTBNA) is an important minimally invasive procedure for non-small cell lung cancer (NSCLC) staging. It is also a valid method for diagnosing extraluminal lesions adjacent to the tracheobronchial tree.

Aim: To evaluate our EBUS-TBNA performance regarding diagnostic yield, safety and learning curve for lung cancer diagnosis and staging.

Material and methods: All patients undergoing EBUS-TBNA for lung cancer diagnosis or staging were included. They were divided into three different groups: paratracheal and parabronchial masses sent for diagnosis (Group 1); peripheral lung lesions with abnormal mediastinal lymph nodes sent for diagnosis and staging (Group 2); NSCLC patients sent for mediastinal staging (Group 3). The learning curve was assessed for yield, accuracy, procedure time, size and number of lesions punctured per patient.

Results: A total of 179 patients were included and 372 lesions were punctured. The overall yield and accuracy were 88% and 92.7%, respectively. In Group 1, EBUS-TBNA was performed in 48 patients and sensitivity was 86.1% and accuracy was 87.5%. For the 87 patients included in Group 2, yield was 86.7%, accuracy was 93.1% and cancer prevalence was 51.7%. The diagnostic yield and accuracy in Group 3 was 95% and 97.7% respectively. EBUS-TBNA practice led to an increase number of sites punctured per patient in a shorter time, without complications.

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Conclusion: EBUS-TBNA is an effective method for diagnosing and staging lung cancer patients. The procedure is clearly safe. Handling and performance improves with the number of procedures executed.

PALAVRAS-CHAVE
Neoplasia do pulmão;
Ecoendoscopia brônquica;
Punção aspirativa;
Diagnóstico;
Estadiamento;
Curva de aprendizagem

Contributo da punção aspirativa transbrônquica guiada por ecoendoscopia brônquica no diagnóstico e estadiamento de cancro do pulmão em 179 doentes.

Resumo
Introdução: A punção aspirativa transbrônquica guiada por ecoendoscopia brônquica linear (EBUS-TBNA) é um importante procedimento minimamente invasivo para o estadiamento do cancro do pulmão de não pequenas células (CPNPC). É, também, um método válido para o diagnóstico de lesões extraluminais adjacentes à árvore traqueobrônquica.
Objetivo: Avaliar o nosso desempenho na execução de EBUS-TBNA relativamente à rentabilidade diagnóstica, segurança e curva de aprendizagem no diagnóstico e estadiamento do cancro do pulmão.
Material e métodos: Incluímos todos os doentes submetidos a EBUS-TBNA para diagnóstico ou estadiamento de neoplasia pulmonar. Estes foram posteriormente divididos em 3 grupos diferentes: diagnóstico de massas paratraqueais e parabrônquicas (Grupo 1); diagnóstico e estadiamento de lesões pulmonares periféricas com gânglios mediastínicos aumentados (Grupo 2); estadiamento de doentes com CPNPC (Grupo 3). A curva de aprendizagem foi avaliada em função da sensibilidade diagnóstica, precisão, duração do procedimento, tamanho e número de lesões puncionadas por doente.
Resultados: Foram incluídos 179 doentes e puncionadas 372 lesões. A sensibilidade e precisão globais foram 88% e 92.7%, respetivamente. No Grupo 1, 48 doentes foram submetidos ao procedimento com uma sensibilidade de 86,1% e precisão de 87,5%. No Grupo 2, com 87 doentes, a sensibilidade foi de 86,7%, a precisão de 93,1% e a prevalência de neoplasia de 51,7%. No Grupo 3, a sensibilidade e precisão foram 95 e 97,7%, respetivamente. A prática de EBUS-TBNA conduziu a um maior número de locais puncionados por doente, em menor período de tempo, sem complicações.
Conclusão: EBUS-TBNA é um método eficaz para o diagnóstico e estadiamento de doentes com cancro do pulmão. É claramente um exame seguro. O número de procedimentos realizados melhora o manuseamento e desempenho da técnica.

Introduction

Lung cancer is the world's leading cause of cancer-related mortality[1]. It is the fourth most common cancer in Portugal with an estimated incidence of 41.9 per 100.000 inhabitants in males and 8.5 per 100.000 inhabitants in females and the second highest cause of cancer death with a mortality rate for men and women of 41.8 and 7.8 per 100.000 person-years, respectively[2]. The high incidence, the mortality and socioeconomic burden makes it obligatory that every effort is made to improve disease prevention, prompt diagnosis and correct staging.

Chest radiographs are often the first exam to be performed to evaluate a suspicious lung lesion. However a contrast thoracic and upper abdomen CT scan is also crucial to give the anatomical view of the thoracic structures and detect the precise location and extent of the disease. More recently fluorodeoxyglucose positron emission tomography (PET) has become increasingly important in lung cancer diagnosis and staging[3]. PET and integrated PET-CT provide anatomical and metabolic information about the primary lung lesion, mediastinal lymph nodes and distant metastasis. Although these exams present important clues, a definitive diagnosis is only achieved by histological or cytological examination.

Flexible bronchoscopy with its accessory sampling techniques (biopsy, brushing and lavage) provides a high diagnostic yield in central endoluminal tumors compared to peripheral lesions and CT-guided transthoracic needle aspiration (CT-TTNA) has a high sensitivity when the lesion is located in the periphery of the lung[4]. If the tumour is centrally located and extraluminal (paratracheal or parabronchial lesions) these procedures have a limited role and conventional transbronchial needle aspiration (TBNA) is a valid option. In clinical practice this is an underutilized method owing to the risk of complications, the high cost of needles and, last but not least, the variable yield, because non-ultrasound guided TBNA is operator dependent[5]. The fact that TBNA can be used simultaneously as a

diagnostic and staging tool make it very attractive to the pulmonologist. In order to improve sensitivity and diminish the risks of complications, technological efforts have been made to perform the procedure under real-time guidance and endobronchial ultrasound (EBUS) guided TBNA has emerged as an important minimally invasive exam to stage and diagnose lung cancer. The procedure started in expert centers and immediately its efficacy and safety for mediastinal lymph node staging was appreciated. Current guidelines advocate EBUS-TBNA as one of the options for minimally invasive mediastinal staging and lung cancer diagnosis[6-9]. Initially, it was reported that a short training of about 10 cases was enough to become competent in EBUS-TBNA[10] but a subsequent study has suggested that the learning curve is longer and also experienced bronchologists vary in their skill and speed of learning[11].

The aim of the study was to evaluate our EBUS-TBNA performance in relation to diagnostic yield, safety and the learning curve for the diagnosis of pulmonary nodules or masses and mediastinal lymph node staging.

Material and Methods

Patients

Throughout a 30 month period, all consecutive patients referred for EBUS-TBNA with the purpose of diagnosing or staging lung cancer were prospectively included. Exclusion criteria were the following: inability to tolerate general anaesthesia; the target lesion was not visualized by EBUS (e.g. aerated lung parenchyma interposition); no lymph node puncture during the procedure (e.g. due to vessel interposition); patients undergoing EBUS for a highly suspicious benign condition; absence of follow-up after non-diagnostic EBUS-TBNA.

The patients were sent from different hospitals with three different clinical settings: Group 1 with a paratracheal or parabronchial mass detected in a thorax CT scan and without a definitive diagnosis after being submitted to conventional bronchoscopy or CT-TTNA (sent for diagnosis); Group 2 with a suspicious peripheral lung cancer lesion and lymph nodes with a CT scan short axis >10 mm and/or a positive PET scan (sent simultaneously for diagnosis and staging); Group 3 with histologically confirmed non-small cell lung cancer (NSCLC) without evidence of distant metastasis sent for lymph node staging (lymph nodes >10 mm in short axis on CT or PET positive).

A thorax CT scan was mandatory before the procedure. The decision to perform PET or PET-CT was left to the discretion of the referring physician. The study was approved by the ethical committee of our institution and a written consent was obtained.

Procedures

EBUS-TBNA was performed under general anaesthesia with a flexible ultrasound bronchoscope (BF-UC160F, Olympus, Japan) in an outpatient setting. All the procedures were performed by one main operator (AB) who had formal training in EBUS-TBNA and in some of them another pulmonologist assisted (DF or LC). The tests were carried out as previously described [12]. The endoscope was introduced through the tracheobronchial tree and the 7.5 MHz transducer was placed in contact with the airway mucosa. The ultrasound images were visualized using specific equipment (EU-C60, Olympus, Japan), a dedicated needle (NA-201SX-4022, Olympus, Japan) was placed inside the target structure, the internal stylet was removed and negative pressure was applied to the connecting syringe. Subsequently, material was collected by repetitive back and forward movements (Figure 1). N3 nodes were punctured first, followed by N2 and lastly ipsilateral hilar N1 nodes, if appropriate. They were classified according to the 7th international TNM staging system[13]. There were at least four needle passes per lesion. Additional punctures were performed when the macroscopic appearance of the acquired material was not satisfactory. The aspirated specimens were expelled into 50% alcohol and lastly a needle wash was made into a phial containing cytolyt preservative solution (Hologic Iberia). A cytophatologist was not present during the exam and rapid on-site examination (ROSE) was not executed. The samples were homogenized in a vortex and centrifuged. The pellet was fixed in preservcyt solution (Hologic Iberia) and processed using the T2000 ThinPrep System (Hologic Iberia) to obtain a single preparation that was stained with the Papanicolaou method. Whenever possible, immunohistochemistry was performed to acquire additional information.

The samples were classified as positive if they provided a clear diagnosis of malignancy or a benign specific disease such as granulomatous findings, and these results were established as evidence. In cases where a definitive diagnosis could not be reached because of insufficient cellular material, absence of malignant cells or suspicious but not conclusive specimens, subsequent surgical diagnostic or staging procedures were recommended, namely mediastinoscopy, thoracoscopy or thoracotomy, and the patient was referred to the thoracic surgery department (RB, CR). If the patient was not fit or refused the suggested interventions, a final diagnosis excluding malignancy was made after 12 months of clinical follow-up.

Statistical methods

The data was prospectively collected and entered into an excel database. It was analyzed with the SPSS statistical software package (SPSS 18.5, Chicago, USA). A descriptive analysis was carried out in which categorical variables were expressed as absolute and relative frequencies and continuous variables as means and standard deviation.

For statistical purposes it was assumed that a positive EBUS-TBNA result for malignancy was a true positive. A benign disease obtained by EBUS-TBNA or confirmed by subsequent methods (invasive or 12 month clinical and radiological follow-up) was a true negative. A negative EBUS-TBNA result that was later confirmed to be positive for malignancy by other invasive methods in the same anatomic location was a false-negative. Sensitivity, specificity, accuracy, and positive (PPV) and negative predictive values (NPV) were calculated using the standard formulas.

To assess the learning curve we evaluated groups of 30 sequential patients, in relation to diagnostic accuracy, sensitivity, complications, procedure time, size and number of lymph nodes or lesions punctured per patient. T-Student

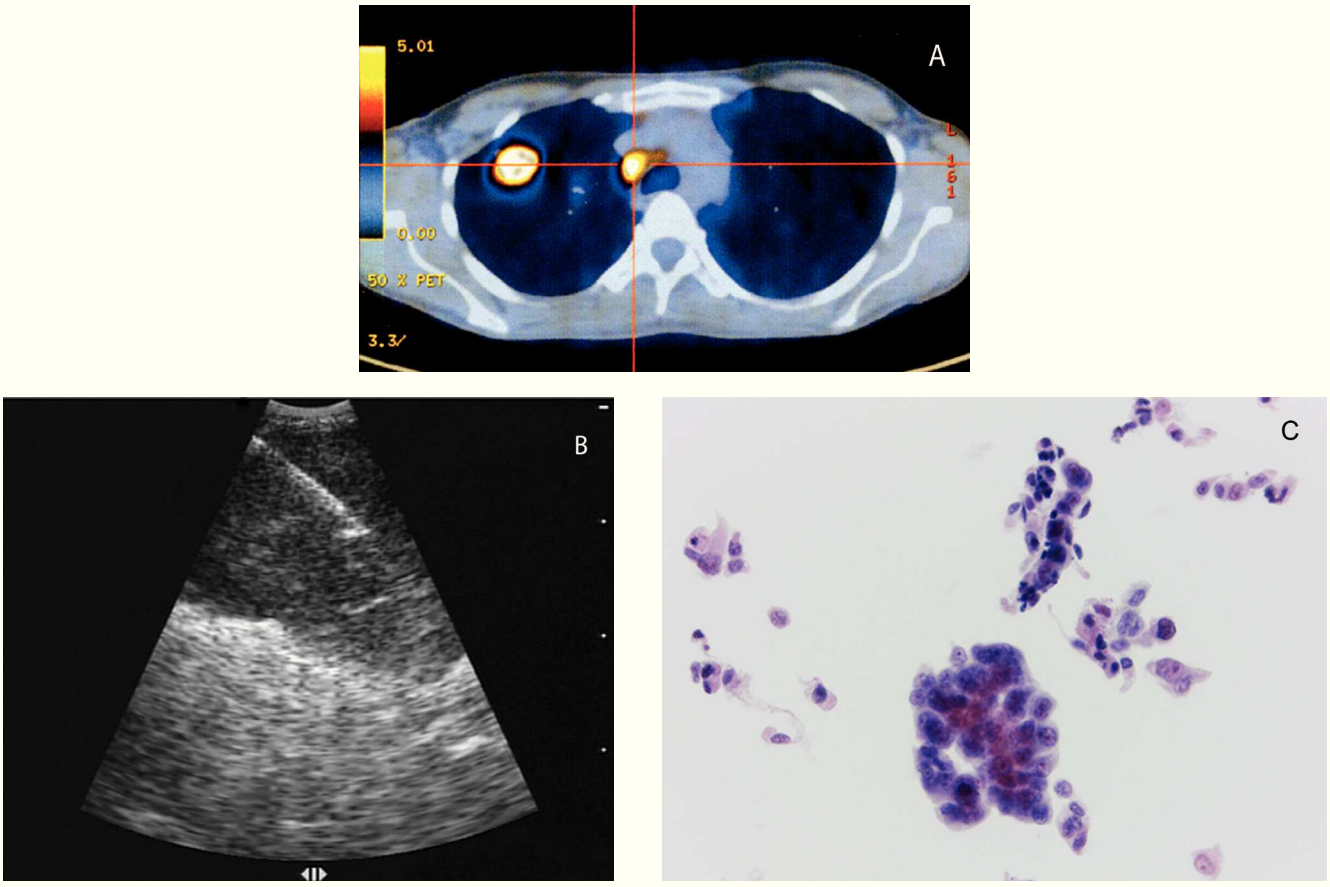

Figure 1 Peripheral right upper lobe lesion with PET positive 2R lymph node station (A); needle inside enlarged hypoecogenic heterogeneous mediastinal lymph node (B); cytological diagnosis of lung adenocarcinoma 400× (C).

and proportion tests were performed to verify if there was a statistical difference between these groups.

Results

Two hundred and six patients were referred for EBUS-TBNA and 187 underwent the procedure for lung cancer diagnosis and/or staging at our institution. Eight patients (4.3%) were excluded based on the exclusion criteria described above. A total of 179 patients met the inclusion criteria (mean age 61.9±11.5 years, range 36-88, 71.5% males) and 126 were current or former smokers (55.9±25.2 packs-year, range 8-140).

All procedures were done under general anaesthesia. A laryngeal mask was used in 26 cases (14.5%), rigid bronchoscope in 10 cases (5.6%) and endotracheal intubation in 143 cases (79.9%). Total procedure mean time was 35 ± 12 minutes. Three hundred and seventy two lesions were punctured by EBUS-TBNA (sonographic mean size 16.3±6mm, range 5-36mm) and the average number of needle passes for each site was 5.8±2.7 times. No complications associated to the technique were experienced however one patient failed extubation after general anaesthesia and was mechanically ventilated for 48 hours until successful weaning, later found out to be due to muscular weakness related to a Lambert-Eaton paraneoplastic syndrome.

The clinical settings for EBUS-TBNA are displayed in Table 1. In Group 1, EBUS-TBNA was performed in 48 patients and whenever possible, the lesion was punctured using different locations (e.g. right upper lobe mass was punctured through the trachea and right main bronchus). The sensitivity for diagnosing lung cancer in this group was 86.1% and accuracy was 87.5%. In two cases the samples were inadequate and further invasive tests excluded malignancy in one patient and confirmed the presence of lung adenocarcinoma with extensive necrosis in another (Table 2). The eight negative cases were submitted to surgery that established the presence of non-Hodgkin lymphoma (n=1), large cell neuroendocrine tumor (n=1), thoracic paraganglioma (n=1), squamous cell carcinoma (n=2), mediastinal goiter (n=1), cicatricial or inflamatory tissue (n=1) and sarcoidosis (n=1).

Group 2 included 87 patients and a total of 195 lymph nodes were punctured at the level of stations right upper paratracheal 2R (n=8), left upper paratracheal 2L (n=5), right lower paratracheal 4R (n=47), left lower paratracheal 4L (n=18), subcarinal 7 (n=64), right hilar 10R (n=25), left hilar 10L (n=20), right interlobar 11R (n=2) and left interlobar 11L (n=6). The sensitivity for this group was 86.7%, specificity was 100%, NPV was 88%, EBUS accuracy was 93.1% and cancer

Table 1 EBUS-TBNA findings and performance

	Group 1 (diagnosis)	Group 2 (diagnosis and staging)	Group 3 (staging)	Overall
Patients (n)	48	87	44	179
PET scan (n)	13	32	30	75
Punctures sites (n)	84	195	93	372
EBUS-TBNA findings	ADC = 14 SCC= 9 NSCLC = 3 SCLC = 11 Thoracic duct cyst = 1 Negative sample = 8 Inadequate sample = 2	ADC = 22 SCC = 4 NSCLC = 7 SCLC = 5 Thyroid carcinoma = 1 Sarcoidosis = 9 Tuberculosis = 6 Negative sample = 32 Inadequate sample =1	ADC N2/N3= 11 SCC N2/N3= 8 Negative sample =24 Inadequate sample = 1	
Cancer prevalence	89.6%	51.7%	45.5%	60.3%
Sensitivity	86.1%	86.7%	95%	88%
Specificity	100%	100%	100%	100%
NPV	45% (95% CI 21-72%)	88% (95% CI 75-91%)	96% (95% CI 80-99%)	85% (95% CI 75-91%)
PPV	100% (95% CI 91-100%)	100% (95% CI 91-100%)	100% (95% CI 83-100%)	100% (95% CI 96-100%)
EBUS accuracy	87.5%	93.1%	97.7%	92.7%

NPV – negative predictive value, PPV – positive predictive value, ADC – adenocarcinoma, SCC – squamous cell carcinoma, NSCLC – non small cell lung cancer, SCLC – small cell lung cancer.

prevalence was 51.7%. One patient with an inadequate sample was sent for mediastinoscopy and the final diagnosis was lung adenocarcinoma. Of the 32 negative cases, 7 patients refused or had no conditions for more invasive procedures and 12 month follow-up proved lesion stability. All other 25 cases were submitted to subsequent surgical procedures (mediastinoscopy, video-assisted thoracoscopy or thoracotomy). In 16 cases, these interventions confirmed the absence of malignancy and the presence of normal or reactive lymphoid tissue (n=14) and sarcoidosis (n= 2). Four patients, with mediastinal lymph nodes >10mm short-axis in thorax CT, were submitted to thoracotomy (lobectomy plus lymph node dissection) and the pathological staging, obtained in the same anatomical locations, proved that the previously EBUS sampled lymph nodes were negative (N0, reactive lymphoid tissue) although the primary pulmonary lesion was positive for lung adenocarcinoma (n=3) and squamous cell carcinoma (n=1). These cases were considered to be true-negatives since the EBUS-TBNA targeted lymph nodes that did not show malignant cells. Among the other EBUS cytological negative cases, the final surgical diagnosis was lymph node metastasis of breast cancer (n=1), renal cell cancer (n=1), atypical carcinoid tumor (n=1) and lymphoma (n=2).

EBUS-TBNA mediastinal staging was done in 44 patients with confirmed NSCLC (Group 3) and lymph node stations 2R (n=2), 2L (n=4), 4R (n=16), 4L (n=12), 7 (n=35), 10R (n=17) and 10L (n=7) were assessed. Diagnostic yield and accuracy were 95% and 97.7%, correspondingly. One inadequate sample case was submitted to mediastinoscopy that

Table 2 Final results of EBUS-TBNA negative and inadequate samples by group of patients

	Group 1 (diagnosis)	Group 2 (diagnosis and staging)	Group 3 (staging)
True-negative	Cicatricial inflammatory tissue (n=2) Mediastinal goiter (n=1) Sarcoidosis (n=1)	Follow-up with lesion stability (n=7) Normal or reactive lymphoid tissue (n=18) Sarcoidosis (n=2)	Normal or reactive lymphoid tissue (n=24)
False-negative	Lung adenocarcinoma (n=1) Non-Hogdkin lymphoma (n=1) Large cell neuroendocrine tumor (n=1) Thoracic paraganglioma (n=1) Squamous cell carcinoma (n=2)	Lung adenocarcinoma (n=1) Breast cancer (n=1) Renal cell cancer (n=1) Atypical carcinoid tumor (n=1) Lymphoma (n=2)	Lung adenocarcinoma (n=1)

Table 3 EBUS-TBNA learning experience

	Procedures					
	1-30	31-60	61-90	91-120	121-150	151-179
Lesion size (mm)	16.9±5.6	17.0±6.9	16.4±5.8	16.8±5.9	15.7±6.2	15.4±5.6
Procedure time (min)	39±13	42±13	38±14	33±10	32±10	30±7
Sites punctured per patient (n)	1.9±0.7	1.8±0.7	2.0±0.9	2.4±1.0	2.2±0.9	2.2±1.0
Sensitivity	81.0%	76.2%	95.5%	91.7%	85.7%	100%
Negative predictive value	71.4%	64.3%	88.9%	94.7%	88.9%	100%
Cancer prevalence	66.7%	70.0%	73.3%	40.0%	46.7%	65.5%
EBUS accuracy	86.6%	83.0%	96.7%	96.7%	93.3%	100%
Complications (n)	0*	0	0	0	0	0

* One patient was mechanically ventilated for 48h due to Lambert-Eaton paraneoplastic syndrome

exposed N2 disease (adenocarcinoma). All patients with a negative EBUS-TBNA cytology underwent mediastinoscopy (n= 16) or thoracotomy (n=8) that did not revealed lymph node metastasis.

EBUS-TBNA overall yield and accuracy were 88% and 92.7%, respectively. The results obtained results helped to prevent more invasive procedures in 112 patients and consequently reduced the potential number of hospital admissions.

Table 3 shows the learning curve for groups of 30 consecutive patients. We found that there was a trend to puncture smaller lesions (not significant). The number of lymph nodes punctured per patient was statistically different after the first 60 procedures (p=0.03) plus it further augmented after 90 procedures (p=0.008) and occurred progressively in a shorter period of time. EBUS-TBNA accuracy, sensitivity and NPV gradually increased with the number of procedures performed although there were no statistical differences between groups.

Discussion

Our results confirm that EBUS-TBNA is a sensitive, accurate and safe technique for diagnosing and staging lung cancer.

EBUS-TBNA was able to establish the diagnosis of lung cancer in a high percentage of cases (86.1%) that had previously been submitted to a non-diagnostic bronchoscopy or CT-TTNA and avoided surgical diagnostic procedures. Similar results were obtained in a study by Tournoy et al.[14], in which 60 patients with centrally located intrapulmonary masses were diagnosed by EBUS-TBNA with a reported sensitivity, NPV and accuracy of 82%, 23% and 77%, respectively. The yield in patients without a definite lung cancer diagnosis is lower than to NSCLC patients referred for staging. Anatomical issues, such as the presence of inflammatory, fibrotic or necrotic tissue around the tumor may explain the lower sensitivity and this hypothesis is supported by the EBUS false-negative case that had a final diagnosis of extensive necrotic lung adenocarcinoma. In order to exceed this issue, we made several punctures in different sites of the lesion. The low NPV (45%) is certainly related to pathologies that are hard to diagnose by cytology (e.g. lymphoma, paraganglioma) so a negative EBUS-TBNA result should always be confirmed by more invasive methods. Recently a study has reported higher diagnostic sensitivity and NPV (97.2%, 85.7% respectively) in a population of 126 patients with suspected lung cancer lesions[15]. This study included seventy-three patients (60%) with central tumors but the lung mass could only be punctured in 41 cases[15]. The higher yield may be due to a high prevalence of lung cancer as well as by the selection of a heterogeneous group of patients, some with endobronchial tumors which could overestimate the results.

Concerning Group 2 patients, lung cancer prevalence was 51.7% reflecting the probability of other non-malignant diseases involving lung parenchyma and mediastinal lymph nodes. Ernst et al.[16] reported an EBUS-TBNA diagnostic sensibility of 91% and NPV of 92.4% in 213 patients with suspected NSCLC and enlarged CT or PET positive hilar lymph nodes. Compared to these previous studies, we can only speculate that the lower sensitivity of our work (86.7%) may be due to the absence of a PET scan in a significant percentage of patients, and the lower cancer prevalence. The present trial proves that in selected cases it is possible to achieve simultaneously a lung cancer diagnosis and staging with a simple minimally invasive technique.

Performance of EBUS-TBNA for mediastinal staging of patients with known NSCLC has been extensively described and our results are consistent with previously published reports. It is important to emphasize that in the 44 NSCLC patients that constituted Group 3, all had radiological mediastinal lymph node enlargement but only 30 (68.2%) had done a PET scan. According to international guidelines every patient sent for EBUS-TBNA should have performed a correct non-invasive mediastinal staging[8]. Although PET is an important staging exam, the notion that positive mediastinal lymph nodes are the result of malignant involvement carries the risk of excluding patients from potentially curative surgery. Yasufuku's work[17] compared CT, PET and EBUS-TBNA for lung cancer lymph node staging and sensitivities were 76.9%, 80.0% and 92.3%, specificities were 55.3%, 70.1% and 100%, and diagnostic accuracies were 60.8%, 72.5% and 98%, respectively. It proves that is fundamental to confirm imaging abnormalities with subsequent invasive methods, if the result alters the clinical management,

since this approach provides a better lung cancer staging and treatment. In fact, in our population N2/N3 prevalence was only 45.5% and surgical treatment could be offered to N0-1 patients. Ultrasonography can, in selected cases, replace surgical techniques, namely mediastinoscopy, since it has a similar diagnostic yield, it is able to offer a wide window to the mediastinum, does not require hospital admission, and has lower morbidity and costs[18-20].

While EBUS-TBNA requires formal training and practice, it is quite safe for the patient. In our series, 372 lesions were punctured and there were no serious complications related to the procedure. In the first thirty procedures sensitivity and accuracy were high and the trend was for continual improvement as the number of exams increased. A correct interpretation of the ultrasound images, accurate puncture location and acquisition of adequate samples in terms of quality and quantity is crucial[21], in addition to having an experienced pathologist to analyze the samples. Previous studies have shown that the presence of a pathologist during the procedure can play an essential role since it reduces the number of inadequate samples, false-negatives and punctures with the advantage of shortening procedure time[22]. In view of the fact that we did not perform ROSE and there was no pathologist available during the procedure we did at least four punctures per lesion to maximize yield, according to published data[23]. In the real-life clinical setting it is of major importance to establish a good communication between the operator and pathologist to acquire a high EBUS-TBNA efficacy.

Another important aspect of the present study is that the procedures were essentially performed by a single chest physician and this may explain a more rapid learning curve. We may assume that experienced bronchologists after proper training may achieve a short EBUS learning curve.

In conclusion, in our experience EBUS-TBNA is a safe, effective and practical technique for obtaining cytological samples from lymph nodes or masses adjacent to the main airways, with clinical impact in lung cancer diagnosis and staging. The potential of EBUS makes it a very important tool in the modern bronchoscopy suite.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study received sufficient information and gave their written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflict of interests

All authors declare that they do not have any conflict of interest related to this work.

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