A retrospective study of endobronchial ultrasound transbronchial needle aspiration *versus* conventional transbronchial needle aspiration in diagnosis/staging of hilar/mediastinal lymph node in lung cancer: Which role in clinical practice?

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Abstract

The conventional-trans bronchial needle aspiration (c-TBNA) has been the first procedure for sampling hilar/mediastinal lymph node for the diagnosis/staging of lung cancer. In the last decade the endobronchial ultrasound trans bronchial needle aspiration (EBUS-TBNA) was introduced in clinical practice and became the first-choice exam in diagnosis and staging of lung cancer. The aim of this study was to compare the diagnostic accuracy (DA), sensitivity and adequacy of c-TBNA and EBUS-TBNA. It was a retrospective and observational multicenter study. The first endpoint was diagnostic accuracy of EBUS-TBNA *versus* c-TBNA. The secondary end-points were sensitivity and adequacy. Two hundred and nine consecutive patients underwent the procedure, 99 EBUS-TBNA and 110 c-TBNA. When lymph nodes with short axis <2 cm the diagnostic accuracy for correct diagnosis was 94.2% in EBUS-TBNA group and 89.7% in c-TBNA group (p=0.01); the sample adequacy was 70.3% and 42%, respectively (p=0.01); the sensitivity was 93% (95% CI, 82-98%) and 86.4% (95% CI, 67.6-95.6%), respectively (p=0.002). In lymph nodes with short axis ≥2 cm the diagnostic accuracy was 95.7% in EBUS-TBNA group and 93% in c-TBNA group (p=0.939); the sample adequacy was 68.7% and 68.3%, respectively (p=0.889); the sensitivity was 95.1% (95% CI, 83-99%) and 92.1%, respectively (95% CI, 78.7-97.7%) (p=0.898). The EBUS-TBNA in patients with lymph nodes size <2 cm presented a statistically significant difference in the DA, adequacy and sensitivity compared to c-TBNA procedure, while there were no significant differences in the DA, adequacy and sensitivity between EBUS-TBNA and c-TBNA in patients with lymph node size ≥2 cm. The results of our study indicated that the EBUS-TBNA should be the first-choice procedure for the diagnosis/staging in lung cancer patients with lymph node size <2 cm. In patients with lymph node size ≥2 cm, instead, both procedures can be used for the diagnosis/staging of lung cancer.

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Introduction

For many decades, conventional trans bronchial needle aspiration (TBNA) has been the first-choice method for the study of hilar/mediastinal lesions, particularly for the diagnosis and staging of lung cancer. More recently, a new method, Endobronchial Ultrasound Transbronchial Needle Aspiration (EBUS-TBNA), has been introduced in clinical practice for the diagnosis and staging of malignant conditions such as lung cancer, lymphoma or metastasis and for other diseases, such as tuberculosis and sarcoidosis [1,2]. This method allows to visualize in real-time the sample of the lymph nodes and the neoplastic mass during bronchoscopy with a linear ultrasound probe into the tip that guides the transbronchial needle aspiration. This technique has improved the diagnostic sampling results of the mediastinal and hilar disease, particularly in lung cancer [3]. In most studies the EBUS presents a high sensitivity from 80% up to 96% [4-8]. The recent European guidelines recommended the use of EBUS or EUS, or combined EBUS/EUS as the first step in the diagnosis/staging in patients with suspicion of lung cancer [1]. However, the EBUS is not available in several hospitals, has higher cost compared to c-TBNA and needs a longer training and learning curve for bronchoscopist in comparison with conventional-trans bronchial needle aspiration (c-TBNA) [9,10]. So, the aim of this study was to compare c-TBNA and EBUS-TBNA in sampling of lymphadenopathies and to evaluate the role of C-TBNA in the era which see EBUS-TBNA as the first-choice procedure in the lung cancer staging.

Materials and Methods

The study was a multicenter retrospective and observational study conducted at the Pulmonary Diseases Unit of the Health Agency "ULSS 2 Marca Trevigiana", District of Vittorio Veneto, and at the Pulmonary Disease Unit of the University Health Agency of Trieste between January 2016 and April 2017. The study was approved by the Institutional Ethics Committee of the Province Treviso and Belluno (Approval n. 2332).

Overall, 209 consecutive patients underwent EBUS-TBNA or C-TBNA from January 2016 to April 2017 to diagnosis/staging malignant lung cancer.

Chest CT was mandatory before the procedure and lymph nodes (LNs) were considered potentially malignant if the short axis diameter was >10 mm. Specifically, we adopted a selective assessment for the staging according to Detterbeck's classification [11]. The choice of using EBUS-TBNA or C-TBNA depended on the expertise of the operator to perform the procedure. We evaluated baseline patient characteristics, complications, and final cytological and histological diagnoses.

The c-TBNA was performed using the standard flexible bronchoscope (models BF-T180; Olympus; Tokyo, Japan) with a Wang 22-gauge cytology needle. All the procedures were performed by expert bronchoscopists. The exams were conducted under minimal sedation with only midazolam and spontaneous breathing. The number of needle passes ranged from 3 to 5. Also EBUS-TBNA was performed by an experienced bronchoscopist. The EBUS (model BF-UC180F; Olympus Corp., Tokyo, Japan) was introduced orally and the needle used was 22-gauge (model NA-201SX-402; Olympus Corp.). Three needle passes per each lymphadenopathy were obtained. EBUS-TBNA were performed in a dedicated bronchoscopic room under deep sedation (Propofol + Fentanyl), if the anesthetist was available, otherwise moderate sedation (Pethidine + Midazolam) or minimal sedation (only Midazolam). The sample obtained was smeared on clean glass slides and fixed in 95% ethanol. Then the sample was processed for the definitive cytologic diagnosis. The specimens could result positive for malignancy, negative for malignancy or inadequate when lymphocytes were not found. Part of the material, in formalin sample cups, was used for definitive histological diagnosis. Moreover, TBNA was subcategorized and analyzed based on the LN size (≥ 2 cm and <2 cm) and LN station, particularly for subcarinal (station 7) in according to the IASLC lymph node classification [12].

The primary end-point was to compare the diagnostic accuracy of EBUS-TBNA *versus* C-TBNA for all stations and then specifically for the station 7. The diagnostic accuracy of a particular procedure can be expressed in terms of sensitivity and specificity in according to definition of Reitsma *et al*. [13]. The secondary end points included sample adequacy, sensitivity and specificity. The sample was considered adequate if it presented cells to diagnose a specific malignant condition (*i.e*., diagnosis of cancer, metastasis), or a preponderance of lymphocytes. The inadequate sample was considered a sample with blood, a preponderance of bronchial cells or other parenchymal cells, a minority or no lymphocytes.

Therefore, the specimen was considered as "true positive" if the sample was positive for malignancy; as "true negative" if the sample was negative for malignancy with lymphocytes confirmed by surgery or 6 months clinical and radiological follow-up by CT demonstrating stability or decrease in the size of lymph node. As "false negative" were defined patients subsequently diagnosed with malignant or other conditions at later investigations (*i.e*., thoracic surgery, exam repetition) or by radiological follow-up with an increase size of lymph nodes.

The statistical analyses were used to describe the study population. Pearson's chi-squared test (or Fisher's exact test) and *t*-test (or Wilcoxon's rank-sum test) were used to determine the significance of differences between the study groups. Statistical analysis was performed with PRIMIT statistical software.

Results

Overall, 209 consecutive patients underwent EBUS-TBNA or C-TBNA from January 2016 to April 2017 to diagnosis/staging malignant lung cancer. Ninety-nine patients underwent the EBUS-TBNA and 110 patients underwent c-TBNA.

The main baseline characteristics of the study population are summarized in Table 1. Overall, the mean age was 67.9 (±10.7) years in EBUS group and 66.7 (±13.2) in conventional group. The most frequently lymph node station sampled was station 7 (EBUS-TBNA 39.5% and c-TBNA 36.8%). There were no significant differences in baseline characteristics between the study arms. There were no major complications or escalation of care related TBNA procedures.

The final results were malignancy in 111 patients (adenocarcinoma, n=62; squamous cell carcinoma, n=21; small cell carcinoma, n=22; NSCLC, n=5; neuroendocrine large cell carcinoma, n=1) and in other patients the lymph nodes were not metastatic.

The TBNA had a diagnostic purpose in 50 patients (22 in EBUS group and 28 in conventional group) and had a staging aim with selective assessment in 159 patients (77 in EBUS group and 82 in conventional group) (p=0.701). The diagnostic accuracy for lymph nodes with short axis <2 cm of EBUS-TBNA and c-TBNA was respectively 94.2% and 89.7% (p=0.01) (Table 2). The sensitivity and adequacy for lymph node with short axis <2 cm of EBUS-TBNA and c-TBNA were respectively 93% (95% CI, 82-98%) and

Table 1. Baseline characteristics of study population.

	EBUS-TBNA n=99	C-TBNA n=110	p value
Age, years (mean±SD)	67.9 (10.7)	66.7(13.2)	0.483
Male sex	65	70	
Nodal station	141	132	
Mean lymph node size ± SD	2.18 (0.83)	2.10 (0.79)	0.409
<2 cm	74	69	
≥2 cm	67	63	
Lymph nodes station			
7	57	50	0.865
4R	40	43	0.670
4L	11	10	0.871
10R	17	20	0.634
10L	3	4	0.939
11R	9	3	0.197
11L	4	2	0.753
Adenocarcinoma	35	27	
Squamous cell carcinoma	11	10	
Small cell carcinoma	13	9	
Non-small cell lung carcinoma	2	3	
Neuroendocrine large cell carcinoma	1	0	

86.4% (95% CI, 67.6-95.6%) (p=0.002), 70.3% and 42% (p=0.01) (Table 2). There were a statistically significant differences for all end points. The diagnostic accuracy for lymph node with short axis ≥2 cm of EBUS-TBNA and c-TBNA was 95.7% and 93%, respectively (p=0.939) (Table 3). The sensitivity and adequacy for lymph node with short axis ≥2 cm of EBUS-TBNA and c-TBNA was respectively 95.1% (95% CI, 83-99%) and 92.1% (95% CI, 78.7-97.7%) (p=0.898), 68.7% and 68.3% (p=0.889) (Table 3). Although the EBUS-TBNA results were higher than those of c-TBNA, they were not significantly different. The subgroup analysis about subcarinal stations are summarized in Tables 4 and 5.

In lymph nodes of the station 7 with short axis <2 cm, the diagnostic accuracy of EBUS-TBNA and c-TBNA was respectively 96.4% and 90% (p=0.005); the sensitivity and the adequacy were respectively 95.6% (95% CI, 78.7-99.6%) and 87.5% (95% CI, 51.5-98.9%) (p=0.024) and 84.8% and 45.5% (p=0.005). There was a statistically significant difference for all end points (Table 4). Instead, in lymph nodes of the station 7 with short axis ≥ 2cm, the diagnostic accuracy of EBUS-TBNA and c-TBNA was respectively 94.4% and 95% (p=0.945); the sensitivity and the adequacy were respectively 93.3% (95% CI, 69.2-99.5%) and 94.1% (95% CI, 71.9-99.6%) (p=0.845) and 75% and 71.4% (p=0.981). There was no significant difference (Table 5).

Discussion

Conventional-TBNA for more than 4 decades has been considered a safe procedure for the studying of mediastinal lymphadenopathies in the diagnosing/staging of lung cancer, lymphoma or metastasis and benignant conditions as tuberculosis and sarcoidosis. The major findings of our study showed that the c-TBNA represents a valid alternative to EBUS in adenopathies ≥2 cm, instead the EBUS was the first-choice procedure for lymphadenopathies with size <2 cm.

This procedure presents an important limitation because it does not allow direct vision of the lesion, while EBUS-TBNA allows to visualize and locate the target LN and then perform the needle aspiration with real time ultrasound guidance. Hence, the aim of our study was to compare the role of c-TBNA and EBUS-TBNA in sampling hilar/mediastinal lymph nodes to staging lung cancer.

There are a lot of studies, in literature, that demonstrated the superiority of EBUS technique in terms of sensitivity, accuracy and adequacy compared to conventional TBNA. The Adams systematic review and meta-analysis showed that EBUS-TBNA had an excellent test performance and specificity focused on mediastinal node staging [14]. Another important systematic review and meta-analysis by Gu showed how the EBUS-TBNA was an accurate, safe and cost-effective tool in lung cancer staging [15]. The Yang meta-analysis and systematic review carried out a high degree of diagnostic accuracy of EBUS-TBNA for diagnosing intrathoracic lymph node metastases in patients with extrathoracic malignancies. These results were obtained from studies of moderate quality [16]. Stoll study showed that the EBUS-TBNA was an optimal modality for diagnosing and staging in lung cancer patients in comparison to c-TBNA. In lymph node sampling the sensitivity of EBUS-TBNA was higher than C-TBNA (85.2% *vs* 54.5%) [17]. On the contrary, in Jiang study there was no significant difference in the diagnostic yield between c-TBNA and EBUS-TBNA performed sequentially [18].

In literature, two other studies compared the diagnostic yield of these two techniques, but in these cases were compared c-TBNA *vs* EBUS-guided TBNA (with radial US probe and not with linear probe). The study of Bellinger *et al*. [19] concluded that EBUS-TBNA and c-TBNA are complementary techniques, and the choice of TBNA methods must be based on a cost-effective choice, lymph node size, and lymph node location. The Arslan study showed that diagnostic yield of EBUS-guided TBNA was superior to c-TBNA's yield at stations other than subcarinal region [20].

The study of Bonifazi *et al*. [21] was the first prospective,

Table 2. Diagnostic accuracy, sensitivity, specificity and adequacy in lymph nodes <2 cm.

Size <2 cm	EBUS-TBNA	C-TBNA	p value
Number	74	69	0.933
Mean lymph node size ± SD	1.52(0.30)	1.56(0.30)	0.427
Sensitivity	93.0%	86.4%	0.002
Specificity	100%	100%	1.00
Diagnostic accuracy	94.2%	89.7%	0.01
Adequacy	70.3%	42%	0.01

Table 3. Diagnostic accuracy, sensitivity, specificity and adequacy in lymph nodes ≥2 cm.

Size ≥2 cm	EBUS-TBNA	C-TBNA	p value
Number	71	66	0.943
Mean lymph node size ± SD	2.70 (0.68)	2.80 (0.72)	0.405
Sensitivity	95.1%	92.1%	0.898
Specificity	100%	100%	1.00
Diagnostic accuracy	95.7%	93.0%	0.939
Adequacy	68.7%	68.3%	0.889

Table 4. Diagnostic accuracy, sensitivity, specificity and adequacy in station 7 lymph node <2 cm.

Subcarinal station <2 cm	EBUS-TBNA	C-TBNA	p value
Number	33	22	0.516
Mean lymph node size ± SD	1.63(0.23)	1.69(0.21)	0.331
Sensitivity	95.6%	87.5%	0.024
Specificity	100%	100%	1.00
Diagnostic accuracy	96.4%	90%	0.005
Adequacy	84.8%	45.5%	0.005

Table 5. Diagnostic accuracy, sensitivity, specificity and adequacy in station 7 lymph node ≥2 cm.

Subcarinal station ≥ 2cm	EBUS-TBNA	C-TBNA	p value
Number	24	28	0.501
Mean lymph node size ± SD	2.76 (0.54)	2.84 (0.59)	0.615
Sensitivity	93.3%	94.1%	0.845
Specificity	100%	100%	1.00
Diagnostic accuracy	94.4%	95%	0.945
Adequacy	75%	71.4%	0.981

randomized controlled trial that compared c-TBNA and linear EBUS-TBNA for the diagnosis of lymphadenopathy of unknow origin. It showed that the sensitivity of EBUS-TBNA was higher than the sensitivity of c-TBNA but this did not represent a significant difference (92% *vs* 82%). However, approximately two thirds of the study population presented lymph node size ≥2 cm. This study also took into consideration the cost of procedures and showed that using c-TBNA and EBUS-TBNA in a complementary way the cost was lower than that of EBUS alone.

The study of Fiorelli *et al*. [22] compared the sensitivity and diagnostic accuracy of c-TBNA in relation to lymph node size (<15 and ≥15 mm) and station (4 and 7). In this study the sensitivity and diagnostic accuracy's values of large lymph node sampled by c-TBNA were significantly higher than the values of small adenopathies. In addition, they proposed an algorithm where in case of lymph node size >15 mm, and in subcarinal station, c-TBNA is the first-choice procedure. In case of negative result, the patients were submitted to EBUS-TBNA. The study did not compare directly the diagnostic yield and sensitivity of the two techniques, conventional and EBUS-TBNA, in terms of lymph node station and size. The study of Levy *et al*. [23] showed that c-TBNA remains a reasonable option, with an acceptable diagnostic yield for sampling mediastinal nodes >= 2 cm at stations 4R, 7, and 11R, especially in the case of presumed sarcoidosis or lymphoma.

Thus, the clinical choice between EBUS-TBNA and c-TBNA in patients with mediastinal lymphadenopathy still remains controversial and it is necessary to consider several factors, like the invasiveness of the procedure, the cost, the risk, the equipment and personal expertise. For these reasons some authors continue to prefer the use of c-TBNA due to its cheapness and easiness of performance, training and learning curve. Moreover, they promote the EBUS-TBNA as a procedure to be adopted when the c-TBNA results in non-diagnostic sampling [9,10,24,25].

In our study we compared the use of c-TBNA and EBUS-TBNA in the diagnosing/staging of malignant diseases. The research was carried out during the period in which the EBUS-TBNA was introduced in clinical practice, while the c-TBNA was already a routine procedure performed for several years. We compared the diagnostic accuracy, sensitivity and sample adequacy according to the size of lymph nodes (<2 cm and >= 2 cm) and then we analyzed these results considering only station 7, the most sampled.

In our study there were no significant differences in the diagnostic accuracy, sensitivity and adequacy between EBUS-TBNA and c-TBNA in patients with lymph node size ³ 2cm. In particular, the DA was 95.8% vs 93.3% for EBUS-TBNA and c-TBNA respectively, the sensitivity was 95.2% *vs* 92.3% and the adequacy was 67.3% vs 68.2%. So, these results suggest that the two procedures, performed on lymph node size >= 2 cm, were comparable (Table 2). Instead, the EBUS-TBNA group with lymph nodes size <2 cm presented a statistically significant difference in terms of diagnostic accuracy, sensitivity and adequacy compared to c-TBNA procedure. We showed that the DA was 94.2% *vs* 89.7%, the sensitivity was 93.0 vs 86.45% and the adequacy was 70.3% *vs* 42% for EBUS-TBNA and c-TBNA, respectively. So, in this case, we considered the EBUS-TBNA as the best diagnostic tool in patients with small adenopathies (<2 cm) (Table 3). The same results were obtained for the station 7: in lymph nodes with short axis <2 cm we found a statistically significant difference between the two methods. Particularly the EBUS-TBNA presented a higher accuracy, sensitivity and adequacy compared to c-TBNA. Instead, for the lymph nodes with short axis ≥2 cm there were no statistically significant differences. Finally, we showed that the type of sedation did not influence our results. In fact, several studies showed that the type of sedation does not influence the diagnostic yield, sensitivity and accuracy [26-28].

The study presents a number of limits: the relatively small sample size, it was a retrospective and multicenter study so different individuals performed the two procedures, all procedures were performed by bronchoscopists with a long-life experience with c-TBNA, the rapid on-site evaluation (ROSE) procedure was not available and the study did not evaluate the costs of procedures.

In our study, EBUS-TBNA has proved to be the most accurate and sensitive procedure for sampling lymph nodes of less than 2 cm regardless of location and therefore we believe that it should be the first-choice procedure in centers where the EBUS is available.

Given that the two methods proved to produce comparable results for lymph nodes with a size >2 cm, we believe that in centers where the EBUS is not available, the c-TBNA represents a valid alternative to EBUS in adenopathies ≥2 cm. Conversely, EBUS-TBNA is the first-choice procedure for sampling mediastinal adenopathies <2 cm and when patients desire maximal assurance that successfully biopsy is achieved. It is advisable to refer to a center that has EBUS given the better performance of this method, to avoid the patient to perform 2 procedures and thus reducing costs. So, despite being the EBUS-TBNA the best diagnostic technique for the diagnosis and staging of lung cancer, c-TBNA plays an important role in the centers not equipped with EBUS, in particular in the sampling of lymph node stations of large size ≥2 cm. Further researches are needed to confirm our results.

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