Original Article

Multicentric study of endobronchial ultrasound-transbronchial needle aspiration for lung cancer staging in Italy

Nicola Rotolo[1], Andrea Imperatori[1], Mario Nosotti[2], Luigi Santambrogio[2], Alessandro Palleschi[2], Lorenzo Dominioni[1], Giorgio Crosta[3], Pierfranco Foccoli[4], Gianluca Pariscenti[4], Eliseo Passera[5], Luigi Bortolotti[5], Giovanni Falezza[6], Maurizio Infante[6], Elisa Daffrè[1], Maria Cattoni[1], Lorenzo Rosso[2]

[1]Center for Thoracic Surgery, Department of Medicine and Surgery, University of Insubria, Ospedale di Circolo, Varese, Italy; [2]Thoracic Surgery and Lung Transplant Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [3]Department of Specialistic Medicine, Unit of Pneumology, ASST Sette Laghi, Hospital of Varese, Varese, Italy; [4]Thoracic Surgery Unit, Spedali Civili, Brescia, Italy; [5]Thoracic Surgery Department, Humanitas Gavazzeni Hospital, Bergamo, Italy; [6]Thoracic Surgery Unit, Ospedale Borgo Trento, Verona, Italy

Contributions: (I) Conception and design: L Dominioni, L Santambrogio, M Nosotti, P Foccoli, L Bortolotti, M Infante; (II) Administrative support: N Rotolo, L Rosso, G Crosta; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: N Rotolo, G Crosta, L Rosso, A Palleschi, G Pariscenti, E Passera, G Falezza, E Daffrè, M Cattoni; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Nicola Rotolo, MD. Center for Thoracic Surgery, Department of Medicine and Surgery, University of Insubria, Ospedale di Circolo, Via Guicciardini, 9, Varese 21100, Italy. Email: nicola.rotolo@uninsubria.it.

Background: Multi-institutional studies of endobronchial-ultrasound transbronchial needle aspiration (EBUS-TBNA) for mediastinal staging in lung cancer are scarce. It is unclear if the high diagnostic performance of EBUS-TBNA reported by experts' guidelines can be generally achieved.

Methods: This is a retrospective study performed in five tertiary referral centers of thoracic surgery in Italy, to assess the EBUS-TBNA diagnostic performance in patients with non-small cell lung cancer (NSCLC). Patient inclusion criteria were: both genders; >18 years old; with suspect/confirmed NSCLC; undergoing EBUS-TBNA for mediastinal node enlargement at computed tomography (size >1 cm, ≤3 cm) and/or pathological uptake at positron emission tomography. Altogether we included 485 patients [male, 366; female, 119; median age, 68 years (IQR, 61–74 years)] undergoing mediastinal staging between January 2011 and July 2016. All EBUS-TBNAs were performed by experienced bronchoscopists, without pre-defined quality standards. Depending on usual practice in each center, EBUS-TBNA was done under conscious sedation, with 21- or 22-Gauge (G) needle, and specimen preparation was cell-block, or cytology slides, or core-tissue. Sampling was classified inadequate in absence of lymphocytes, or when sample was insufficient. We analyzed the EBUS-TBNA procedural steps likely to influence the rate of adequate samplings (diagnostic yield).

Results: EBUS-TBNA sensitivity, negative predictive value (NPV) and accuracy respectively were 90%, 78% and 93% in the whole cohort. At multivariate analysis, use of 21-G needle was associated with better diagnostic yield (P<0.001). Center and specimen processing technique were not independent factors affecting EBUS-TBNA diagnostic yield.

Conclusions: In this multicentric study, EBUS-TBNA was a highly sensitive and accurate method for NSCLC mediastinal node staging. Results indicate better performance of EBUS-TBNA with 21-G needle, and suggest that specimen processing technique could be chosen according to the local practice preference.

Keywords: Endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA); lung cancer staging; accuracy; diagnostic yield

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Introduction

Treatment and prognosis of non-small cell lung cancer (NCSLC), the leading cause of cancer death worldwide, requires accurate staging. The 2014 guidelines of the European Society of Thoracic Surgeons indicate endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) as the initial approach for pathological evaluation of mediastinal lymph nodes (1,2). In the last 15 years EBUS-TBNA has increasingly been used for minimally invasive diagnosis of mediastinal-hilar lymph node metastases in patients with NSCLC, and in selected cases this technique has replaced mediastinoscopy, video-thoracoscopy and traditional transbronchial biopsy (2).

The aim of this study is to evaluate the EBUS-TBNA diagnostic performance for staging hilar-mediastinal lymph nodes in an Italian multi-institutional cohort of lung cancer patients, and to analyze some of the factors influencing the diagnostic yield.

Methods

A retrospective, multicenter study of patients with NSCLC undergoing EBUS-TBNA between January 2011 and July 2016 was conducted in the interventional bronchoscopy units of five thoracic surgery centers in northern Italy (Milan, Policlinico Universitario; Bergamo, Clinica Humanitas; Brescia, Spedali Civili; Varese, Università Insubria Ospedale di Circolo; Verona, Ospedale Universitario Borgo Trento). In each participating center the patient inclusion criteria for study were: both genders; ≥18 years old; with suspect/histologically confirmed NSCLC, undergoing EBUS-TBNA for suspect N2 [mediastinal lymph node enlargement (>1 cm, ≤3 cm in size) at chest computed tomography (CT) scan, and/or pathological uptake at positron emission tomography scan]. For all patients, we collected the following data: gender, age, biopsy needle gauge, sample processing technique, EBUS-TBNA cytohistological results, further mediastinal staging procedures (mediastinoscopy; video-assisted thoracoscopic surgery; chest CT) performed in patients with negative EBUS-TBNA findings, procedural complications. All data were anonymized and saved in a dedicated database for analysis (RN, author responsible for data protection). The 7th edition of NSCLC TNM staging system was used (3). Biopsy was classified inadequate in the absence of lymphocytes or when sampled material was insufficient. We classified as positive a sample with malignant cells and assumed this to be a true positive finding, false positive EBUS-TBNA results being rare (4). Adequate aspirates without malignant cells were classified as negative. In the present study, the gold standard for final classification of EBUS-TBNA negative mediastinal nodes was: in resected patients, the mediastinal lymphadenectomy pathology finding; in unresected cases, the chest CT finding at 1-year follow-up. Each center gave approval for conducting the case file review in anonymized form. Ethical approval was not required, as this study was observational. De-identified data were used for analyzing the results. Individual patient consent was waived due to the study retrospective nature.

Procedure

The EBUS-TBNA procedures were performed with a linear echo-endoscope by expert interventional pulmonologists or thoracic surgeons according to the usual practice in each center, without pre-defined standards. Conscious sedation with intravenous midazolam and fentanyl was used in all participating institutes. The Doppler function was used in selected patients. Target lymph nodes were identified under direct ultrasound guidance and were sampled using either 21- or 22-Gauge (G) needle, according to the usual practice in each center. Each lymph node was biopsied with at least three needle passes, each pass including 5 to 15 agitations within the targeted node. Specimens were allocated into liquid fixative suitable for cell-block preparations (all centers), or into formalin for core biopsy histology (Varese, Verona and Brescia centers only). Among the five participating centers, specimen rapid on-site evaluation (ROSE) was performed only in selected patients of Brescia and Verona centers. The choice of specimen preparation method was left to the local pathologist's preference and experience; in some cases a combination of two preparations (cytology slides and cell-block) was used for evaluating the specimen.

Statistical analysis

The EBUS-TBNA performance in diagnosing malignancy was calculated in the pooled series of the five centers, according to standard definitions [sensitivity: true positive/(true positive + false negative); negative predictive value (NPV): true negative/(true negative + false negative); diagnostic accuracy: (true positive + true negative)/(true positive + false positive + true negative + false negative)]. Chi-square test was used to examine the association of two

Table 1 Characteristics of the 485 patients

Characteristics	Patients, n [%]
Gender	
Male	366 [75]
Female	119 [25]
Median age, IQR (years)	68, 61–74
Biopsy needle gauge	
21-G	178 [37]
22-G	307 [63]
No. of node stations sampled per procedure	
1	327 [68]
2	122 [25]
3	34 [7]

IQR, interquartile range; G, gauge.

Table 2 Proportion of adequate EBUS-TBNA samples in 485 non-small cell lung cancer patients, as related to needle gauge, specimen preparation technique and center

Factors	Adequate sample rate [%]	P value
Biopsy needle gauge		<0.001
21-G	176/178 [99]	
22-G	260/307 [85]	
Specimen preparation		<0.001
Core-tissue	62/64 [97]	
Cytology slides with ROSE	32/40 [80]	
Cytology slides without ROSE	35/43 [81]	
Cell-block	217/248 [88]	
Cell-block + cytology slides	90/90 [100]	
Center		<0.001
Milan	194/222 [87]	
Bergamo	98/98 [100]	
Varese	76/77 [99]	
Brescia	41/58 [71]	
Verona	27/30 [90]	

ROSE, rapid on-site evaluation.

or more categorical variables. Univariate and multivariate analysis were performed to identify among the following factors those influencing the EBUS-TBNA diagnostic yield: needle gauge, specimen processing technique, center. P value <0.05 was considered statistically significant. The statistical analyses were done using MedCalc statistical software version 17.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

Results

Altogether in the five participating centers 485 patients undergoing EBUS-TBNA and fulfilling the inclusion criteria of study were identified. The patients' characteristics are listed in *Table 1*. The EBUS-TBNA cases contributed by each center were: Milan, n=222; Bergamo, n=98; Varese, n=77; Brescia, n=58; Verona, n=30. Findings in the pooled series of the five centers were as follows: the first node station most frequently sampled was station 4 (45% of cases), followed by station 7 (32%). Station 2 nodes were biopsied in 6% of patients, station 10 in 13%, station 11 in 4%. No major complications were observed. In 49 patients the EBUS-TBNA sampling was found to be inadequate; thus, the rate of adequate samples overall was 90% (436/485). In 301 patients a diagnosis of malignant involvement of mediastinal nodes was obtained (true positive). In 105 cases the EBUS-TBNA result was true negative, in 30 cases it was false negative. In the pooled series of 485 EBUS-TBNAs the sensitivity, NPV and accuracy were respectively 90%, 78% and 93%.

Table 2 summarizes the EBUS-TBNA diagnostic yield (rate of adequate samples) by needle gauge, by specimen processing technique and by center. A significant difference of diagnostic yield was observed comparing 21- *vs.* 22-G needle (P<0.001), the different specimen preparation techniques (P<0.001), and the five centers (P<0.001).

At multivariate analysis, 21-G needle correlated with better diagnostic yield, whereas specimen processing technique and center were not independent factors of EBUS-TBNA diagnostic yield (*Table 3*).

Discussion

In our pooled series of 485 lung cancer patients undergoing mediastinal staging for suspect N2 involvement, the EBUS-TBNA technique had 90% sensitivity, 78% NPV and 93% accuracy. To our knowledge this is the largest Italian series of analyzed EBUS-TBNA results, consisting exclusively

Table 3 Univariate and multivariate analysis of factors affecting EBUS-TBNA diagnostic yield

Factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Needle size (21- *vs*. 22-G)	0.06	0.02–0.26	<0.001	0.01	0.002–0.09	<0.001
Specimen preparation (core-tissue *vs*. cytology slides with ROSE *vs*. cytology without ROSE *vs*. cell-block *vs*. cell-block + cytology slides)	1.13	0.90–1.41	0.28			
Center (Milan *vs*. Bergamo *vs*. Varese *vs*. Brescia *vs*. Verona)	0.60	0.45–0.81	<0.001	1.70	0.92–3.14	0.09

OR, odds ratio; CI, confidence interval.

of NSCLC patients with clearly defined criteria for study entry. Our results are well within the range of EBUS-TBNA sensitivity (52–92%), NPV (57–93%) and accuracy (84–96%) calculated from the data reported in a recent systematic review and meta-analysis (5). The generally high accuracy of EBUS-TBNA has led to wide diffusion of this technique for minimally invasive diagnosis and staging of NSCLC. For this purpose the ACCP evidence-based practice guidelines recommend EBUS-TBNA as the first choice method (6), while mediastinoscopy and other surgical approaches for mediastinal node biopsy are indicated for EBUS-TBNA negative cases at high risk of lung cancer metastases (7). Consequently, the number of mediastinoscopies has dropped significantly after the introduction of EBUS-TBNA for mediastinal staging of lung cancer (8).

In our pooled series of NSCLC patients undergoing mediastinal staging by EBUS-TBNA, the specimen processing technique and the center were not independent factors influencing diagnostic yield, in agreement with previous reports of EBUS-TBNA performance in heterogeneous populations of neoplastic and non-neoplastic patients (9,10). Needle 21-G independently correlated with the EBUS-TBNA diagnostic yield.

Regarding the needle gauge, our rate of adequate samplings with 21-G needle (99%) and with 22-G needle (85%) was higher than the respective rates reported in the literature (72% and 78%) (11). This difference is likely contributed to by the fact that our study population consisted exclusively of NSCLC patients. In our pooled series, the specimen adequacy rate was significantly higher with 21- relative to 22-G needle, in contrast with other authors' findings (11-13).

ROSE of samples in our study was used in only 40 EBUS-TBNA cases in total, cumulated in Brescia and Verona centers, and this technique provided no significant advantage. However, our limited experience with ROSE does not allow firm conclusions about the role of this technique. A recent review indicates that ROSE does not modify EBUS-TBNA diagnostic yield and does not affect the number of needle passes, the duration of the procedure, nor the complication rate (9). Conversely, ROSE reduces the number of additional lymph node samplings, especially when EBUS-TBNA represents the first diagnostic procedure in case of suspect lung cancer (9).

Regarding the specimen processing techniques, cell-block was the most frequently used method in the pooled series. The other methods adopted for processing EBUS-TBNA specimens were cytology slides and core-tissue. In our study and in the literature, the comparison of cytology slides, core-tissue and cell-block methods showed that none of these preparation techniques was superior to the others (9,10). The combined reading of specimens prepared with two techniques (cytology slides and cell-block) leads to better diagnostic results, but it has the disadvantage of being more expensive and more time-consuming (14,15).

Concerning patient sedation, all centers in our study used conscious sedation with fentanyl and midazolam, obtaining overall an adequate sample rate of 90%, similar to that reported in the literature (16,17).

This study has limitations, mostly due to its retrospective nature. First, the five centers participating in the study did not follow a standardized EBUS-TBNA procedure, thus increasing the variability of diagnostic findings. Second, the results were obtained in a selected cohort entirely consisting of cancer patients; this selection may likely account for the high sensitivity of EBUS-TBNA that was recorded, because the diagnostic performance correlates with the prevalence of malignancy (18,19).

Conclusions

In this Italian multicentric study of patients with NSCLC, the EBUS-TBNA technique showed high sensitivity and accuracy

as a diagnostic tool for mediastinal staging. Multivariate analysis showed significant correlation between use of 21-G needle and EBUS-TBNA diagnostic yield. Center and specimen processing method did not independently affect diagnostic yield, suggesting that these procedural steps could be decided according to the bronchoscopist's and pathologist's usual practice.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Ethical approval was not required, as this study was observational. De-identified data were used for analyzing the results. Individual patient consent was waived due to the retrospective nature of the study.

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