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EBUS-TBNA for mediastinal staging of centrally located T1N0M0 non-small cell lung cancer clinically staged with PET/CT

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Abstract

Background and Objective: To evaluate the diagnostic accuracy and clinical usefulness of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for mediastinal staging of centrally located T1N0M0 non-small cell lung cancer (NSCLC) clinically staged with positron emission tomography/computed tomography (PET/CT).

Methods: We conducted a study that included patients with centrally located T1N0M0 NSCLC, clinically staged with PET/CT who underwent EBUS-TBNA for mediastinal staging. Patients with negative EBUS-TBNA underwent mediastinoscopy, video-assisted mediastinoscopic lymphadenectomy (VAMLA) and/or lung resection with systematic nodal dissection, that were considered the gold standard. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), overall accuracy of EBUS-TBNA for diagnosing mediastinal metastases (N2 disease) and the number needed to treat (NNT: number of patients needed to undergo EBUS-TBNA to avoid a case of pathologic N2 disease after resection) were calculated.

Results: One-hundred eighteen patients were included. EBUS-TBNA proved N2 disease in four patients. In the remaining 114 patients who underwent mediastinoscopy, VAMLA and/or resection there were two cases of N2 (N2 prevalence 5.1%). The sensitivity, specificity, NPV, PPV and overall accuracy for diagnosing mediastinal metastases (N2 disease) were of 66%, 100%, 98%, 100% and 98%, respectively. The NNT was 31 (95% CI: 15–119).

Conclusion: EBUS-TBNA in patients with central clinically staged T1N0M0 NSCLC presents a good diagnostic accuracy for mediastinal staging, even in a population with low prevalence of N2 disease. Therefore, its indication should be considered in the management of even these early lung cancers.

KEYWORDS

cT1N0, EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration, mediastinum, staging, non-small cell lung cancer, NSCLC

Pere Serra Mitjà and Bruno García-Cabo contributed equally to this study.

INTRODUCTION

Mediastinal staging is an essential step in the work-up of patients with non-small cell lung cancer (NSCLC). Current guidelines for NSCLC mediastinal staging[1,2] recommend starting with non-invasive image-based techniques such as computed tomography (CT) and positron emission tomography (PET) alone or in combination (PET/CT). However, positive and most of the negative results of PET/CT need to be confirmed by means of invasive techniques. More specifically, three clinical situations of normal mediastinum on PET/CT have been related with high risk of occult nodal mediastinal metastases: tumours with clinical (c) size ≥3 cm (≥T2 tumours), cN1 nodal disease on PET/CT and centrally located nodules (central cT1N0M0). As a result, only patients with peripheral nodules clinically staged T1N0M0 after PET/CT are recommended to proceed directly to resection without invasive mediastinal staging.

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive technique that is currently recommended by the guidelines as a first-choice technique for invasive mediastinal staging.[1,2] The reported sensitivity of EBUS-TBNA for NSCLC mediastinal staging depends on the appearance of the mediastinum on PET/CT.[3] A meta-analysis of Gu et al.[3] showed differences of sensitivity of EBUS-TBNA for mediastinal staging between patients with normal (76%) and abnormal (94%) mediastinum on PET/CT. More recently, two meta-analyses,[4,5] focused on EBUS-TBNA for NSCLC mediastinal staging in patients with normal mediastinum on PET/CT, showed a pooled sensitivity of EBUS-TBNA of 49%, that is significantly lower than that reported for overall patients with NSCLC.[3] The role of EBUS-TBNA for each specific clinical scenario of normal mediastinum on PET/CT where invasive staging is recommended (cN1, ≥T2 and central cT1N0M0) has been scarcely studied. To the best of our knowledge, only two studies[6,7] investigated the usefulness of endosonography in cN1 tumours, both with a reported sensitivity of 38%. Based on this poor sensitivity, some authors have claimed that EBUS-TBNA should not be the technique of choice for invasive mediastinal staging of patients with cN1 tumours.

The diagnostic accuracy of EBUS-TBNA for mediastinal staging of central cT1N0M0 tumours has never been reported; and its clinical usefulness, measured as number of patients needed to treat (NNT), in such scenario, is unknown. Our aim was to evaluate the diagnostic accuracy and clinical usefulness of EBUS-TBNA for mediastinal staging of patients with cT1N0M0 NSCLC after PET/CT with an indication of invasive staging based on its central location.

METHODS

Study design and patients

We conducted a two-centre study that consisted of a retrospective analysis of two prospectively built databases. Patients with pure-solid, centrally located cT1N0M0 NSCLC staged with PET/CT who underwent EBUS-TBNA for mediastinal staging from January 2020 to June 2022 were included. The central tumour location was based on the European Society of Thoracic Surgeons (ESTS) definition[1]: any tumour lying in the inner two-thirds of the hemithorax according to the drawing of concentric lines from the midline.

Patients with tumours staged N0/N1 after EBUS-TBNA underwent video-mediastinoscopy, video-assisted mediastinoscopic lymphadenectomy (VAMLA) and/or lung resection with systematic nodal dissection (SND), that were considered the gold standard for the present study. Patients with previous lung resection or mediastinoscopy, patients with ground-glass opacities and/or sub-solid nodules and those with negative EBUS-TBNA that could not undergo surgical staging were excluded from the analysis.

SUMMARY AT A GLANCE

The diagnostic performance of EBUS-TBNA for mediastinal staging of centrally located T1N0M0 NSCLC has never been reported. Our study shows that EBUS-TBNA presents a good diagnostic performance, even in patients with low prevalence of N2 disease. Its indication should be considered in the management of even these early lung cancers.

EBUS-TBNA

EBUS was performed using a flexible bronchoscope (BFUC180F, Olympus Optical Co Ltd., Tokyo, Japan) with a distal probe capable of producing linear parallel scans of the mediastinal and peribronchial tissues and a working channel suited for the performance of TBNA under direct ultrasound guidance. General anaesthesia was performed by an anesthesiologist using topical lidocaine spray and intravenous midazolam, propofol and/or fentanyl according to standard recommendations[8]; and patients were mechanically ventilated through laryngeal mask. EBUS-TBNA staging included sampling of every lymph node (LN) measuring ≥5 mm starting from contralateral hilar and mediastinal nodal stations and proceeding to the subcarinal and ipsilateral mediastinal and hilar nodal stations, if malignancy was not detected by rapid on-site examination (ROSE) (at least one pass per LN consistent with benignity—normal lymph-node tissue/lymphocytes—was obtained). If N3 disease was detected, the procedure was then terminated. In ipsilateral mediastinal or subcarinal nodal stations, if malignancy was detected, then the needle was changed to avoid contamination with malignant cells,[9] and the sampling continued to the remaining ipsilateral mediastinal and subcarinal nodal stations yet to be sampled in order to identify multiple N2 involvement (N2b).

Surgical staging

Every patient with N0/N1 tumours after EBUS-TBNA was discussed independently in the thoracic multidisciplinary tumour board of each institution. In one of the institutions, these patients underwent surgical exploration of the mediastinum (VAMLA or video-mediastinocoscopy) before lung resection. In the other institution, only patients with N1 disease after EBUS/TBNA, comorbidities and/or high surgical risk underwent video-mediastinoscopy to gain confidence before lung resection.

Cervical video-mediastinoscopy was performed based on the recommendations of the ESTS[1] and included sampling of right and left inferior paratracheal and subcarinal nodal stations regardless of nodal size. The way VAMLA was performed has already been described.[10] SND was performed in patients undergoing resection following the recommendations of The Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery.[11]

Statistical analysis

Data were entered into a database and analyzed using version 15 of STATA. Categorical variables were expressed as absolute and relative frequencies, continuous variables as means and standard deviations and non-normally distributed data as medians and interquartile ranges. The prevalence of nodal disease was estimated and the relation between prevalence and clinical features was calculated by logistic regression using the *logistic* command of STATA. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and overall accuracy of EBUS-TBNA to detect N2 disease were calculated using the standard formulas.

The number needed to treat (NNT) was defined as the number of patients needed to undergo EBUS-TBNA to avoid a case of N2 disease after resection (pN2). NNT was estimated as 1/ARR (absolute risk reduction), where ARR is CER (control event rate)—EER (experimental event rate), considering CER as the rate of pN2 disease after resection if all patients had undergone resection without a previous EBUS-TBNA; and EER, the rate of pN2 disease in patients undergoing resection after EBUS-TBNA. We used a Monte Carlo approach to estimate the 95% confidence interval.

To estimate the NNT depending on clinical features, we applied the same formulas to the subgroups of patients with those clinical features (e.g., only patients with adenocarcinoma).

RESULTS

One-hundred eighteen patients were included. Table 1 describes patients' characteristics. During EBUS-TBNA a mean of 5.1 nodal stations and a mean of 8.8 LNs were sampled. EBUS-TBNA proved N2 disease in 4 patients (Figure 1), while the remaining 114 patients presented no mediastinal metastases after EBUS-TBNA (2 cases presented N1 disease and 112 cases presented N0 disease after EBUS-TBNA). Of these, 34 patients underwent video-mediastinoscopy or VAMLA that did not diagnose any case of N2 disease and all of these patients underwent lung resection with SND. One of them presented pN2 after resection and SND. Of the 80 patients with negative EBUS-TBNA who underwent resection directly, only one patient presented pN2 disease. Thus, the prevalence of N2 disease in our series was 5.1% (6/118): four cases diagnosed by means of EBUS-TBNA and two by means of resection and

TABLE 1 Patients' characteristics.

Gender, number (%)	Male	84 (71.2)
	Female	34 (28.8)
Age (years) mean (SD)	68.0 (±8.1)	
Tobacco status, number (%)	Never smoker	16 (13.6)
	Current smoker	45 (38.1)
	Former smoker	57 (48.3)
Tumour location, number (%)	Right upper lobe	42 (35.6)
	Middle lobe	7 (5.9)
	Right lower lobe	21 (17.8)
	Left upper lobe	36 (30.5)
	Left lower lobe	12 (10.2)
Histologic type, number (%)	Adenocarcinoma	76 (64.5)
	Squamous-cell carcinoma	29 (24.6)
	NSCLC	7 (5.9)
	Atypical carcinoid	3 (2.5)
	Large-cell carcinoma	2 (1.7)
	Neuroendocrine carcinoma	1 (0.8)
Tumour size (mm), mean (SD)	21.3 (±6.0)	
T1 category, number (%)	T1a	11 (9.3)
	T1b	45 (38.1)
	T1c	62 (52.6)
Number of lymph nodes sampled through EBUS-TBNA, number (SD)	8.8 (±3.3)	
Number of nodal stations sampled through EBUS-TBNA, number (SD)	5.1 (±1.2)	
Final pN categories, number (%)	pN0	104 (88.1)
	pN1	8 (6.8)[a]
	pN2	6 (5.1)[b]

Abbreviations: EBUS-TBNA, endobronchial ultrasound transbronchial needle aspiration; NSCLC, non-small cell lung cancer.

[a]Eight cases with final pN1 disease, two diagnosed by means of EBUS-TBNA (both confirmed as pN1 after resection) and six cases diagnosed by means of resection (two cases of hilar pN1 and four of peripheral pN1).

[b]Six cases with final N2 disease, four diagnosed by means of EBUS-TBNA and two cases diagnosed by means of resection (of these two patients with pN2 disease, one of them presented skip metastases (N2 without N1 disease), both presented single station involvement (pN2a)).

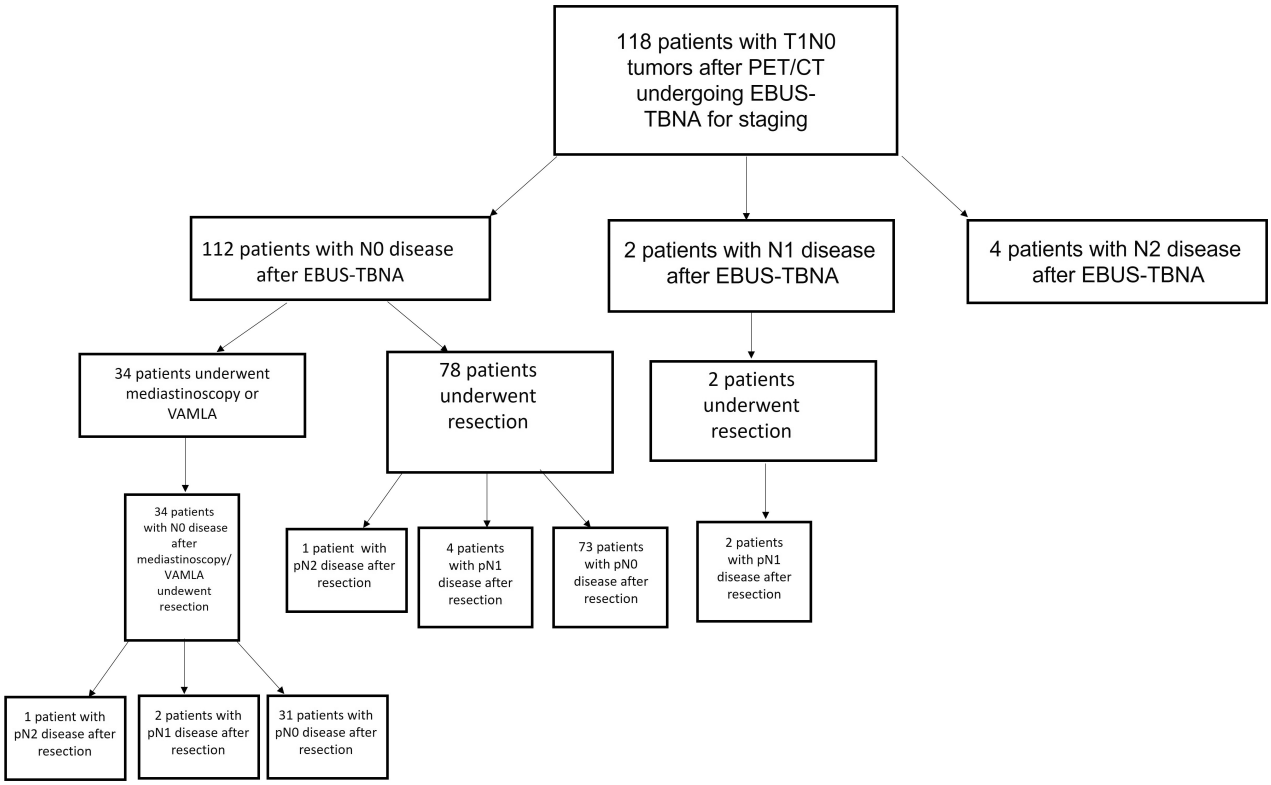

FIGURE 1 Patients' flowchart.

pathologic study of the resected specimens. Patients with N2 disease diagnosed through EBUS-TBNA underwent neoadjuvant chemo-radiotherapy; thus, EBUS-TBNA results clinically impacted in these 4 out 6 patients who could benefit from induction therapy. Of the 2 patients with pN2 disease diagnosed after resection (EBUS-TBNA false negatives), both presented single station involvement (pN2a): one at station 4L and the other at station 5 (out of the reach of EBUS-TBNA and mediastinoscopy). The first one had a metastatic focus of 4 mm while the other had extracapsular involvement (although radiologically was N0). Mediastinal nodal disease was not associated with sex, age, smoking habit, T1 subcategory or histologic type (Table 2). Apart from these six patients with N2 disease there were another eight patients with nodal involvement (N1 disease): four with hilar N1 disease and four with peripheral N1 disease (overall prevalence of $N \geq 1$ disease—any nodal disease—11.8%). Two out of four patients with N1 hilar disease were diagnosed by means of EBUS-TBNA (Table 3).

The sensitivity, specificity, NPV, PPV and overall accuracy of EBUS-TBNA for diagnosing mediastinal metastases (N2 disease) in patients with NSCLC and central tumours staged cT1N0M0 after PET/CT were 66%, 100%, 98%, 100% and 98%, respectively.

The overall NNT was 31 (95% CI: 15–119), but it was lower in patients with tumours located in upper lobes (21 [95% CI: 10–79]), tumours classified as T1c (24 [95% CI: 10–70]) and adenocarcinoma (26 [95% CI: 11–∞]) (Table 4).

DISCUSSION

Our study demonstrates that, in patients with centrally located NSCLC clinically staged T1N0M0 after PET/CT, EBUS-TBNA attains good overall diagnostic accuracy for N2 detection. However, given the low prevalence of occult mediastinal nodal metastases in this population and the low sensitivity of EBUS-TBNA, the NNT is high.

The reported pooled sensitivity of EBUS-TBNA for mediastinal staging of NSCLC with normal mediastinum on PET/CT is very low.[4,5] Malignant LNs with normal appearance on PET/CT usually contain microscopic foci of metastases that are more difficult to detect than large metastases replacing the normal nodal tissue in bulky LNs. However, apart from this pathologic feature, procedural factors may play a role in this reported low sensitivity. In the meta-analysis of Leong et al.,[5] more than half of the included studies had ≤2 LNs sampled per patient during EBUS-TBNA. Sampling 1 or 2 LNs during EBUS-TBNA can be enough for diagnosing mediastinal metastases in patients with enlarged LNs on PET/CT (although insufficient for a complete mediastinal staging[12]) but insufficient in patients with normal PET/CT. In this setting, another study by our group, focused on the usefulness of EBUS-TBNA for NSCLC staging in patients with normal mediastinum on PET/CT,[13] described a sensitivity of 84%. This higher sensitivity is probably secondary to a more extensive sampling given that the reported median number of nodal stations and LNs sampled was 5 and 9, respectively. In this current series, the median number of nodal stations and LNs sampled is similar

TABLE 2 Prevalence of N2 disease by clinical characteristics, number (%).

Gender	Male	4 (66.7)
	Female	2 (33.3)
Tobacco status	Never smoker	0 (0)
	Current smoker	5 (83.3)
	Ex-smoker	1 (16.7)
Tumour location	Right upper lobe	3 (50.0)
	Left upper lobe	3 (50.0)
Histologic type	Adenocarcinoma	4 (66.6)
	NSCLC	1 (16.7)
	Large-cell carcinoma	1 (16.7)
T1 category	T1a	1 (16.7)
	T1b	2 (33.3)
	T1c	3 (50.0)

Abbreviation: NSCLC, non-small cell lung cancer.

TABLE 3 Diagnostic performance of EBUS-TBNA for detecting occult nodal disease.

		EBUS-TBNA diagnostic performance for detecting any nodal occult disease ($N > 0$)[a]	
		EBUS $N = 0$ (112)	**EBUS $N > 0$ (6)**
Final *N* status (surgical specimens)[b]	pN0	105	0
	pN >0	7	6
		EBUS-TBNA diagnostic performance for detecting mediastinal nodal disease ($N > 1$)[c]	
		EBUS N0-1 (114)	EBUS N2 (4)
Final *N* status (surgical specimens)[b]	pN0-1	112	0
	pN2	2	4
		EBUS-TBNA diagnostic performance for detecting hilar nodal disease (hilar N1)[d]	
		EBUS $N = 0$ (110)	EBUS N1 (2)
Final *N* status (surgical specimens)	pN0	108	0
	pN1	2	2

[a]Diagnostic performance of EBUS-TBNA for diagnosing any *N* occult disease: sensitivity 46% (6/13), specificity 100% (105/105), negative predictive value 93% (105/112), positive predictive value 100% (6/6) and overall accuracy 94% (111/118).
[b]EBUS-TBNA positive results for N2 disease were not surgically confirmed. However, false positive are very uncommon.
[c]Diagnostic performance of EBUS-TBNA for diagnosing N2 occult disease: sensitivity 66% (4/6), specificity 100% (112/112), negative predictive value 98% (112/114), positive predictive value 100% (4/4) and overall accuracy 98% (116/118).
[d]Diagnostic performance of EBUS-TBNA for diagnosing hilar nodal disease (hilar N1) (patients with final diagnosis of N2 disease were excluded, patients with peripheral N1 were considered true negative): sensitivity 50% (2/4), specificity 100% (108/108), negative predictive value 98% (108/110), positive predictive value 100% (2/2) and overall accuracy 98% (110/112).

to the previous one, but the attained sensitivity (66.6%) is lower. Probably these differences in sensitivity are secondary to differences in prevalence of N2 disease in both series (14.3% and 5.1%), because differences in prevalence may affect EBUS-TBNA sensitivity.[14]

TABLE 4 Overall number needed to treat (NNT) and differences depending on clinical characteristics.

Condition		***N***	**Control event rate**	**NNT**	**95% CI**
All patients		118	5.1%	31	15–119
Tumour location	RUL and LUL	78	7.7%	21	10–79
	RLL and ML and LLL	40	0%	NA	NA
Tumour size	T1a and T1b	48	6.2%	51	16–∞
	T1c	70	4.3%	24	10–70
Histologic type	Adenocarcinoma	76	5.3%	26	11–∞
	Non-adenocarcinoma	42	4.8%	44	14–∞

Abbreviations: 95% CI, 95% confidence interval; LLL, left lower lobe; LUL, left upper lobe; ML, middle lobe; *N*, number; NA, not applicable (the control event rate is already 0%); NNT, number needed to treat; RLL, right lower lobe; RUL, right upper lobe.

To the best of our knowledge, our study is the only one that describes the diagnostic features of EBUS-TBNA in patients with centrally located stage IA (cT1N0M0) NSCLC, but not in those with the overall stage I NSCLC. In 2021, Kukhon et al.[15] described their experience with EBUS-TBNA in patients with central and peripheral radiological stage I NSCLC; that is, tumours sized ≤4 cm with absence of nodal disease on PET/CT. In their series, the sensitivity and NPV of EBUS-TBNA were not described (the outcomes of patients with negative EBUS-TBNA were not detailed) and the reported NNT to detect N2 disease was 15. This NNT is lower than that reported in our study. However, in the study of Kukhon et al., the NNT was not estimated as the number of patients needed to undergo EBUS-TBNA to avoid a case of pN2 disease after resection, but as the total number of EBUS-TBNA divided by number of positive EBUS-TBNA procedures. Thus, we consider that the results of both studies are not comparable.

With the introduction of lung screening programs, the incidence of early-stage NSCLC is likely to increase. Randomized controlled trials on NSCLC screening[16,17] have shown a higher incidence of stages I and II NSCLC in the screening arm compared with the control arm and with previous clinical series.[18,19] The feasibility of performing invasive mediastinal staging to all patients with early-stage NSCLC is controversial, even considering only patients with normal mediastinum on PET/CT, but with a current indication for invasive staging. Patients with tumours with normal mediastinum on PET/CT and an indication for invasive staging include a wide population with different prevalence rates of occult N2 disease, ranging from 26%–40.7% in patients with N1 on PET/CT,[6,20] to 11%–22% in patients with tumours sized >3 cm[10,21] or 4.6%–6.4% in patients with central T1N0 tumours.[10,22] Moreover, central cT1N0 tumours or peripheral cT2N0 or cT1N1 tumours are difficult to find in clinical practice while tumours sharing the three characteristics (e.g., central T2N1 tumours), with an added risk of occult N2 disease, are commonly seen.

Therefore, the prediction of risk of N2 in patients with normal mediastinum on PET/CT in clinical practice is difficult to estimate, although there are two apparent patterns: high likelihood of occult N2 disease in cN1 and low likelihood in cT1N0. Actually, the prevalence of occult N2 disease in tumours classified as cT1N0 is low, regardless of the location (central or peripheral), ranging from 4.6% to 8% in different series.[22–24] In the setting of our series, the prevalence of occult N2 (5.1%) is similar to that of other series exclusively including patients with cT1N0 tumours but lower than in overall patients with normal mediastinum on PET/CT. This finding explains the NPV of our study since NPV is related with prevalence. As an example, in our series, considering the same rate of sensitivity for EBUS-TBNA, for prevalence values of 1%, 5% and 20%, the NPV would be 100%, 98% and 91%, respectively.

The current prediction models HAL and HOMER[25] can estimate the probability of occult nodal disease in patients with NSCLC and their results have been validated in a multicenter study.[26] However, the question yet to be answered is what probability should be considered as a threshold to proceed to resection or to invasive staging.

The usefulness of a clinical intervention depends not only on the NNT, but also on the costs, the harms and the outcomes of different options. In this setting, the benefits of neoadjuvant therapy for N2 disease have been widely demonstrated.[27] Previous studies[28–30] have shown shorter survival rates in patients incidentally diagnosed as pN2 after resection (even after a proper staging procedure) compared with patients with a clinical diagnosis of N2 who received neoadjuvant therapy and resection showing ypN0. Moreover, with the promising results of the latest randomized control trials on neoadjuvant chemo-immunotherapy for patients with resectable NSCLC in stages IB-IIIA[31,32] the selection of patients with nodal disease before resection has become crucial. In this setting, in our series of 118 patients, 6 (42.8%) out of 14 patients with final diagnosis of nodal disease were diagnosed by means of EBUS-TBNA and could benefit from neoadjuvant treatment.

One of the major limitations of our study is the small sample size and even smaller event rate that leads to analyze the NNT results with caution. The NNT depends on the patient's baseline risk of the target event. In patients with early-stage NSCLC it is known that certain clinical characteristics[23] (histological type, tumour size among others) confer a higher risk of occult N2 disease. Thus, the NNT obtained in our study depends on the characteristics of our population as well as the diagnostic performance of EBUS-TBNA in our institutions, that may differ from others. However, we encourage other authors to publish their results in this clinical situation to select a population at a higher risk NNT.

In conclusion, the diagnostic accuracy of EBUS-TBNA in patients with central cT1N0M0 tumours is high, even in a population with low prevalence of N2 disease. Therefore, its indication should be considered in the management of even these early lung cancers.

AUTHOR CONTRIBUTIONS

Pere Serra Mitjà: Conceptualization (equal); investigation (equal); methodology (equal); writing – original draft (equal). **Bruno García-Cabo:** Conceptualization (equal); data curation (equal); investigation (equal); supervision (equal); writing – original draft (equal). **Ignasi Garcia-Olivé:** Formal analysis (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Joaquim Radua:** Formal analysis (equal); writing – original draft (equal). **Ramón Rami-Porta:** Conceptualization (equal); investigation (equal); writing – original draft (equal). **Lluís Esteban:** Data curation (equal); methodology (equal); writing – review and editing (equal). **Bienvenido Barreiro:** Investigation (equal); methodology (equal); writing – review and editing (equal). **Sergi Call:** Investigation (equal); methodology (equal); writing – review and editing (equal). **Carmen Centeno:** Investigation (equal); methodology (equal); writing – review and editing (equal). **Felipe Andreo:** Investigation (equal); methodology (equal); writing – review and editing (equal). **Carme Obiols:** Formal analysis (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Jose Manuel Ochoa:** Investigation (equal); methodology (equal); writing – review and editing (equal). **Mireia Martínez-Palau:** Investigation (equal); methodology (equal); writing – review and editing (equal). **Nina Reig:** Investigation (equal); methodology (equal); writing – review and editing (equal). **Mireia Serra:** Investigation (equal); methodology (equal); writing – review and editing (equal). **José Sanz-Santos:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (equal).

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

HUMAN ETHICS APPROVAL DECLARATION

The Internal Review Board of the Hospital Universitari Mútua Terrassa approved the study protocol (FAMT/PA22-060/22 June 2022) and, given the retrospective design and the minimal risk posed to patients by the use of their anonymized data, patients' informed consent was waived.

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