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The Value of a Systematic Protocol Using Endobronchial Ultrasound and Endoscopic Ultrasound in Staging of Lung Cancer for Patients with Imaging iN0–N1 Disease

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Keywords
Endobronchial ultrasound · Endoscopic ultrasound · Staging · Lung cancer · Radiographically normal mediastinum

Abstract
Introduction: We hypothesize that systematic, combined, and multidisciplinary study of the mediastinum (endobronchial ultrasound [EBUS] and endoscopic ultrasound [EUS]) in patients with NSCLC with radiologically normal mediastinum improves the results of mediastinal staging obtained with EBUS alone. ***Material and Methods:*** A retrospective study of the prospective database collected on the patients with NSCLC with a radiologically normal mediastinum and an indication for systematic staging with EBUS and EUS. EBUS staging was followed by EUS in patients in which the results from the pathological analysis of EBUS were negative. ***Results:*** Forty-five patients were included in the analysis. The combination of EBUS followed by EUS provided better results than EBUS alone: sensitivity (S) 95% versus 80%, negative predictive value (NPV) 96.15% versus 86.21%, negative likelihood ratio 0.05 versus 0.20, and post-test probability 3.8% versus 13.8%. This represents an increase in S (15%), the validity index (6.6%), and NPV (9.9%) compared to EBUS alone. There were 4 false negatives (FNs) (8.8%) with the EBUS test alone. After adding EUS, 3 more cases were positive (6.6%) and only 1 FN (2.2%). ***Conclusions:*** In patients with NSCLC and a radiographically normal mediastinum, a systematic and combined staging with EBUS and EUS show higher sensitivity in the detection of mediastinal metastasis than with the use of EBUS alone. The high accuracy of the test means that the use of mediastinoscopy is not necessary to confirm the results in these patients. Since the availability of EUS is low, it may be advisable for the interventional pulmonologist to receive training in EUS-b.

Introduction

Accurate staging is essential in lung cancer management. Both the treatment and prognosis depend not only on its histological type but also on the stage of the disease [1–3].

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Imaging techniques such as thoracic computerized tomography (CT) and positron emission tomography (PET) are used as a first-line modality to rule out mediastinal and distant metastatic disease. The appearance of lymph nodes larger than 10 mm on the CT or PET-positive mediastinal lymph nodes or both increase the probability of metastatic disease yet the accuracy of both tests is suboptimal. Hence, tissue samples are recommended to confirm or rule out metastasis. This is applicable to both group of patients with and without mediastinal involvement on the radiographic studies, especially among those with central lesion and suspected to have N1 disease [4–6]. This group with N0–N1 disease is especially important because even with tumor <3 cm, we can find occult lymph node metastasis [7–9].

The clinical practice guidelines recommend sampling the mediastinum with minimally invasive techniques, such as endobronchial ultrasound (EBUS) or endoscopic ultrasound (EUS) with fine-needle aspiration, both of which show a diagnostic yield comparable to the mediastinoscopy, which remains the gold standard to date [2, 4–6]. Several meta-analyses have shown a higher yield in staging by combining EBUS and EUS as a single technique because it makes it possible to access most lymph node stations and is more sensitive in the detection of lymph node metastasis than EBUS or EUS alone (global sensitivity [S] 0.86–0.91%) [10–15]. This increase in S by combining both tests depend on the quality of the procedure [16]. Therefore, mediastinoscopy is only recommended when puncture techniques are negative and there is still a high probability of malignancy [17]. This high post-test probability of malignancy was defined by De Leyn et al. [4, 6] in the ESTS guidelines, and it is described as a probability of lymph node involvement over 10%. Consequently, a negative predictive value (NPV) under 90% or a negative likelihood ratio (–LR) over 10 would require a mediastinoscopy after negative results with EBUS and EUS [4, 6]. However, some authors advise against mediastinoscopy in patients with a radiographically normal mediastinum even when puncture techniques are negative [18, 19].

Several authors use this combined technique with a single scope (EBUS + EUS-b), with a high diagnostic yield [11, 20, 21]. The disadvantage of the use of this combined technique with a single probe is the lack of training in gastrointestinal endoscopy, mainly in Spain [22].

In lung cancer patient with radiographically obvious mediastinal involvement, the diagnostic yield with the combined use of both tests has been previously demonstrate [10–13, 15]. Systematic staging in these patients with the sampling of all the lymph node stations regardless of PET with CT (PET-CT) uptake shows better results because it can detect lymph node metastases that are not detected by these imaging tests. Therefore, systematic staging is recommended for these patients, combined with EBUS and EUS [23, 24]. However, there are only a few studies that analyze the diagnostic yield of this combined approach in patients with a radiographically normal mediastinum [19, 21, 25]. The rate of false negatives (FNs) in the group of patients with a radiographically normal mediastinum is low although more predominantly in regions that cannot be reached with EBUS [26]. However, the combined EBUS and EUS procedure is more time and resource consuming than the sum of each test performed separately [27]. Therefore, it is important to select patients with a radiographically normal mediastinum who will benefit most from this procedure.

A team approach between a gastrointestinal endoscopy and interventional bronchoscopy teams makes it possible to perform a complete examination of the mediastinum in a single procedure while preserving all guarantees regarding yield and safety. We hypothesize that the systematic, combined, and multidisciplinary assessment of the mediastinum in patients with NSCLC and a radiographically normal mediastinum (EBUS and EUS) can improve the results of staging provided by EBUS alone and should therefore be recommended as a routine procedure for this group.

Objective

Our objective was to analyze the added value of a systematic, combined, and multidisciplinary assessment with EBUS and EUS in a single procedure when compared with EBUS alone in the staging of non-small cell lung cancer in patients with a radiographically normal mediastinum.

Material and Methods

Study Design

This was a retrospective analysis of prospectively collected data from a single center that included all consecutive patients with NSCLC, who met the criteria for surgery and underwent EBUS and EUS for mediastinal staging according to current clinical practice guidelines [2, 4–6]. All patients had undergone imaging tests, chest CT, and/or PET-CT.

Mediastinal involvement was established when the patient presented lymph nodes larger than 10 mm and/or nodes with a standardized uptake value (SUV) over 2.5 [28]. Patients with lymph

node involvement in CT and/or PET were excluded. Patients with a radiologically normal mediastinum were included in the study. The patient cohort was divided into different groups: patients with suspicion of N1 involvement; patients with a central tumor; patients with a peripheral tumor larger than 3 cm, and patients with tumor with low SUV.

Procedure

The procedure was performed as an outpatient under local anesthesia and moderate sedation in the bronchoscopy room with a BFUC180 ultrasound bronchoscope (Olympus Optical Co. Ltd, Tokyo, Japan) and an Olympus UE160 ultrasound endoscope (Olympus Optical Co. Ltd). The puncture aspiration was performed with a 22G needle (NA-201XS-4022; Olympus Optical Co.) for EBUS and a 25G needle (NA-220H/8025) for EUS. The procedure was performed by an experienced pneumologist as well as gastroenterologist.

EBUS was performed first, and if the results were negative on the rapid on-site evaluation (ROSE) performed by the pathologist, the gastroenterology specialist carried out EUS [27]. A systematic examination of the ipsilateral and contralateral mediastinum was performed (stations 2, 4, 7, 10, 11, 8, and 9), together with the celiac trunk and the left suprarenal gland, and all the lymph nodes larger than 5 mm were aspirated, starting with N3. The stations 4L and 7 were sampled via both endobronchial and esophageal ultrasound when they were observed in the 2 tests.

The ROSE determined that the sample was positive if malignant cells were observed, negative when lymphocytes were found, or inadequate when none of the previous findings were observed and the test revealed bronchial cells, necrosis, blood cells, or insufficient material for a diagnosis. The presence of malignant cells was considered a true positive since false positives with EBUS-EUS are very rare [29]. The gold standard was histology from mediastinoscopy or surgical resection in patients without N2–N3 involvement.

Statistical Analysis

A descriptive study was carried out with the categorical variables expressed as absolute and relative frequencies. The χ^2 test was applied to the bivariate analysis of these variables, and the Fisher's exact test was conducted when the expected frequencies were lower than 5. In all contrasts, statistical significance was established for a p value ≤0.05. Continuous variables were expressed as mean value and standard deviation and their differences were calculated with the difference in means and 95% confidence interval (CI). The Student's t test was used to establish the correlation between dichotomous qualitative and quantitative variables. Agreement was calculated with kappa coefficient. The validity of EBUS, EUS, and the combined tests was determined with the usual formulas. The Youden's index was also calculated for the different tests. The post-test probability was calculated with Fagan nomograms and the NNT, that is, the number of EUS procedures that had to be performed to detect one more case with lymph node metastasis that had not been previously detected by EBUS. It is the inverse of the absolute risk reduction (ARR) and we calculated the reduced risk of a FN result with combined EBUS and EUS compared to EBUS alone.

The statistical analysis and processing of data were carried out with the Statistical Package for Social Sciences (SPSS) v. 23. In some of the procedures, the programs Epidat 3.1 and Epidat 4.2 were also used.

Results

Between June 2012 and September 2018, 293 patients underwent noninvasive staging for suspected NSCLC of the lung. In all cases, EBUS and EUS were indicated for the staging. Two hundred and twenty-three patients were excluded because they showed mediastinal involvement on the imaging tests. Out of the remaining 70 patients, 25 were excluded because EUS was not available for staging (35.7%). Therefore, finally, 45 patients with a radiologically normal mediastinum were analyzed (shown in Fig. 1). The patients with suspicion of N1 involvement were 23 (51.1%); patients with a central tumor: 15 (33.3%); patients with a peripheral tumor larger than 3 cm: 5 (11.1%); and patients with low SUV: 2 (4.5%).

Out of the 45 patients with average age of 67.9 ± 8.7 years, 39 were men (86.7%). Gender and age showed no influence on the rate of mediastinal involvement (p = 0.5563 and p = 0.2580, respectively) (Table 1).

In 16 patients (35.6%), EBUS was positive for N2 or N3 on the ROSE and no EUS was conducted. In the 9 cases in which ROSE was not available and the 20 cases with negative ROSE, EUS was carried out after the EBUS staging (64.4%). The presence or absence of ROSE did not affect the final diagnostic yield of the test (p = 0.8637). The agreement between the results from ROSE and the final EBUS and EUS diagnosis was 76% (kappa 0.52; 95% CI: 0.193–0.851), which represents substantial agreement.

All patients without N2–N3 involvement in EBUS and EUS underwent surgery except for one, who underwent mediastinoscopy. In total, 139 punctures were performed on lymph nodes with an average size of 8.81 ± 3.38 mm and an average maximum SUV of 1.17 ± 2.90. The most commonly sampled stations were 7 and 4R (shown in Fig. 2). The number of punctures per patient was 3.33 ± 1.40.

No severe complications were registered in any of the procedures. Mild desaturation was observed in 7 patients: 3 who only underwent EBUS and 4 in which the combined test was performed. No statistical differences were observed regarding complications between the procedure with EBUS alone and the combined EBUS and EUS test (p = 0.441).

One hundred and seven EBUS punctures were performed in 45 patients, and a valid sample was obtained in 93.4% of the cases. Out of these 45 patients, 16 were positive (35.5%) and 11 of them had N2–N3 involvement (24.4%). In addition, 4 patients were FNs (8.8%), 3 of them in the central tumor group, and 1 in the N1 involve-

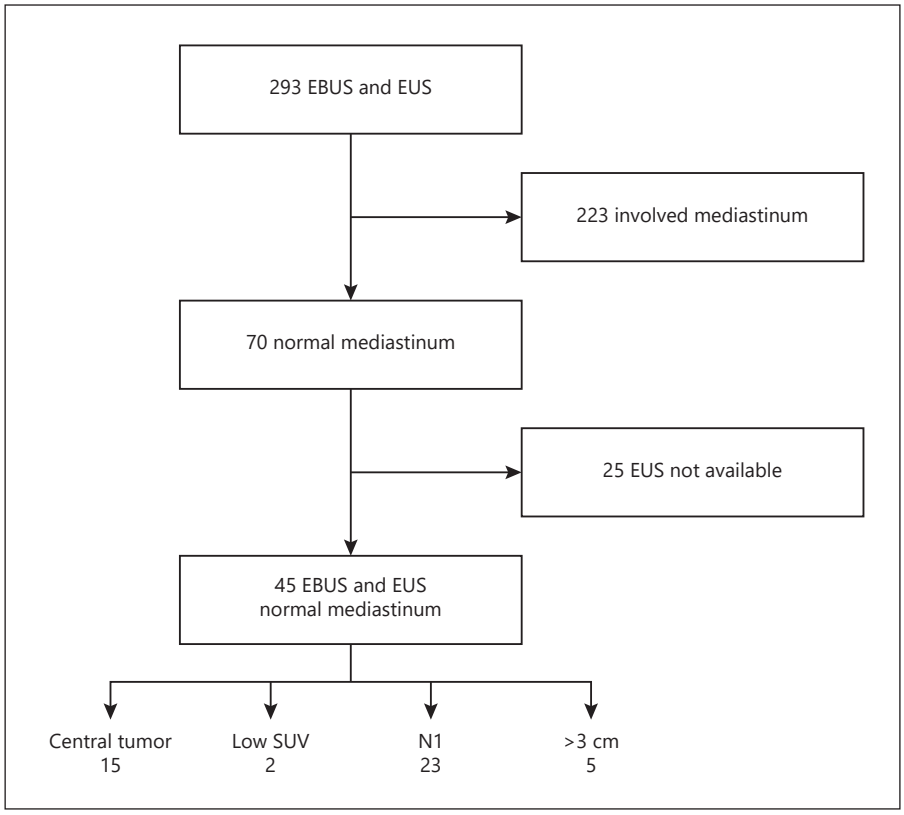

Fig. 1. Flow chart. Selection of the patients.

Table 1. General demographics of the 45 patients

Sex, *n* (%)	
Male	39 (86.7)
Female	6 (13.3)
Median age	67.9±8.7 years
Tumor localization, *n* (%)	
Right	26 (57.8)
Left	19 (42.2)
Type of normal mediastinum, *n* (%)	
Central tumor	15 (33.3)
N1 involvement	23 (51.1)
>3 cm	5 (11.1)
Low SUV	2 (4.5)

SUV, standardized uptake value.

ment group. In 3 of those cases, the involved stations were accessible with EBUS (Table 2).

Regarding EUS, 32 punctures were performed in 29 patients (64.4%), with a valid sample in 81.2% of the cases and 3 positive results (6.6%). In these patients, the diagnosis was obtained with this test alone, and it led to a change in the staging (Table 2). In 2 cases, the stations punctured with EBUS were negative or not valid; however, station 7 was positive with EUS. Both patients moved from N0 to N1 involvement to N2. In the other patient, station 4R was negative in EBUS and station 7 was not valid. In the EUS, station 9 was positive. These diagnoses obtained exclusively with EUS led to an increase in S by 15% and in the accuracy of the test by 6.6% (Table 3).

With the combined EBUS and EUS tests, 139 punctures were performed, with a valid sample in 90.5% of the cases. In all the patients, a valid sample was obtained in some of the stations analyzed. Out of the 45 patients, 19 were positive with EBUS and EUS (42.2%), 5 of whom were N1 (26.3%), 11 were N2 (57.9%), and 3 were N3 (15.8%). Therefore, the rate of N2–N3 cases detected by EBUS and EUS was 31.1% (14 patients). There was only 1 FN (2.2%) who was detected after surgery and presented micrometastasis of squamous cell carcinoma in station 4R. The number of combined EBUS and EUS tests required to reduce FN results by 1 (NNT) was 33, and the ARR for FNs was 3%.

The final prevalence of the metastatic disease at any stage N was 44.4%, and in the case of N2–N3 involvement, it was 33.3%. N2–N3 prevalence was higher in the group of patients with a central tumor (6 cases, 40%), with

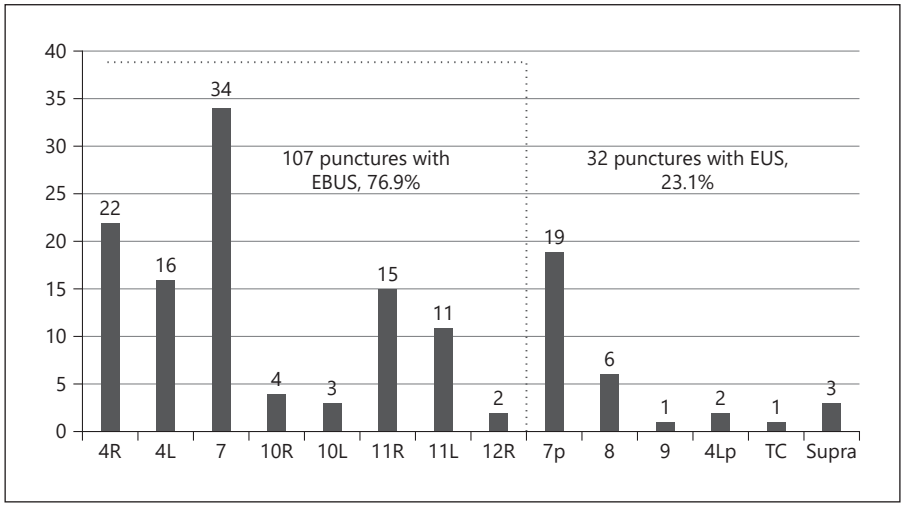

Fig. 2. Region stations punctured by EBUS and EUS. 7p, station 7 punctured with EUS; 4Lp, station 4L punctured with EUS; TC, lymph node in celiac trunk; Supra, left suprarenal gland; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound.

Table 2. FNs with EBUS and EUS and exclusive diagnoses with EUS

Normal mediastinum type	EBUS punctured stations	EUS punctured stations	FN station	Exclusive diagnosis with EUS	EBUS stage	Final stage	Notes
Central tumor	4R–, 4L–,7–	4L–, 7–	4R	No	N0	N2	Micrometastasis in 4R in surgery
Central tumor	4R–, 4L nv,7 nv	7+, 4L–	7	Yes	N0	N2	+ In 7 with EUS
Central tumor	7–	7+, TC–	7	Yes	N0	N2	+ In 7 with EUS
N1	4R–, 7 nv	9+, 7–	9	Yes	N0	N2	9+, not accessible with EBUS

nv, nonvalid sample; TC, celiac trunk; FNs, false negatives; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound.

Table 3. Improvement in statistical values

	S, %	NPV, %	Accuracy, %	Positive patients	–LR	Pp, %
EBUS	80 (59.9–100)	86.2 (71.9–100)	91.1 (81.7–100)	16	0.20 (0.08–0.48)	13.8
EBUS and EUS	95 (82.9–100)	96.1 (86.8–100)	97.8 (92.4–100)	19	0.05 (0.01–0.34)	3.8
Variation	+15	+9.9	+6.6	+3	−0.15	−10

NPV, negative predictive value; –LR, negative likelihood ratio; Pp, post-test probability; S, sensitivity; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound.

5 positive cases for N2 and 1 for N3, followed by patients with suspicion of N1 involvement (8 cases, 34.8%), with 6 positive cases for N2 and 2 for N3. In the rest of groups with a radiologically normal mediastinum, there were no positive cases with N2–N3 involvement.

EBUS was used to diagnose correctly 91.11% of the patients (95% CI: 81.69–100%), with a S of 80% (95% CI: 59.97–100%), a NPV of 86.21% (95% CI: 71.93–100%), and a –LR of 0.20 (Table 4). The post-test probability represented with Fagan nomograms was 13.8% (Fig. 3). When EUS was added, a correct diagnosis was reached for 97.78% of the patients (95% CI: 92.36–100%), with S: 95% (95% CI: 82.95–100%), VPN: 96.15% (95% CI: 96.84–100%), and –LR: 0.05 (Table 3). The post-test probability represented with Fagan nomograms was 3.8% (shown in Fig. 3). In summary, the combined EBUS and EUS tests in patients with a radiologically normal mediastinum represent an increase in S (15%), the validity index (6.6%),

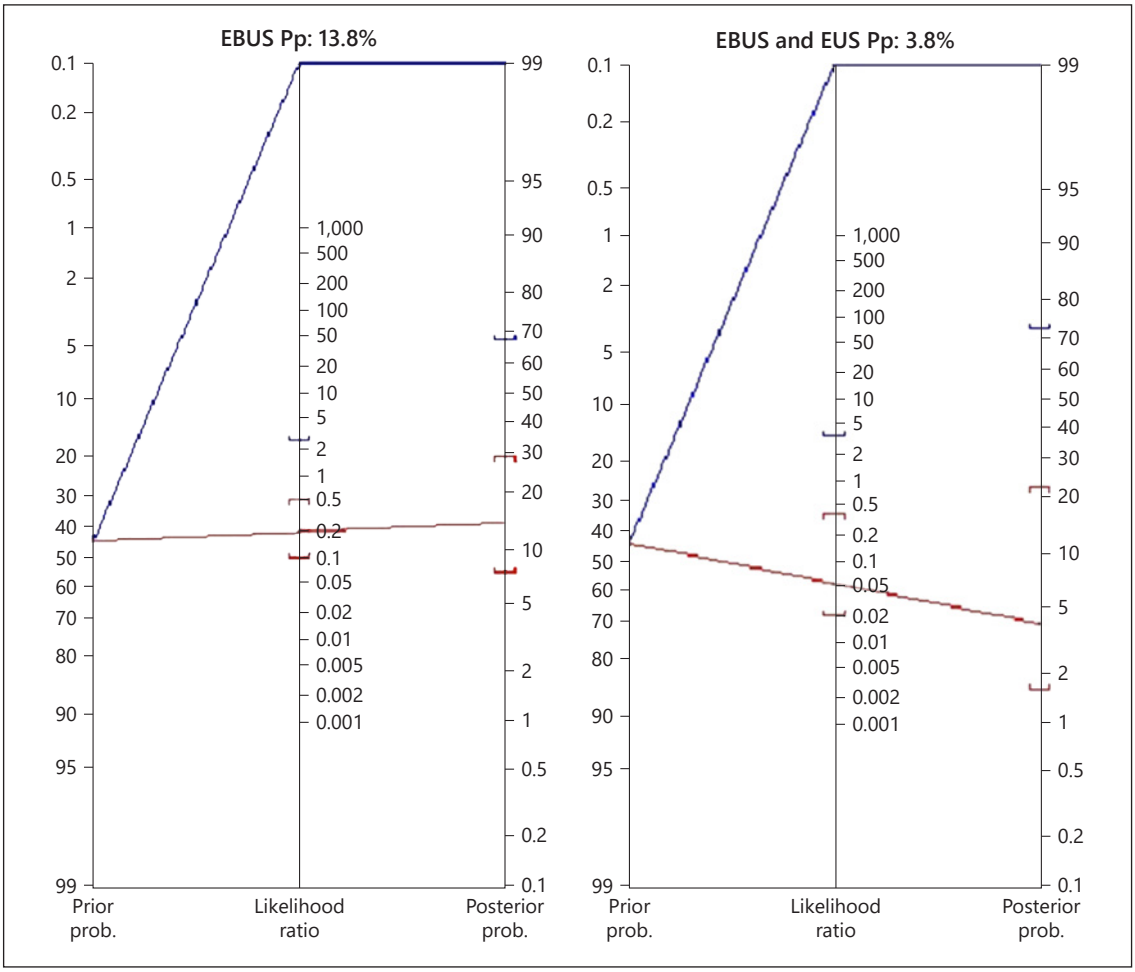

Fig. 3. Fagan nomograms in EBUS and EBUS-EUS. Pp, post-test probability; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound.

and NPV (9.9%) when compared with EBUS alone, which significantly increases the probability to achieve the correct diagnosis (Table 3).

Discussion

This study shows that the systematic use of the combined EBUS and EUS tests in the staging of patients with NSCLC and a radiologically normal mediastinum increases the S to detect occult metastasis by up to 15.4% (92.3% vs. 76.9%) when compared with EBUS alone. This increase in S had already been observed in other studies, as it has been published in several meta-analyses, such as those by Dhooria et al. [11] and Korevaar et al. [13], who report an improvement by 11% and 12%, respectively. More recently, Crombag et al. [24] observed an improve-

Table 4. Precision statistics of EBUS and EBUS-EUS

	EBUS, % (95% CI)	EBUS and EUS, % (95% CI)
Sensitivity	80 (59.97–100)	95 (82.95–100)
Specificity	100 (98–100)	100 (98–100)
Validity index	91.11 (81.69–100)	97.78 (92.36–100)
PPV	100 (96.88–100)	100 (97.37–100)
NPV	86.21 (71.93–100)	96.15 (86.84–100)
YI	0.80 (0.62–0.98)	0.95 (0.85–0.01)
–LR	0.20 (0.08–0.48)	0.05 (0.01–0.34)
Pp	13.8	3.8
Prevalence of N2–N3	24.4	31.1

CI, confidence interval; –LR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; YI, Youden's index; Pp, post-test probability.

ment by 9% when performing EBUS and EUS-b systematically in staging. However, these studies include patients with mediastinal involvement in the imaging tests (PET-CT), and they do not establish a difference with patients without mediastinal involvement. Only 2 meta-analyses have been published that analyze the influence of EBUS on the staging of this type of patients. One of those studies analyzes the influence of EBUS as a single procedure [30]. The second one, published by Leong et al. [14], includes 13 studies, but only 3 of them analyze the influence of the combined EBUS and EUS tests [19, 21]. Based on those studies, the S of the combined test was 71%, compared to 52% for EBUS alone, which represents an increase in S by 19%. Therefore, staging with combined EBUS and EUS in patients with a radiologically normal mediastinum is the most adequate option because it can diagnose 4.9% more cases.

These data are similar to those found in our study, in which 6.6% more cases were diagnosed, 24.4% of which changed from N0 to N2; 6.6% changed to N3; and 11.1% changed from N0 to N1. All these results are clinically relevant, which supports the utility of this type of staging. In that meta-analysis [14], the calculated NNT for the combined test compared with EBUS alone was 21 procedures, which is slightly lower than what we observed in our study, with an NNT of 33, with an ARR of 3%. This analysis is also shown in the study by Korevaar et al. [13], in which 25 combined procedures are required to reduce 1 FN result although the series includes patients with mediastinal involvement in the imaging tests. It could seem that this is a high number, but we need to consider that the clinical benefit is large, since lung cancer is a serious condition. In addition, correct staging prevents unnecessary thoracotomies and unwanted secondary effects and it reduces health costs [31]. On the other hand, adding EUS to the EBUS procedure does not involve an increase in complications, which means that the cost-benefit is ultimately positive [32].

In our center, EUS was decided, instead of EUS-b, due to the lack of training of the interventional pneumologist. It is necessary to highlight that there is no specific training for this procedure in Spain, as well as in other countries, which accounts for the lack of adherence of endoscopists to the staging guidelines [33, 34]. On the other hand, the studies show that both the combined EBUS and EUS strategies and the EBUS and EUS-b procedures are valid options for staging. Although some authors have reported higher S values with the first one (87% vs. 84%) [15], and others with the second one (85% vs. 88%) [12], the results are similar for both approaches.

In both cases, the test is performed at the same time, which means that the patient is only subject to one procedure. EUS has some advantages over EUS-b, such as better visualization or a better access for punctures. Its main disadvantage, apart from the costs derived from the use of 2 endoscopes and 2 explorers, is the lack of availability to perform the test as a single procedure together with EBUS, in order to spare patients from undergoing 2 examinations and from everything these involve. In our series, the gastrointestinal specialist was not available in up to 35% of the cases. Therefore, we believe that the interventional pulmonologist must receive training in EUS-b and incorporate this technique in combined staging procedures [35]. In fact, considering these results, EBUS and EUS-b are performed systematically to all patients in our center.

Apart from the improvement in S, we observed an improvement in the global yield of the test, as well as in VPN and −LR. This improvement was due to the fact that the combined test was able to detect more cases of metastatic involvement than EBUS alone. A decrease in FN results was also observed (from 4 cases in EBUS alone to 1 case in EBUS and EUS), which were in almost all cases found in regions that could be accessed with EBUS, as has been described by other authors [26, 36]. The only case that was not detected in the combined procedure was due to the presence of micrometastasis, which cannot be detected by any of these tests. We must highlight the fact that puncturing the same region shows a good diagnostic yield, which may be explained by the nonuniform presence of metastasis in the lymph node, as has been described in other studies [19, 37]. This problem could be solved with other techniques such as EBUS elastography [38]. Only one case was found in a station that could not be accessed with EBUS (station 9). It is necessary to point out that the use of EUS in these patients did not only lead to a correct diagnosis but was the only method that could provide it, so that diagnosis and staging were obtained in a single procedure, thus preventing unnecessary procedures and complications, as some authors recommend [39]. However, there is controversy on the need to use this combined strategy in patients with a normal mediastinum because the rate of mediastinal involvement in stations that are not accessible with EBUS (8 and 9) without an involvement of upper mediastinal stations is low [40, 41]. This was also observed in our series and, in spite of it, S increased when EUS was added.

The decision to start with EBUS and continue with EUS if the first test was negative is supported by studies that show a significant increase in S and significant staging changes when this strategy is implemented, rather

than starting with EUS and continuing with EBUS because this second strategy has no impact on S and does not have much influence on staging changes [28].

With regard to the rate of metastatic mediastinal involvement in patients with a radiologically normal mediastinum, the studies published in the literature show figures that range between 20% and 42%, with a rate of 21% for patients with central tumors and 30% for patients with radiological N1 tumors, which makes it advisable to perform EBUS [17, 19, 41–44]. In our series, we also observed similar rates of metastatic mediastinal involvement, which supports the need to apply invasive techniques for the staging of this type of patients in our hospitals. It is true that the prevalence of metastatic disease in our series is higher in the group with central tumors and tumors with N1 involvement than in other series. However, we must highlight that, in our study, the procedure is systematic and detailed, as other authors recommend [16], which means that all the accessible stations were explored with both procedures and all the lymph nodes larger than 5 mm were punctured. We do not know how thorough the procedure was in other published series with a lower prevalence, since the procedure is not explained in detail, which is also reflected in their interobserver variability [34, 45]. On the other hand, the lack of consensus for the definition of central tumors also explains the variability in the rate of metastatic involvement [46].

In our series, these data also confirm that the diagnostic yield of EBUS and EUS is clearly higher than EUS alone (97% vs. 91.4%), with a NPV that rises from 88% to 95.6% and a decrease in −LR from 0.20 to 0.05. This increase in the diagnostic yield had already been observed by other authors [19] in this type of patients with a radiologically normal mediastinum, with similar results to what was found in our series (NPV: 86% vs. 91%). This author advises against confirmation mediastinoscopy although the procedure is recommended by the other authors [14].

Therefore, if the puncture tests are negative, mediastinoscopy is recommended if the post-test probability of malignancy is >10% [6]. In our series, the post-test probability was 3.8%. Consequently, no confirmation mediastinoscopy was performed. However, in the cases in which the staging could not be completed, we recommend mediastinoscopy prior to surgery because the post-test probability in these cases is 13.8%, which is higher than what is established in the literature [6]. According to the data in our study, confirmation mediastinoscopy is not necessary when staging is performed with combined EBUS and EUS, as other authors have pointed out [18, 47, 48].

We must mention some limitations in our study since it is a single-center analysis in which the endoscopists and the bronchoscopists had a vast experience with the procedure. Thus, the results may not be extrapolated to other centers. The number of patients studied is also small yet these data stand well with the similar past studies. On the other hand, in a significant number of patients, EUS was not available thus reducing the total number of analyzed patients. For this reason, it is important that interventional pulmonologist receive training with this technique.

Conclusions

In patients with NSCLC and a radiologically normal mediastinum, a systematic and combined staging strategy with EBUS and EUS leads to increased sensitivity in the detection of mediastinal metastases compared with EBUS alone, which may justify their routine use. The high accuracy of the test means that mediastinoscopy is not required to confirm the results in these patients. Moreover, the combined technique has an added clinical value because some patients are diagnosed exclusively with EUS. The combined strategy of EBUS and EUS with a multidisciplinary approach is useful and effective in the staging of NSCLC but since the availability of EUS is low, we recommend that interventional pulmonologists receive training with EUS-b.

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Statement of Ethics

All patients signed a written informed consent and the research was approved by ethical board of the Salamanca University Hospital (no.: 27032016). Published research comply with internationally accepted standards for research practice and reporting.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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No external sources were required to carry out this study.

Author Contributions

Rosa Cordovilla contributed to the design of the work, acquisition the samples by EBUS, analysis and interpretation of data for the work, drafting the work, redaction the manuscript, and revision of the manuscript. Marco López-Zubizarreta and Miguel Iglesias contributed to acquisition of samples by EBUS, analysis and interpretation of data for the work, and revision of the manuscript. Antonio Velasco and Alberto Álvarez contributed to acquisition of samples by EUS and revision of the manuscript. Marta Rodríguez and Asunción Gómez contributed to analysis of samples and revision of the manuscript. Miguel Ángel Hernández-Mezquita contributed to inclusion of patients, drafting the work, and revision of the manuscript.

Data Availability Statement

All data that support the findings of this research are not available on internet due to the current legal framework in Spain (LOPDGDD 3/2018, ref: BOE-A-2018-16673). Further enquires can be directed to the corresponding author.

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