



## Original Article

## Significance of the Presence of Lymphocytes in the Cytological Analysis of Transbronchial Needle Aspiration

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## ABSTRACT

**Aim:** To evaluate the clinical relevance of the presence of lymphocytes in transbronchial needle aspiration (TBNA) samples from pathological mediastinal lymph nodes in patients with suspected lung cancer.

**Methods:** Retrospective observational study evaluating the negative predictive value (NPV) of TBNA samples with evidence of lymphocytes but no atypical cells.

**Results:** A total of 266 TBNA were performed in 252 patients with pathological mediastinal lymphadenopathy. One hundred and fifteen TBNA samples showed evidence of malignant cells (43%) and 94 (35%) samples were considered inadequate (absence of adequate cytological material or exclusive presence of bronchial epithelial cells). Out of the 57 TBNA samples remaining that contained lymphocytes without atypia (21%), 15 could not be confirmed. Thirty-two TBNA samples were confirmed with alternative diagnostic techniques and 10 were confirmed after clinical and radiological follow-up. The NPV of the 32 samples that were confirmed with alternative diagnostic techniques was 84%, which decreased to 76% when we included the 10 TBNA samples confirmed after clinical and radiological follow-up.

**Conclusions:** The presence of lymphocytes without atypia in TBNA samples does not rule out the neoplastic invasion of the lymph node analyzed.

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## Significado de la presencia de linfocitos en el análisis citológico de la punción transbronquial aspirativa

## RESUMEN

**Objetivo:** Analizar el significado de la presencia de linfocitos en las muestras de punción transbronquial aspirativa (PTA) de adenopatías mediastínicas (AM) en pacientes con sospecha de cáncer de pulmón (CP).

**Métodos:** Estudio observacional retrospectivo que evalúa el valor predictivo negativo (VPN) de las muestras de PTA con evidencia de linfocitos pero sin células atípicas.

**Resultados:** Se realizaron 266 PTA a 252 pacientes con AM patológicas. En 115 PTA se evidenció la presencia de metástasis ganglionares (43%), y 94 (35%) fueron consideradas como no valorables (ausencia de material citológico evaluable o presencia exclusiva de células epiteliales bronquiales). De las 57 muestras de PTA restantes que contenían linfocitos sin atipias (21%), en 15 no se pudo confirmar el diagnóstico; en 32 se confirmó mediante técnicas diagnósticas alternativas y en 10 mediante seguimiento clínico-radiológico. El VPN de las 32 muestras confirmadas con técnicas diagnósticas alternativas fue del 84% y descendió al 76% cuando se incluyeron las 10 PTA en las que se disponía de seguimiento clínico-radiológico.

**Conclusiones:** La presencia de linfocitos sin atipias en la muestra de PTA no excluye la invasión neoplásica del ganglio analizado.

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## Palabras clave:

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## Introduction

It is estimated that 30–44% of patients with lung cancer (LC) have mediastinal lymph node metastasis at the time of diagnosis.<sup>1</sup> Its presence determines the prognosis and the therapeutic plan of the disease. According to international clinical guidelines, the high percentage of false positives (FP) that are obtained with imaging techniques (computed tomography [CT] and positron emission tomography [PET]) in studying mediastinal lymphadenopathy (ML) warrant the cytological or histological confirmation of the presence of neoplastic infiltration.<sup>2</sup> Due to its elevated sensitivity and specificity, mediastinoscopy is considered the “gold standard” technique for staging mediastinal tissue.<sup>3,4</sup> Mediastinoscopy, however, is a surgical technique that carries with it high hospital costs as well as important morbidity and mortality.<sup>5</sup> On the other hand, transbronchial needle aspiration (TBNA) plays a recognized role in the bronchoscopic evaluation of patients with suspicion for LC.<sup>6,7</sup> Unlike mediastinoscopy, TBNA does not require general anesthesia, surgery or hospitalization, and it can be done at the time of the diagnostic bronchoscopy, merely increasing the duration of the exploration by a few minutes. These factors mean that the financial costs and personnel involved in performing TBNA are much less than in mediastinoscopy.

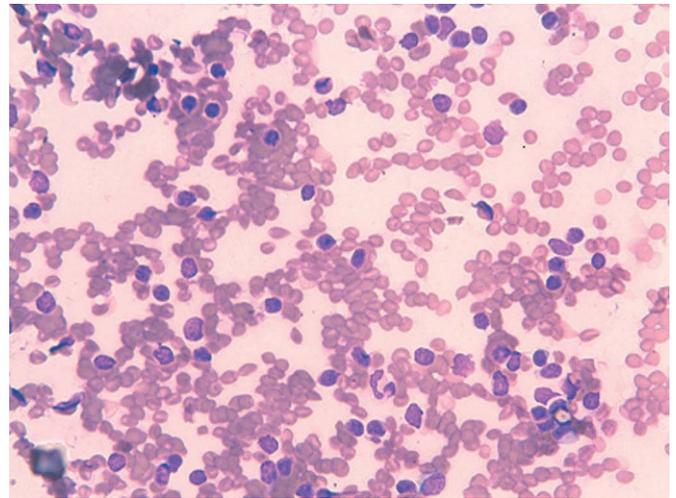
Nevertheless, there is some controversy about the overall cost-effectiveness of TBNA in the mediastinal staging of LC. Different published series show sensitivities that range from 36 to 82%, a fact that is explained by the greater or lesser influence of certain factors, such as the experience of the bronchoscopist or the prevalence of neoplastic disease in the study population.<sup>8–11</sup> According to the published series, one of the factors that could most influence the diagnostic cost-effectiveness of TBNA is the different consideration given to the negative samples.<sup>12</sup> The presence of lymphocytes in the cytological analysis of the sample is said to demonstrate that the aspiration is nodal and, therefore, that the sample is adequate. Said consideration is based on the study by Baker et al.<sup>13</sup> in which the predictive value of a negative result was calculated separately depending on whether the sample had lymphocytes or not. In this study, the presence of lymphocytes in a negative sample had a predictive value of 78%, a value quite superior to the 36% obtained when the negative sample did not contain lymphocytes. Nonetheless, the study by Baker is based on the analysis of a very small number of cases in which only 9 samples analyzed contained lymphocytes. Determining the negative predictive value (NPV) of TBNA is of great clinical relevance that because, if it were high, it would avoid having to perform more invasive explorations to confirm the absence of lymphatic metastasis.

With the aim of ascertaining the NPV of TBNA with lymphocytic content, we have carried out a retrospective analysis of a total of 266 TBNA samples obtained in a single center from patients with suspicion for LC.

## Methods

Ours is a retrospective observational study analyzing the TBNA performed in the bronchoscopy unit in a Spanish third-level hospital between January 2006 and December 2009. For the main objective of the study, we included only those TBNA carried out in patients with suspicion of LC and presence, as seen on CT, of ML of increased size (minor axis equal to or greater than 10 mm) and approachable by TBNA.

The details concerning TBNA in our center have been described previously.<sup>12</sup> In brief, endoscopic exploration was done under conscious sedation with either sublingual midazolam or midazolam and intravenous fentanyl, depending on the criteria of the endoscopist. In all cases, eXcelon 21G cytology needles (Boston Scientific, Spencer, IN, USA) were used. The number of punctures performed on each



**Figure 1.** Representation of a transbronchial needle aspiration sample with presence of abundant lymphocytes on a hemorrhagic background.

patient varied depending on the criteria of the endoscopist, ranging from 2 to 4 for each lymph node station studied.

For the objective of the present study, TBNA with the presence of neoplastic cells were considered true positives (TP). TBNA with presence of lymphoid cells and absence of atypia were considered true negatives (TN) only when they were verified by means of alternative diagnostic techniques or when the final diagnosis was not LC. The TBNA with lymphoid cells and absence of atypia in which the alternative diagnostic techniques showed the presence of neoplastic infiltration in the lymph node being studied, were considered false negatives (FN). Finally, those TBNA that, without presence of atypia, were considered adequate due to the presence of lymphoid cells and could not be verified by other techniques due to either the patient's lack of willingness or the inoperability of the lesion were classified as unconfirmed.

The quality of the TBNA samples was based on the abundance of the existing lymphocytic population. In order to find out whether this quality could influence the prevalence of FN, we carried out a semi-quantitative analysis of the 5 samples catalogued as FN and compared with 5 samples taken randomly from the TN group. In each case, the pathologist, who had no knowledge of the definitive diagnosis, established the quality of the sample depending on the presence of lymphocytes in three categories: abundant, moderate or scarce (fig. 1).

With the aim of including the greatest number of cases possible in the study, a subanalysis was completed which also included the patients with unconfirmed samples. The sample being studied was considered TN when the PET of the ML being studied did not show pathological capture and a radiological follow-up by CT of at least 6 months in which there was no evidence of nodal growth. On the other hand, a sample was considered FN when the PET of the specific ML was positive and/or there was a reduction in size of the lymph node with chemotherapy.

## Statistical Analysis

The results of the quantitative variables were expressed as mean  $\pm$  standard deviation. For the qualitative variables, absolute frequencies and percentages were used. NPV was determined with the equation:  $NPV = TN / (TN + FN)$ .

The prevalence of lymphatic affectionation in the population studied was calculated with the formula:  $(TP + FN) / N$ ,  $N$  being the total number of patients with definitive diagnosis of LC. Proportions were

compared by means of the chi-squared test. P < 0.05 was considered significant.

**Results**

We evaluated a total of 266 TBNA from 252 patients with suspicion for LC and presence on CT of pathologic-sized ML (smallest diameter equal or greater than 10 mm). Out of the 252 patients, 238 underwent one TBNA and 14 underwent two TBNAs. As shown in figure 2, out of the 266 TBNA, 115 samples (43%) showed the presence of nodal metastasis, 94 (35%) were not evaluable (absence of evaluable cytological material or exclusive presence of bronchial epithelial cells) and in 57 (21%) there was evidence of lymphoid cells with no presence of atypia. LC diagnosis was confirmed in 208 of the 252 patients, which means a prevalence of this disease in the study population of 82%. We observed no complications related with TBNA. Out of the 57 samples showing evidence for lymphoid cells with no presence of atypia, a total of 15 TBNA were excluded. Thirteen corresponded to patients who did not continue in the study due to advanced age, presence of distant metastasis (stage IV) or death prior to definitive diagnosis. Likewise, we excluded 2 TBNA from patients diagnosed with small-cell carcinoma who started with chemotherapy immediately after determining the definitive histological diagnosis. Therefore, the final study cohort was made up of 42 TBNA with lymphocytic content and absence of atypia.

The 42 TBNA belonged to 40 patients, 34 (81%) of which were males and 8 (19%) females. Mean age of the study group was 64 ± 11. Definitive diagnosis for LC was obtained in 24 cases (57%), squamous carcinoma being the most frequent histological type (table 1).

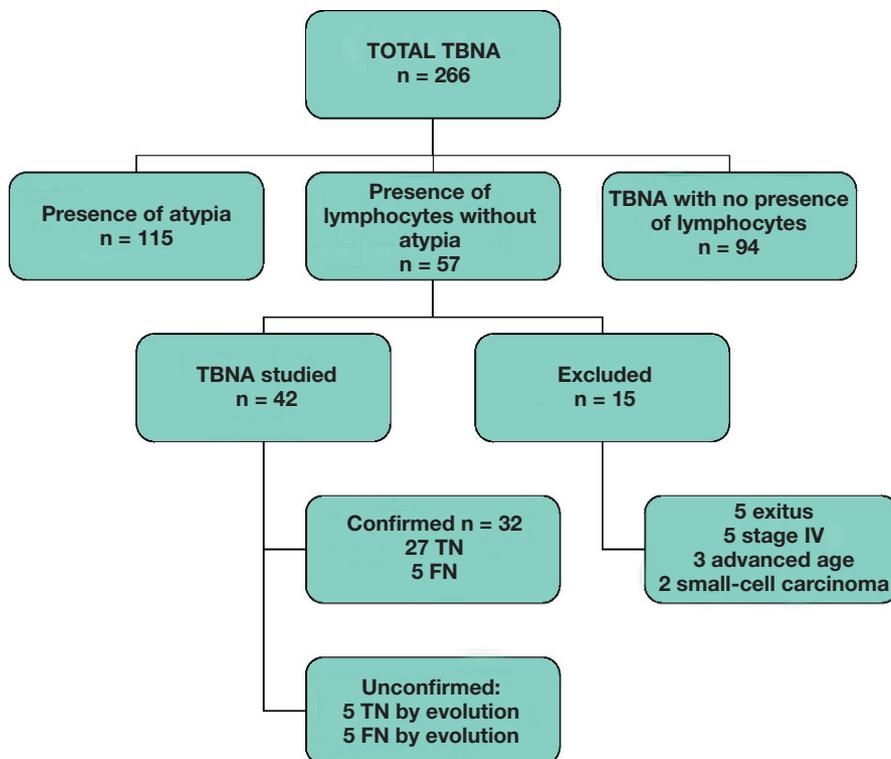
Following the anatomical outline described by Wang,<sup>14</sup> the lymph node stations evaluated were: subcarinal in 23 cases (55%), right paratracheal in 16 cases (38%), left paratracheal in 2 cases (5%) and precarinal in 1 case (2%).

**Table 1**  
Definitive histological diagnosis of the 42 cases included

| Diagnosis                           | N  | %   |
|-------------------------------------|----|-----|
| <i>Pulmonary neoplasia</i>          | 24 | 57  |
| Squamous carcinoma                  | 11 | 26  |
| Adenocarcinoma                      | 8  | 19  |
| Non-small-cell carcinoma            | 4  | 9.5 |
| Small-cell carcinoma                | 1  | 2.5 |
| <i>Other</i>                        | 18 | 43  |
| Infection                           | 6  | 14  |
| Inflammatory origin                 | 4  | 9.5 |
| Extrapulmonary neoplasia metastasis | 2  | 4.8 |
| Melanoma                            | 2  | 4.8 |
| Hematological neoplasia             | 2  | 4.8 |
| Other                               | 2  | 4.8 |

*Predictive Value of the TBNA Samples with Confirmed Lymphocytes and Absence of Atypia*

In 23 of the 42 cases in which TBNA showed presence of lymphocytes and absence de atypical cells, an alternative diagnostic technique was used. Specifically, in 5 cases we performed endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), in 2 mediastinoscopy and in 12 thoracotomy. In 4 additional patients, the alternative diagnostic technique was the repetition of the TBNA, confirming a benign diagnosis in 3 cases (negative PET and radiological follow-up of a minimum of 6 months) and FN was identified in the last case. In 9 patients, the definitive diagnosis was not LC. Specifically, 2 cases were diagnosed with lymphoproliferative syndrome, 1 case of sarcoidosis and 6 cases of lung infection/inflammatory process with complete clinical-radiological solution.



FN false negative; TBNA: transbronchial needle aspiration; TN: true negative.

**Figure 2.** Distribution of transbronchial needle aspirations in patients with suspicion for lung cancer, from January 2006 to December 2009.

**Table 2**

Transbronchial needle aspiration with lymphocytes and without atypia, confirmed by means of alternative diagnostic techniques and classified as true negatives

|                                 |    |      |
|---------------------------------|----|------|
| Age                             | 64 | ± 12 |
| Sex                             |    |      |
| Male                            | 21 | 78%  |
| Female                          | 6  | 22%  |
| Lymph node station              |    |      |
| Subcarinal                      | 16 | 59%  |
| Right paratracheal              | 9  | 33%  |
| Left paratracheal               | 1  | 4%   |
| Precarinal                      | 1  | 4%   |
| Definitive diagnostic procedure |    |      |
| Follow-up                       | 9  | 33%  |
| Repeated TBNA                   | 3  | 11%  |
| EUS-FNA                         | 4  | 15%  |
| Mediastinoscopy                 | 1  | 4%   |
| Thoracotomy                     | 10 | 37%  |
| Definitive diagnostic histology |    |      |
| Lung neoplasia                  | 11 | 41%  |
| Other                           | 16 | 59%  |

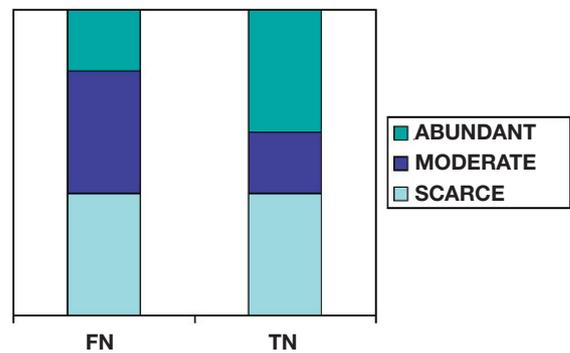
EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; TBNA: transbronchial needle aspiration.

In this way, we considered 32 of the 42 TBNA studied to be confirmed.

Out of the 32 TBNA samples confirmed, we found evidence for TN in 27 cases and for FN in 5 cases ([Table 2] and [Table 3]). Therefore, the NPV of the presence of lymphocytes without atypia in the TBNA samples was 84%.

*Predictive Value of the Unconfirmed Samples of TBNA with Lymphocytes and Absence of Atypia*

The 10 remaining TBNA that could not be confirmed were classified by evaluation (see “Methods” section) as 5 TN and 5 FN (table 4). When these samples were included in the analysis, overall NPV went from 84 to 76%.



FN: false negative; TN: true negative.

**Figure 3.** Concentration of lymphocytes in the transbronchial needle aspiration samples (scarce, moderate and abundant) in the group of true negatives (n = 5) and false negatives (n = 5).

FN: false negative; TN: true negative.

*Predictive Value and Lymph Node Area*

The NPV of the TBNA, when considering the total of 42 samples with lymphocytes, was 87% in the subcarinal area and 63% in the paratracheal territories (right and left) (p = 0.06).

*Semiquantitative Analysis of the Lymphocytic Population*

The semiquantitative analysis of the presence of lymphocytes in the TBNA samples of the 5 FN and their comparison with 5 TN is shown in figure 3. There were no differences between the abundance of lymphocytes in the TBNA sample and the incidence of FN.

**Discussion**

The results of the present study show that the NPV of the presence of lymphocytes in the TBNA sample of patients with suspicion for LC ranges between 76 and 84%. In other words, and from a clinical

**Table 3**

Transbronchial needle aspiration (TBNA) with lymphocytes and without atypia, confirmed by alternative diagnostic techniques and classified as false negatives

| Patient | Sex  | Age | Lymph node station | Definitive diagnostic technique | Definitive histological diagnosis |
|---------|------|-----|--------------------|---------------------------------|-----------------------------------|
| 1       | Male | 70  | 4L                 | EUS-FNA                         | Adenocarcinoma                    |
| 2       | Male | 60  | 7                  | Thoracotomy                     | Squamous carcinoma                |
| 3       | Male | 55  | 4R                 | Mediastinoscopy                 | Non-small cell carcinoma          |
| 4       | Male | 61  | 4R                 | Repeated TBNA                   | Adenocarcinoma                    |
| 5       | Male | 63  | 4R                 | Thoracotomy                     | Adenocarcinoma                    |

EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration.

**Table 4**

Transbronchial needle aspiration (TBNA) with lymphocytes and without atypia, confirmed by clinical-radiological follow-up

| Patient | Sex    | Age | Lymph node station | Histological diagnosis   | PET      | Classification by evolution |
|---------|--------|-----|--------------------|--------------------------|----------|-----------------------------|
| 1       | Male   | 65  | 4R                 | Adenocarcinoma           | Positive | FN                          |
| 2       | Male   | 67  | 4R                 | Small-cell carcinoma     | Positive | FN                          |
| 3       | Male   | 70  | 7                  | Squamous Carcinoma       | Positive | FN                          |
| 4       | Male   | 73  | 4R                 | Squamous carcinoma       | Positive | FN                          |
| 5       | Female | 82  | 7                  | Non-small-cell carcinoma | Negative | FN                          |
| 6       | Female | 45  | 7                  | Adenocarcinoma           | Negative | TN                          |
| 7       | Male   | 57  | 7                  | M1 melanoma              | Negative | TN                          |
| 8       | Male   | 64  | 7                  | M1 adenocarcinoma colon  | Negative | TN                          |
| 9       | Male   | 67  | 7                  | Squamous carcinoma       | Negative | TN                          |
| 10      | Male   | 86  | 4R                 | Adenocarcinoma           | Negative | TN                          |

FN: false negative; TN: true negative.

viewpoint, if we consider lymph node areas analyzed with TBNA that is negative for malignant cells but contains lymphocytes as disease-free, this can result in incorrect staging or "downstaging" in 16-24% of cases.

Classically, it has been considered that the true utility of TBNA lies in its high specificity and positive predictive value for confirming the existence of lymphatic metastasis.<sup>15</sup> It is assumed that positive TBNA is always a TP if the technical recommendations for performing this technique are followed. In contrast, the clinical information provided by a negative TBNA has not been thoroughly evaluated. In fact, one of the limitations of TBNA is that, as it is a blind exploration, it often does not provide adequate cytological material for analysis, either because the target lymph node area has not been tapped or simply because the bronchial wall is not crossed.<sup>12</sup> On the other hand, the majority of the series published about the cost-effectiveness of TBNA do not verify the negative results with surgical techniques, making it difficult to know the true NPV.<sup>16,17</sup> This is because a high percentage of the patients included in said studies are not candidates for surgery due to either local or distant extension of the neoplastic disease, deficient ventilatory reserve or the presence of serious comorbidities.<sup>8</sup> For this reason, some authors evaluate the NPV of the TBNA as a range that oscillates between from the worst-case (all negative TBNA are considered FN) to the best-case scenarios (all negative TBNA are TN).<sup>18</sup>

In a descriptive study including 34 patients with surgical confirmation of TBNA results, Baker et al.<sup>13</sup> demonstrated for the first time the relevance of the presence of lymphocytes in the sample. These authors found evidence that the NPV of TBNA with presence of lymphocytes was 78%, occurring on 9 occasions in their series. However, when the sample did not provide any cell strain or provided only bronchial epithelial cells, which occurred on 25 occasions, the NPV hardly reached 36%. Likewise, in a study of a total of 230 TBNA, Fernández-Villar et al.<sup>11</sup> demonstrated the presence of negative samples with abundant lymphoid cells in 25 cases (10.9%). Out of these 25 patients, 8 underwent some type of surgical technique for mediastinal evaluation and sample negativity was confirmed in 7 (NPV 87.5%). Based on the results obtained in the commented studies, despite the small sample size, there has been a generalized concept that TBNA containing lymphocytes are the only samples adequate for cytological analysis.

A detailed examination of the limited number of studies published that use surgical techniques to evaluate the negative results of TBNA revealed methodological variations that impede establishing firm conclusions on the relevance of the presence of lymphocytes in negative samples. In the majority of the cases analyzed, the cellularity of the negative samples is not specified. In addition, in some series, TBNA is performed either without the information of the CT or it is done systematically in one single lymphatic area (subcarinal). These methodological variations could partially justify the different NPV of the TBNA obtained by different authors, ranging from 57% in the Disdier et al. series<sup>19</sup> to 80% in the Harrow et al. series.<sup>8</sup> Fernández-Villar et al. have recently published one of the most numerous series about the cost-effectiveness of TBNA in the diagnosis of mediastinal lymphadenopathies of very different etiologies. In this study, the NPV of the patient subgroup with presence of lymphocytes was 67%.<sup>20</sup>

In the present study, out of a total of 32 negative TBNA samples with presence of lymphocytes and confirmed by alternative diagnostic techniques, NPV was 84%. This is very similar to the 80% obtained by Harrow et al., authors of the most complete study that has been published to date.

There are various mechanisms that can explain the FN in TBNA samples containing lymphocytes. One possibility is that the samples with very little lymphocytic material were obtained from extra-lymphatic tissue. In keeping with this hypothesis, we analyzed semi-quantitatively the samples obtained in the 5 FN cases in our series,

evaluating the lymphocytic density and comparing it with that of a TN control group. As shown in figure 3, there did not seem to be differences in the lymphocytic content between the FN and TN, although the number of cases evaluated was very small. Another theoretical possibility to explain the FN is that the ML evaluated were affected by micrometastasis or areas of focal lymphocytic infiltration,<sup>21</sup> so it would potentially be plausible for the TBNA sample to correspond with a non-invaded area of a metastatic lymph node. In this regard, studies are necessary to evaluate whether taking a greater number of TBNA samples could increase the NPV of the technique.

The present study has a series of limitations that should be evaluated in order for the results to be correctly interpreted. It is a retrospective analysis in which potentially influential variables, such as the number of aspirations carried out in each TBNA or specific diameter of the ML, were not evaluated. On the other hand, it is known that the efficacy of TBNA depends on the prevalence of the metastatic lymphatic disease in the study population,<sup>16</sup> which in this series was 82%. The results obtained could vary with a lower prevalence of metastatic disease. Finally, we did not include in the effectiveness analysis the TBNA of patients without surgical confirmation. This represents a bias in selection, given that it can be assumed that we use surgical techniques for confirmation in patients in less advanced stages of the disease that have surgical potential and with limited morbidity.<sup>8,15,16,18</sup> Nevertheless, in the present series a total of only 10 negative samples containing lymphocytes were not evaluated, as the result could not be confirmed with surgical techniques. This represents 43% of the total, a percentage much lower than the 80% reported by Harrow et al.<sup>8</sup> When we included the patients with adequate samples of lymphocytic content, but without confirmation using alternative techniques, who met the pre-established clinical criteria, the NPV considering the TBNA of 42 samples dropped to 76%. In our study, it does not seem that the information provided by additional techniques such as PET improved the NPV of TBNA. Additional prospective studies along this line are necessary.

In conclusion, the results of the present study show that 16% of patients with pathological ML on CT that are evaluated by means of TBNA and whose result shows lymphocytic cellularity have metastasis in the lymph node area analyzed. This percentage rises to 24% when adequate TBNA without cytological confirmation are also considered. Under these circumstances, it seems recommendable to perform mediastinoscopy in those cases that are candidates for lung resection surgery, especially when there are associated comorbidities or severe ventilatory limitation.

## Conflict of Interest

The authors declare having no conflict of interest.

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