ORIGINAL ARTICLES

Transbronchial Needle Aspiration in the Study of Mediastinal Lymph Nodes: Yield and Cost-Effectiveness

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OBJECTIVE: The role of different techniques for mediastinal staging in patients with suspected lung cancer is a subject of debate. The aim of this study was to analyze the diagnostic yield and cost-effectiveness of transbronchial needle aspiration in the mediastinal staging of lung cancer in patients being evaluated in a tertiary hospital.

PATIENTS AND METHODS: This was a retrospective, observational study of the results of transbronchial needle aspiration in patients with suspected lung cancer and mediastinal lymph node involvement. A cost-effectiveness analysis of the systematic use of this technique was also performed.

RESULTS: One-hundred ninety-four patients (85% men, 15% women) were evaluated. The diagnosis of lung cancer was confirmed in 157 (81%). Cytology samples obtained by transbronchial needle aspiration were adequate in 147 (76%) of the 194 cases. When only the adequate samples were included in the analysis, transbronchial needle aspiration showed a sensitivity of 88%, specificity of 100%, positive predictive value of 100%, negative predictive value of 64%, and efficiency of 90%. Mediastinoscopy was avoided in 44 (34%) of the 127 patients with localized non-small cell lung cancer, with an estimated saving of €119 456.

CONCLUSIONS: Transbronchial needle aspiration has a high diagnostic yield and obviates the need for mediastinoscopy in a significant percentage of cases. This finding is of diagnostic and economic significance.

Key words: *Lung cancer. Staging. Mediastinal lymph nodes. Fiberoptic bronchoscopy.*

Función transbronquial aspirativa en el estudio de las adenopatías mediastínicas: rentabilidad y coste-beneficio

OBJETIVO: Existe controversia sobre el papel de las diferentes técnicas diagnósticas en la estadificación del mediastino en pacientes con sospecha de cáncer de pulmón. El objetivo del estudio ha sido analizar la rentabilidad diagnóstica y el coste-beneficio de la punción transbronquial aspirativa (PTA) en la estadificación mediastínica del cáncer de pulmón, en pacientes evaluados en un hospital de tercer nivel.

PACIENTES Y MÉTODOS: Se ha realizado un estudio observacional retrospectivo, en el que se han analizado los resultados de las PTA practicadas a pacientes con sospecha de cáncer de pulmón y adenopatías mediastínicas patológicas. También se ha evaluado el coste-beneficio de la aplicación sistemática de esta técnica.

RESULTADOS: Se evaluó a 194 pacientes (un 85% varones y un 15% mujeres), en 157 de los cuales (81%) se confirmó el diagnóstico de cáncer de pulmón. La muestra citológica que se obtuvo de la PTA fue adecuada en 147 de los 194 casos (76%). Cuando se analizaron las muestras adecuadas, la sensibilidad de la PTA fue del 88%, la especificidad del 100%, el valor predictivo positivo del 100%, el valor predictivo negativo del 64% y el valor global del 90%. En 44 de los 127 casos (34%) con cáncer de pulmón no microcítico localizado se evitó la realización de una mediastinoscopia, lo que representó un ahorro económico estimado de 119.456 €.

CONCLUSIONES: La PTA es una técnica con una elevada rentabilidad diagnóstica que puede evitar la realización de una mediastinoscopia en un porcentaje significativo de pacientes, con las consiguientes implicaciones terapéuticas y económicas que ello conlleva.

Palabras clave: *Cáncer de pulmón. Estadificación. Adenopatías mediastínicas. Fibrobroncoscopia.*

Introduction

Correct mediastinal evaluation is essential in the staging of lung cancer. At the time of diagnosis, between 30% and 44% of patients with lung cancer have mediastinal lymph node metastases; this situation affects the prognosis and therapeutic approach.[1] Lymph nodes with a

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minimum diameter greater than 1 cm on computed tomography (CT) are considered to have a high probability of malignant infiltration.[2,3] As the specificity of this morphometric criterion does not exceed 65%,[2,4] malignant infiltration of the lymph node must be confirmed using a technique that provides material for cytologic or histologic study.[5] Positron emission tomography, an imaging study based on the metabolic activity of the lesion under study, has shown greater sensitivity and specificity than CT in the evaluation of the mediastinum.[6] However, as with CT, there are around 25% false positives, making histologic confirmation a requirement.[7,8] Mediastinoscopy is therefore considered the gold standard technique for mediastinal staging, as it has a sensitivity and specificity of 80% to 90%.[9,10] However, it is a surgical technique with a high hospital cost and related morbidity and mortality that cannot be ignored.[11]

Transbronchial needle aspiration (TBNA) is a bronchoscopic technique that enables cytologic or histologic samples to be obtained from lesions adjacent to the tracheobronchial tree.[12] Its principal advantage over mediastinoscopy is that it can be performed during diagnostic fiberoptic bronchoscopy, increasing the duration of the study by only a few minutes. Moreover, it does not require general anesthesia, an operating theater, or hospital admission, and the costs are therefore much lower. The results obtained with TBNA in mediastinal staging are highly inconsistent, however, and published series show a wide variability in yield.[4,13-15] Factors affecting diagnostic yield include the experience of the examiner, lymph node region studied, use of ultrasound guidance for localization of the lymph node, size of needle used, number of punctures performed, and the physical presence of the pathologist to perform immediate analysis of the samples.[13,14,16-18] For this reason, the publication of a series of patients seen at a single center, where TBNA was always performed with the same technical characteristics, by the same bronchoscopists, and with analysis by the same pathologists, should resolve the issue of the yield of this technique in the evaluation of the mediastinum.

The objective of this study was therefore to analyze the diagnostic yield of TBNA in the staging of lung cancer in a population of patients evaluated in a tertiary hospital. The secondary objective was to analyze the cost-effectiveness of the systematic use of TBNA for mediastinal evaluation in the study population.

Patients and Methods

We performed a retrospective, observational study to analyze the results of TBNA carried out in the bronchoscopy unit of a tertiary hospital between January 1998 and December 2005. The patients included in the study were referred from the respiratory-care day hospital, where patients with suspected lung cancer are evaluated after referral from the emergency department or from primary care centers attached to this hospital. The clinical-therapeutic decisions are discussed in a multidisciplinary lung cancer committee, with the participation of chest physicians, thoracic surgeons, radiologists, radiotherapists, oncologists, and pathologists.

For the principal objective of the study, we included patients with suspected lung cancer with no evidence of distant metastases and in whom thoracic CT identified mediastinal lymph nodes with a minimum diameter greater than 1 cm, in direct contact with the tracheobronchial wall and in areas accessible to needle aspiration. The exact site of puncture was established after detailed analysis of the images by an expert radiologist (P.L.), using the anatomic system described by Wang.[19] The lymph node group selected was the one that would permit the highest staging (N3 versus N2) or which was most easily accessible to the endoscopist. In order to avoid positive cytology caused by puncture of the primary tumour, those patients in whom the scan showed contact between the tumour and the lymph nodes selected for study were excluded. Those patients in whom there was malignant infiltration of the mucosa overlying the area of puncture were also excluded. Based on this approach, positive TBNAs were considered true positives and negative TBNAs were confirmed using surgical techniques (mediastinoscopy, thoracotomy) or through clinical and radiologic follow-up. A diagnosis of sarcoidosis was based on established cytologic criteria,[20] and the diagnosis of nonspecific inflammatory disease was always confirmed by clinical and radiologic follow-up.

Fiberoptic bronchoscopy with TBNA did not require any different preparation or follow-up than usual for diagnostic bronchoscopy. Sedation was performed with intravenous or sublingual midazolam on the criterion of the endoscopist, with pulse oximeter monitoring. The FB14-V fiberoptic bronchoscope (Pentax Europe GmbH, distributed by Sistemas Integrales de Medicina, S.A., Madrid, Spain) was used. In order to prevent contamination of the working channel of the bronchoscope, the needle aspiration was always the first endoscopic procedure to be performed (before bronchial lavage or possible biopsy of the primary tumour). MW-122 cytology needles (Mill-Rose Laboratories, Mentor, Ohio, USA) were used in all patients. The number of punctures performed in each patient varied according to the criterion of the endoscopist, being between 1 and 4 for each lymph node station studied. The material obtained from each puncture was spread on a microscope slide and sent for cytology.

Samples with evidence of lymphoid cellularity, indicative of puncture of a lymph node, and all samples with malignant cells were considered adequate.

For the cost-effectiveness analysis, the financial cost of the diagnostic processes was calculated in euros using the data published by other authors in Spain.[21] The final cost per process was calculated by adding the cost of the different procedures necessary to reach the diagnosis.

Statistical Analysis

Quantitative variables are expressed as mean (SD) and qualitative variables as percentages and absolute frequencies.

The sensitivity, specificity, positive predictive value, negative predictive value, and overall yield of TBNA were calculated using 2 2 contingency tables, applying the following definitions:

Sensitivity = true positives/(true positives + false negatives)

Specificity = true negatives/(false positives + true negatives)

Positive predictive value = true positives/(true positives + false positives)

Negative predictive value = true negatives/(true negatives + false negatives)

Overall yield = (true positives + true negatives)/total number of cases

The prevalence of lymph node disease in the study population was calculated using the following formula: (true positives + false negatives)/total number of patients with a definitive diagnosis of lung cancer.

Results

The study population was formed of 194 patients, 164 (85%) men and 30 (15%) women, with a mean (SD) age of 62 (13) years. All the patients had suspected lung cancer and enlarged mediastinal lymph nodes visible on CT and accessible to TBNA. The definitive diagnosis was lung cancer in 157 (81%) patients and other diseases in 37 (19%); the most common histologic type of lung cancer was adenocarcinoma with 55 cases, representing 28% of the total, followed by squamous cell carcinoma (17%) and small cell carcinoma (15%) (Table 1). TBNAs alone was sufficient to reach the definitive cytohistologic diagnosis in 31 (20%) of the 157 cases of lung cancer and in 6 (16%) of the 37 cases of other diseases. The prevalence of metastatic lymph node disease in this series was 71%.

Adequate cytology samples were obtained by TBNA in 147 (76%) of the 194 patients in the study. Of these, 108 were true positives, 25 were true negatives, and 14 were false negatives. The diagnostic yield of TBNA was analyzed using 3 different criteria: *a)* considering inadequate samples as false negatives; *b)* excluding cases with inadequate cytology samples; and *c)* using only the adequate samples from patients with a definitive diagnosis of lung cancer (Table 2).

Based on the anatomic system described by Wang,[19] the lymph node stations evaluated were: low paratracheal (4R and 4L) in 84 (43%) patients, subcarinal (7) in 99 (51%), and high paratracheal (2R or 2L) and hilar (10 and 11) in 11 (6%) patients. The diagnostic yield from each lymph node station evaluated is shown in Table 3 and for each histologic type of lung cancer in Table 4.

Diagnostic TBNA rendered mediastinoscopy unnecessary in 44 (34%) of the 127 cases of localized non-small cell lung cancer. In addition, no further diagnostic techniques were required in 11 patients with small cell lung cancer, in 7 patients with distant metastases, and in 2 patients with sarcoidosis.

There were no complications related to the needle aspiration except for a few cases of mild bleeding at the puncture site and which resolved spontaneously.

Using the framework described by Gullón and coworkers,[21] establishing the cost of fiberoptic bronchoscopy at €77.42 and the additional cost of TBNA at €64.66, the total cost of the fiberoptic bronchoscopies performed in the present study was the following: [(€77.42 + €64.66) 194]=€27 563.

TBNA provided the definitive diagnosis of the disease in 44 of the 194 patients evaluated, avoiding the need for mediastinoscopy in these patients. Taking into account that the cost of this surgical technique is €3000, the estimated saving from the systematic use of needle aspiration in the evaluation of patients with suspected localized lung cancer and enlarged mediastinal lymph nodes was: (€3000 44)-(€66.46 194)=€119 456. The estimated saving for every 10 patients evaluated was therefore €6154.

TABLE 1
Definitive Histologic Diagnoses for the 194 Patients Included

Diagnosis	No. of Patients	%
Lung cancer	157	81
Squamous cell carcinoma	34	17
Adenocarcinoma	55	28
Large cell carcinoma	6	3
Small cell carcinoma	30	15
Non-small cell lung cancer	32	16
Others	37	19
Inflammatory origin	18	9
Metastasis from an extrapulmonary tumor	10	5
Lymphoma	4	2
Mesothelioma	1	0.50
Carcinoid	1	0.50
Hamartoma	1	0.50
Sarcoidosis	2	1

TABLE 2
Yield of Transbronchial Needle Aspiration in the Diagnosis of Mediastinal Lymph Nodes

	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %	Overall Yield, %
Total number of samples	64	100	100	29	68
Adequate samples	88	100	100	64	90
Adequate samples + definitive diagnosis of lung cancer	94	100	100	57	95

TABLE 3
Diagnostic Yield of Transbronchial Needle Aspiration According to the Lymph Node Station Evaluated

Lymph Node Station	4		7		Others (2, 10, 11)	
	Total TBNA (n=84)	Adequate TBNA (n=70)	Total TBNA (n=99)	Adequate TBNA (n= 8)	Total TBNA (n=11)	Adequate TBNA (n=8)
Sensitivity, %	74	91	56	86	60	86
Specificity, %	100	100	100	100	100	
Positive predictive value, %	100	100	100	100	100	100
Negative predictive value, %	37	69	25	62	20	50
Overall yield, %	77	93	62	90	64	87

Abbreviation: TBNA, transbronchial needle aspiration.

TABLE 4
Diagnostic Yield of Transbronchial Needle Aspiration According to Histologic Type in the Group of Patients with Lung Cancer (n=157)

	Squamous		Adenocarcinoma		Small Cell Lung Cancer		Others[a]	
	Total TBNA (n=34)	Adequate TBNA (n=22)	Total TBNA (n=55)	Adequate TBNA (n=40)	Total TBNA (n=32)	Adequate TBNA (n=26)	Total TBNA (n=36)	Adequate TBNA (n=30)
Sensitivity, %	52	88	67	92	61	76	80	97
Specificity, %	100	100	100	100	100	100	100	100
Positive predictive value, %	100	100	100	100	100	100	100	100
Negative predictive value, %	26	71	15	50	8	27	–	–
Overall yield, %	59	91	69	92	62	77	80	97

Abbreviation: TBNA, transbronchial needle aspiration.
[a]Non-small cell lung cancer and large cell carcinoma.

Discussion

The present study demonstrates that TBNA is a useful and cost-effective technique for the evaluation of pathologic mediastinal lymph nodes in patients with suspected lung cancer. When the samples that satisfied the established cytologic criteria were analyzed, the sensitivity of TBNA was 88%, with an overall yield of 90%. The use of this technique made mediastinoscopy unnecessary in 44 patients, leading to an estimated saving of €119 456.

A number of authors have evaluated the efficacy of TBNA in the staging of lung cancer.[4,13-18] The novelty of the present study derives from the analysis of a large number of patients evaluated at a single center, where the same health professionals used the same procedures; this reinforces the significance of the results obtained. However, there are certain limitations that must be taken into account for the correct interpretation of our results. First, the study was retrospective and the population was not randomly selected: TBNA was performed on those patients in whom CT revealed lymph nodes of sufficient size, in accessible situations, and in direct contact with the tracheobronchial wall. The inclusion of patients without these predefined selection criteria could have reduced the diagnostic yield of the technique. Another potential limitation is that there was no surgical confirmation of positive diagnoses based on needle aspiration, although a number of studies have demonstrated that false positives are very uncommon when measures are adopted to avoid contamination of the bronchoscope and strict cytopathologic criteria are established.[13,14,16,22-24]

Series published to date on TBNA differ in the reported diagnostic yields, with figures varying from 36% to 82%.[4,14,15] Disdier and Rodríguez de Castro,[13] in one of the few studies with histologic confirmation of all cases included, found a diagnostic sensitivity of only 36%. The fact that thoracic CT did not reveal mediastinal lymph nodes in 9 (27%) of the 33 patients included in their study and that needle aspiration was performed in 6 patients without previous CT could explain the low sensitivity found by these authors. However, as has been demonstrated by Holty and coworkers[25] in a recent meta-analysis, the discrepancy in diagnostic sensitivity between the different series published could be due to differences in the prevalence of mediastinal metastases in each study population. For example, in the series published by Disdier and Rodríguez de Castro,[13] the prevalence of metastatic lymph node disease was 47%, compared to 71% in the present study.

Another factor that led to the high diagnostic yield of TBNA in the present series was that only the punctures with adequate cytologic samples were analyzed, excluding those samples in which no lymph node-derived lymphocytic material was observed. Although this exclusion represents a selection bias, we considered that when a sample was inadequate for cytologic analysis it should not be included in the study of the yield of the technique. Twenty-four percent of the samples were judged inadequate, a similar proportion to the 21% found by Fernández-Villar and coworkers[18] in a recently published study of factors that predict the results of TBNA and one of the largest series in the literature on this technique. When the 47 inadequate samples in the present study were considered to be false negatives, the sensitivity of TBNA fell to 64%, a similar figure to that reported by Fernández-Villar and coworkers and approaching the figure of 76% found in the meta-analysis of 910 patients by Toloza and coworkers.[26] A number of factors can decrease the proportion of inadequate samples and increase the diagnostic yield of the technique.[13,14,16-18] First, it has been demonstrated that the immediate examination of the aspiration sample by an experienced pathologist can provide in situ information on the quality of the sample, enabling the technique to be repeated if the sample is inadequate. In addition, endoscopic ultrasound, which provides real-time ultrasound visualization of the lymph node, has been shown to be one of the most useful techniques in evaluation of the mediastinum. The diagnostic yield of endoscopic ultrasound is comparable to that of mediastinoscopy, and even superior to mediastinoscopy for the diagnosis of mediastinal lymph nodes in the paratracheal and subcarinal regions.[27] Although there is no question of the clinical utility of endoscopic ultrasound,[28,29] its high cost means that it is only available in a few centers in Spain. In those hospitals that do not have endoscopic ultrasound, blind TBNA continues to be a very useful alternative, as demonstrated in the present series by the fact that this technique reduced the number of mediastinoscopies

required by 34%, representing an estimated economic saving of €119 456, before even considering the benefits for the patient by avoiding a thoracic surgical intervention. Other studies performed in Spain have also demonstrated a significant financial saving through the systematic use of this technique.[30,31]

Attention must be drawn to the fact that TBNA was the only technique required to reach the diagnosis in 31 (20%) of the 157 confirmed cases of lung cancer and that, as reported in other series,[32] it enabled other, nonmalignant thoracic diseases such as sarcoidosis to be diagnosed (Table 1).

Furthermore, the present study has confirmed the safety of TBNA, as the only adverse effect observed was occasional, localized bleeding at the puncture site, with no sequelae. The greatest limitation of the technique is the negative predictive value; in our series this reached 64%, making it necessary to confirm negative results surgically.

In summary, the present study showed that TBNA has high sensitivity and specificity in patients with suspected lung cancer and mediastinal lymph node involvement. It enables the diagnosis of extension to be made, avoiding the need for mediastinoscopy in a significant number of patients, with the therapeutic and financial benefits that this brings.

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