

Transbronchial Needle Aspiration of Diseased Mediastinal Lymph Nodes: Predictors of Positive Findings

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OBJECTIVE: To assess the factors that may determine the effectiveness of transbronchial needle aspiration through a flexible bronchoscope in the diagnosis of diseased mediastinal lymph nodes in patients with lung or extrapulmonary tumors.

METHODS: Prospective study carried out at 2 hospitals between 1998 and 2004 that included all transbronchial needle aspirations performed on patients who had diseased mediastinal lymph nodes larger than 10 mm and nonlymphoid neoplasms. Univariate and multivariate analysis of the diagnostic results of transbronchial needle aspiration were performed according to the type and location of the primary neoplasm and the lymph node station biopsied, the diameter of the affected node, endoscopic findings, and the results of other bronchoscopic techniques.

RESULTS: The study evaluated the transbronchial needle aspiration of 230 lymph node stations in 207 patients. Histologic examination revealed 151 cases (72.9%) of non-small cell lung cancer, 42 cases (20.3%) of small cell lung cancer, and 14 cases (6.8%) of extrapulmonary cancer. The best predictors of obtaining a diagnostic sample were a diameter of the diseased node greater than 20 mm (odds ratio [OR], 2.4; 95% confidence interval [CI], 1.2-4.7; $P=0.01$) and a histologic diagnosis of small cell lung cancer (OR, 2.7; 95% CI, 0.9-8.2; $P=0.07$).

CONCLUSIONS: The size of the diseased node and the tumor type are the best predictors of obtaining a diagnostic sample with transbronchial needle aspiration of diseased mediastinal lymph nodes in patients with lung or extrapulmonary tumors.

Key words: *Transbronchial needle aspiration. Lymph nodes: mediastinal, diseased. Bronchoscope, flexible.*

Factores predictores del resultado de la punción-aspiración transtraqueal de adenopatías mediastínicas neoplásicas

OBJETIVO: Analizar los factores que pueden influir en la efectividad de la punción transtraqueal (PTT) a través del broncoscopio flexible en el diagnóstico de adenopatías mediastínicas en pacientes con neoplasias pulmonares o extrapulmonares.

MÉTODOS: Estudio prospectivo realizado entre 1998 y 2004 en el que se incluyeron todas las PTT realizadas a pacientes con adenopatías mediastínicas superiores a 10 mm y neoplasias no linfoides de 2 centros hospitalarios. Se realizó un análisis univariado y multivariado entre los resultados diagnósticos de la PTT según el tipo y la localización de la neoplasia primaria y la estación ganglionar analizada, el diámetro de la adenopatía, los hallazgos endoscópicos y los resultados de otras técnicas broncoscópicas.

RESULTADOS: Se incluyeron en el estudio 230 PTT de estaciones ganglionares distintas de 207 pacientes. Las estirpes histológicas fueron en 151 casos (72,9%) carcinomas no microcíticos pulmonares, en 42 (20,3%) carcinomas microcíticos y en 14 (6,8%) carcinomas extrapulmonares. Las variables que mejor predijeron la obtención de muestras diagnósticas fueron el diámetro de la adenopatía superior a 20 mm (*odds ratio* [OR] = 2,4; intervalo de confianza [IC] del 95%, 1,2-4,7; $p = 0,01$) y que el tipo de neoplasia fuera un carcinoma pulmonar microcítico (OR = 2,7; IC del 95%, 0,9-8,2; $p = 0,07$).

CONCLUSIONES: El tamaño de la adenopatía y el tipo de neoplasia son los factores que mejor predicen la obtención de muestras adecuadas en la PTT de adenopatías mediastínicas en pacientes con neoplasias pulmonares o extrapulmonares.

Palabras clave: *Punción transtraqueal. Adenopatías mediastínicas. Broncoscopio flexible.*

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Introduction

Mediastinal lymph node involvement has significant prognostic and therapeutic implications in neoplastic disease.¹ Transbronchial needle aspiration is a relatively new bronchoscopic technique that allows cell and tissue

samples to be obtained from lesions adjacent to the tracheobronchial tree.²⁻⁶ It is currently in most widespread use for the staging and diagnosis of lung cancer, both of which may be performed in the same diagnostic procedure.⁷⁻¹⁴ Numerous studies have demonstrated its usefulness, safety, and cost effectiveness.^{8,10,12,14-16} However, it continues to be an underused technique.^{5,17-20} This underutilization has been linked to the bronchoscopy technique itself and to difficulties associated with the processing and interpretation of the fluid aspirates in cytology.^{6,18,21} In recent years, it has been demonstrated that endobronchial ultrasound, virtual bronchoscopy, and computed tomography (CT) fluoroscopy could improve the results achieved using this technique.^{9,22-24} However, these complementary techniques are neither available at nor within the reach of the majority of hospitals, and very few groups use them to perform transbronchial needle aspiration.^{8,9,21,25,26} Studies that have analyzed variables associated with greater effectiveness of transbronchial needle aspiration of lymph node tumors have identified the following factors: size of the lesion determined by chest CT, type of needle used, carcinoma type, site of both the primary tumor and the diseased lymph node, and the presence of indirect signs of disease at the site into which the needle is introduced.^{3,8,13,14,27-29} However, some of these studies have yielded conflicting results^{14,30} and other aspects, such as the effectiveness of transbronchial needle aspiration in extrapulmonary tumors with mediastinal metastasis, have not been considered. The aim of the present study was to assess the factors that may influence the effectiveness of transbronchial needle aspiration of diseased mediastinal lymph nodes shown by chest CT to be increased in size in patients with either lung or extrapulmonary tumors.

Methods

A prospective observational study was undertaken between June 1998 and May 2004. Transbronchial needle aspiration was performed in all patients with suspected neoplastic disease who, at the time that fiberoptic bronchoscopy was performed, had diseased mediastinal lymph nodes with a short axis of at least 10 mm in diameter visible in the paratracheal or peribronchial region by chest CT. All such aspirations were included in the study when the patient received a final diagnosis of lung or extrapulmonary tumors. The technique was performed by experienced bronchoscopists and supervised pulmonology residents at Hospital Xeral-Cíes and Clínica POVISA, Vigo, Spain. Together, the 2 hospitals serve a population of approximately 375 000 individuals. Prior to the procedure, monitoring and preparation was performed as for any diagnostic bronchoscopy. Following the procedure, a specifically designed questionnaire was completed to gather patient details, age, sex, description, and site of the lesions observed by chest CT, and bronchoscopic findings. Subsequently, the results of cytologic and histologic analyses were included (bronchial aspiration, bronchial lavage, bronchial brushing, and bronchial and transbronchial biopsy).

The risks of the different bronchoscopic procedures were explained to all patients and in all cases a signed informed consent form was obtained.

Transbronchial needle aspiration of the enlarged lymph node stations was performed following topical anesthesia with 2% lidocaine. Contamination of the bronchoscope with aspirated secretions was avoided. The procedure was usually performed before exploration of the bronchial tree and prior to other bronchoscopic techniques. The number of passes was left to the judgment of the bronchoscopist; generally, between 2 and 4 passes were performed for each lymph node station studied. A cytopathologist was normally present during the procedure. Samples were immediately fixed in 95% alcohol.

The aspiration site was elected following detailed analysis of the chest CT scan based on previous recommendations.^{5,6} Cases in which there was a lesion in the tracheobronchial mucosa at the puncture site (visible tumor or infiltration) were not included in the study. Samples were considered "valid" when they contained abundant neoplastic cells, or a large number of lymphoid cells, indicative of aspiration of a lymph node. Samples indicative of lymph node puncture that were not confirmed by surgery (mediastinoscopy, mediastinotomy, thoracoscopy, or thoracotomy), either due to patient refusal or the tumor being inoperable/nonresectable, were excluded from the final analysis. Samples that were atypical or unclear were classified as "nondiagnostic." As in previous studies, all samples containing neoplastic cells, as well as those indicative of lymph node puncture that were surgically confirmed, were considered "diagnostic" samples.¹¹ MW-122 cytology needles (Mill-Rose, Mentor, Ohio, USA) were used in all cases. Various models of Olympus fiberoptic and video fiberoptic bronchoscopes were used (Olympus Optical Co., Hamburg, Germany).

Statistical Analysis

Results were expressed as percentages and absolute frequencies for qualitative variables, and as medians and interquartile range (IQR) for quantitative variables. Comparison of discrete variables was performed using the χ^2 test or Fisher's exact test. Quantitative variables were analyzed using the Mann-Whitney U test. Statistical significance was established at $P < .05$. All factors that were associated with obtaining diagnostic samples in the univariate analysis and in which the value of P was less than .20 (providing a better adjustment for potentially confounding variables) were included in the multivariate analysis, which was performed using a backwards stepwise logistic regression model, with calculation of the odds ratio and the 95% confidence interval. In this model, diameter of the diseased lymph node was classified as less than the median diameter or greater than or equal to it, and tumor type was classified as small cell lung carcinoma or other type of cancer. A calibration analysis was also performed using the Hosmer-Lemeshow goodness-of-fit χ^2 statistic to determine the fit of the model. All analyses were performed using version 9.0 of the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA).

Results

The study included 230 punctures of mediastinal lymph node stations (199 performed in Hospital Xeral-Cíes and 31 in Clínica POVISA) performed in 207



Figure. Lymph node stations studied.

patients with known neoplastic disease or in whom nonlymphoid cancer had been diagnosed. In 185 patients, transbronchial needle aspiration was performed in a single lymph node station, in 21 patients the procedure was performed in 2 different stations, and in 1 patient it was performed in 3 stations. One hundred sixty nine patients (81.6%) were men and 38 (18.4%) were women; the median age was 63 (IQR, 54-71) years.

One hundred fifty one patients (72.9%) presented non-small cell lung carcinoma (61 adenocarcinomas, 49 undifferentiated large cell carcinomas, and 41 squamous carcinomas), 42 patients (20.3%) had small cell lung carcinomas, and 14 patients (6.8%) had extrapulmonary carcinomas (6 patients with breast cancer, 2 with renal cancer, 2 with cancer of the larynx, 1 with ovarian cancer, 1 with cancer of the colon, 1 with prostate cancer, and 1 with cancer of the esophagus). In 87 patients (42%), transbronchial needle aspiration was the only technique that led to diagnosis of the tumor. The chest CT scan showed only diseased mediastinal lymph nodes in 34 patients (16.4%), while additional lesions indicative of tumors were seen in the right lung of 114 patients (55.1%), in the left lung of 56 patients (27.1%), and in both lungs in 3 patients (1.4%). Aspirate cytology was positive in 43 patients (20.8%), negative in 136 (65.7%), and not performed in 28 patients (13.5%). Endobronchial lesions were visible in 80 patients (38.6%).

The sites of the 230 lymph node stations studied are shown in the Figure. The median diameter of the short axis of the diseased lymph nodes was 20 mm (IQR, 15-30 mm): 87 were between 10 and 19 mm, 75 between 20 and 29 mm, 32 between 30 and 39 mm, and 36 had a diameter of 40 mm or more. The tracheobronchial mucosa was normal at 163 puncture sites (70.9%) and 66 patients (28.7%) showed signs of extrinsic compression, edema, erythema, or broadening of the carina. The median number of passes performed was 2 (IQR, 2-3). A sufficient number of neoplastic cells for diagnosis was obtained in 157 aspirates (68.3%); cells

TABLE 1
Univariate Analysis of Predictors of Obtaining Diagnostic Samples Following Transbronchial Needle Aspiration of Diseased Mediastinal Lymph Nodes*

Factors	Diagnostic Samples	P
Pulmonary lesion (CT) [†]		.3
Right	84/114 (73.7%)	
Left	44/56 (78.6%)	
Mediastinum alone	31/38 (81.6%)	
Bilateral	4/4 (100%)	
Aspirate cytology		.6
Negative	109/140 (77.9%)	
Positive	32/43 (74.4%)	
Endobronchial lesion		.6
Yes	66/83 (79.5%)	
No	88/114 (77.2%)	
Lymph node station		.8
Right paratracheal	89/117 (76.1%)	
Subcarinal	44/55 (80%)	
Left paratracheal	21/29 (72.5%)	
Others [‡]	10/12 (83.3%)	
Diameter of the diseased lymph node, mm		<.001
10-19	49/76 (64.5%)	
20-29	54/71 (76.1%)	
30-39	28/30 (93.3%)	
≥40	33/36 (91.7%)	
Indirect signs [§]		.08
Yes	54/64 (84.4%)	
No	109/148 (73.6%)	
Tumor type		.02
Small cell lung carcinoma	38/42 (90.5%)	
Non-small cell lung carcinoma	114/152 (75.0%)	
Extrapulmonary tumors	12/19 (63.2%)	

*CT indicates computed tomography.

[†]Site of lesions indicative of lung tumors.

[‡]Seven precarinal lesions, 4 in the main bronchi, and 1 paraesophageal lesion.

[§]Signs of extrinsic compression, edema at the puncture site, or broadening of the carina.

^{||}Seven breast tumors, 4 renal, 2 laryngeal, 2 ovarian, 2 tumors of the colon, 1 of the prostate, and 1 esophageal.

TABLE 2
Logistic Regression of Predictors of Obtaining Diagnostic Samples in Transbronchial Needle Aspiration of Diseased Mediastinal Lymph Nodes*

Factors	Adjusted OR	95% CI	P
Diameter ≥20 mm	2.4	1.2-4.7	.01
Presence of indirect signs	1.3	0.6-3.0	.4
Non-small cell lung carcinoma	2.7	0.9-8.2	.07

*OR indicates odds ratio; CI, confidence interval.

from the bronchial wall, mucus, or blood, or few neoplastic cells and/or lymphocytes were obtained in 48 aspirates (20.9%); and large numbers of lymphoid cells indicative of lymph node puncture were obtained in 25 aspirates (10.9%). Of these latter aspirates, 17 were not confirmed by other techniques either because of patient refusal or because the tumor was nonresectable or inoperable; these aspirates were excluded from further analysis. Surgical biopsy was performed in the remaining 8 patients; 7 of those biopsies were negative and 1 positive. Thus, the final sample comprised 213 needle aspirates of lymph node stations: 164 (77%) diagnostic samples (157 containing neoplastic cells and

7 confirmed lymph node punctures) and 49 (23%) nondiagnostic samples (48 without neoplastic cells or lymphocytes and 1 with abundant lymphocytes and surgical biopsy of lymph node metastasis of squamous carcinoma). The univariate analysis of predictors of obtaining a diagnostic sample by transbronchial needle aspiration is shown in Table 1. Table 2 shows the results of the logistic regression analysis.

No complications associated with the aspiration procedure, other than slight hemorrhage at the puncture site in some cases, were observed.

Discussion

Unlike other bronchoscopic techniques, transbronchial needle aspiration offers a unique opportunity to obtain samples from mediastinal masses and diseased mediastinal lymph nodes.³⁻⁶ In lung cancer, transbronchial needle aspiration can provide information on malignant spread to the mediastinal lymph nodes at the same time that diagnostic bronchoscopy is performed,^{3,10,29} often in patients with inoperable or nonresectable tumors in whom a positive aspirate result acts as a prognostic factor or provides definitive diagnostic information that makes further studies unnecessary.^{3,8,13} Transbronchial needle aspiration allows samples to be obtained from the paratracheal, retrotracheal, subcarinal, and hilar regions.^{3,29} Its sensitivity in the staging of bronchogenic carcinoma ranges from 37% to 72%, with a specificity of greater than 90%.³ This heterogeneity in the published results could be due to differences in the methods used, the experience of the bronchoscopists with the technique, selection of the patients, sample processing, and whether or not the technique was compared with surgical procedures.^{3,8,18,21,30} The following factors have been shown to be associated with a higher frequency of positive results with transbronchial needle aspiration of diseased mediastinal lymph nodes in patients with neoplastic disease: the presence of tumors visible by bronchoscopy^{3,17}; localization of the tumor on the right-hand side^{8,13}; signs of compression due to lymph node enlargement^{4,30}; broadening or reddening of the carina^{8,13,27,28,30}; aspiration of the right paratracheal and subcarinal lymph node stations^{8,11,14}; the model and type of needle used^{3,8,30}; and that the tumor is a small cell bronchogenic carcinoma.^{8,9,14} However, conflicting results have been obtained regarding the influence of some of these factors.^{14,30} Furthermore, the identification of such factors was not the principal aim of the majority of the studies and only 2 undertook a multivariate analysis of the independent influence of each of the factors.^{8,14} In our study, the only factor that was independently associated with obtaining diagnostic samples was the diameter of the short axis of the diseased lymph node measured by chest CT. Although tumor type was not statistically significant ($P=.07$), we believe this factor may nevertheless have notable clinical significance.

As in the multicenter study of Harrow et al⁸ and the study by Sharafkhaneh et al,¹⁴ the probability of obtaining a diagnostic result in our series increased progressively with the diameter of the diseased lymph node; however, above a certain diameter (24 mm in the series of Harrow et al⁸ and 30 mm in that of Sharafkhaneh et al¹⁴ and in our study) the likelihood of obtaining positive results does not appear to increase. This observation could be influenced by the fact that larger diseased lymph nodes are more likely to contain large areas of tumor necrosis.⁸

Although in our study patients with small cell carcinoma had larger diseased mediastinal lymph nodes than patients with other types of tumor (30 mm [IQR, 21-41.2 mm] vs 20 mm [IQR, 15-31 mm]; $P=.001$), small cell carcinoma essentially remained an independent predictor. The relevance of small cell carcinoma as a predictor has been attributed to its higher biological aggressiveness and the lower adhesion of the tumor cells.^{8,14}

In this study, we observed no differences in the results obtained for the different lymph node stations. A number of studies have found the diagnostic yield to be higher in the right paratracheal and subcarinal regions than in the left paratracheal area.^{8,11,14} Although the reason is not entirely clear, those who have made those observations have stated that they could be due to a less aggressive approach on the part of bronchoscopists when performing transbronchial needle aspiration to the left because of the risk of accidental puncture of one of the large vessels located close to that lymph node station.^{8,11,14} The size of the diseased lymph nodes in the left paratracheal area was similar to those in the right paratracheal and subcarinal regions (20 mm [IQR, 14.2-36.5 mm] vs 20 mm [IQR, 15-30 mm]; $P=.7$). However, in 11 of the 29 (37.9%) stations aspirated in the left paratracheal area, the patient presented small cell lung carcinoma, while this was only true of 28 of the 172 (16.3%) aspirated right paratracheal and subcarinal stations ($P=.01$), a factor that could have influenced the final results in our study. A similar situation was observed when the lung tumor was located on the right side.

Although the presence of indirect signs of the existence of diseased mediastinal lymph nodes (tracheal compression, erythema or edema of the mucosa, or broadening of the carina) enhanced the possibility of obtaining a diagnostic result, this observation did not achieve statistical significance, particularly following adjustment for lymph node size and type of tumor. The effect of indirect signs of disease on the probability of obtaining a diagnostic result is probably due to the fact that such signs are more common in larger diseased lymph nodes (29 mm [IQR, 20-39 mm] vs 20 mm [IQR, 15-27.5 mm]; $P=.0001$).

In slightly more than a third of cases, transbronchial needle aspiration was the only technique that permitted cytologic diagnosis of neoplastic disease. That figure is much higher than that obtained in the multicenter study of Harrow et al⁸ (18%) but similar to results obtained by

other authors (34% to 38%).^{11,14} Hospital Xeral-Cíes, one of the hospitals in which the study was performed, receives patients for thoracic surgery from 6 other hospitals in the provinces of Pontevedra and Ourense, and some of the patients in whom transbronchial needle aspiration was performed had been referred following the absence of diagnosis using other bronchoscopic techniques in the referring hospital. Consequently, the population can be considered to be partially selected.

The main limitations of this study were similar to those described elsewhere for the evaluation of transbronchial needle aspiration in the diagnosis and staging of lung carcinoma.^{3,8,10,11,14} Firstly, given the high reported specificity of the technique,²⁻¹⁴ positive aspirates were not confirmed using surgical procedures. Secondly, the majority of negative aspirates were also not confirmed due to the large number of patients with inoperable or nonresectable disease. We believe that the classification of all negative aspirates as nondiagnostic and the exclusion of aspirates that were indicative of lymph node puncture but were not confirmed surgically will have minimized this limitation in our study.

In summary, taking into account the limitations mentioned, the size of the diseased lymph node and, to a lesser extent, the type of tumor appear to have the greatest influence on the probability of obtaining diagnostic samples by transbronchial needle aspiration of diseased mediastinal lymph nodes in patients with either lung or extrapulmonary tumors. When the diameter of the lymph node is greater than 30 mm and the tumor is a small cell lung carcinoma, the technique achieves an effectiveness of close to 100%. Despite the diagnostic yield being lower in other types of tumor, especially extrapulmonary tumors, or in diseased lymph nodes with a smaller diameter, the safety, cost effectiveness, and reduced invasiveness of transbronchial needle aspiration compared with surgical techniques indicate that this procedure should be the first choice in patients with suspected cancer who present diseased lymph nodes in the paratracheal or peribronchial areas that have a diameter of greater than 10 mm in chest CT.

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