



Accuracy of closed pleural biopsy in the diagnosis of malignant pleural effusion

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ABSTRACT

Objective: Previous studies have demonstrated that closed pleural biopsy (CPB) has a sensitivity of less than 60% for diagnosing malignancy. Therefore, controversy has recently emerged regarding the value of CPB as a diagnostic test. Our objective was to assess the accuracy of CPB in diagnosing malignancy in patients with pleural effusion.

Methods: This was a prospective 8-year study of individuals who underwent CPB to establish the etiology of pleural effusion. Information on each patient was obtained from anatomopathological reports and medical records. When CPB findings showed malignancy or tuberculosis, the biopsy was considered diagnostic, and that was the definitive diagnosis. In cases in which biopsy histopathological findings were nonspecific, a definitive diagnosis was established on the basis of other diagnostic procedures, such as thoracoscopy, thoracotomy, fiberoptic bronchoscopy, biochemical and cellular measurements in pleural fluid, and/or microbiological tests. The accuracy of CPB was determined with 2 × 2 contingency tables. **Results:** A total of 1034 biopsies from patients with pleural effusion were studied. Of those, 171 (16.54%) were excluded from the accuracy analysis either because of inadequate samples or insufficient information. The results of the accuracy analysis were as follows: sensitivity, 77%; specificity, 98%; positive predictive value, 99%; negative predictive value, 66%; positive likelihood ratio, 38.5; negative likelihood ratio, 0.23; pre-test probability, 2.13; and post-test probability, 82. **Conclusions:** CPB is useful in clinical practice as a diagnostic test, because there is an important change from pre-test to post-test probability.

Keywords: Biopsy; Pleural effusion, malignant/diagnosis; Pleural effusion, malignant/epidemiology.

INTRODUCTION

Previous evidence has demonstrated that the performance of blind closed pleural biopsy (CPB) as a diagnostic test for malignancy is poor, since the reported sensitivity is less than 60%; therefore, in some countries, CPB is considered obsolete and its use tends to disappear.^(1,2)

Currently, the interventional pulmonologist has two options for obtaining histological samples of pleural tissue: CPB or medical thoracoscopy. The first is an old technique,^(3,4) and the second is currently considered the gold standard⁽²⁾; however, both procedures have advantages and disadvantages. The CPB described by Cope and Abrams^(3,4) in the mid-20th century is an alternative method of obtaining pleural tissue without the need for a surgical procedure. Its use for more than 5 decades is attributed to its ease of performance, its low cost, the tolerability by the patient, and the fact that, within a short period of time, it allows a decision about the management of the case.⁽⁵⁾ Nevertheless, it is a purely diagnostic procedure, which does not bring any gains in terms of treatment or symptom relief to the patient as occurs with medical thoracoscopy or video-assisted thoracoscopy.

At our institution, approximately 400 new cases of intrathoracic malignancy are diagnosed every year, and, of those, approximately 40% have pleural effusion. The initial approach to pleural effusion is to perform a thoracentesis so that the pleural fluid can be analyzed biochemically and cytologically. In cases of nondiagnostic thoracentesis and in the presence of lymphocytic exudate, a definitive diagnosis is established by histopathological analysis of samples obtained by image-guided or non-image-guided CPB or by video-assisted thoracoscopy.

Because at our hospital we continue to perform CPB in cases of lymphocytic exudative pleural effusion of unknown etiology, the objective of the present study was to assess the accuracy of CPB in establishing a diagnosis of malignancy in patients under investigation for pleural effusion.

METHODS

This was a prospective study of patients with pleural effusion who underwent CPB to establish the etiology of the effusion, over an 8-year period at a referral hospital for respiratory diseases in Mexico City. The study was approved by the Research Ethics Committee of the *Instituto Nacional de Enfermedades Respiratorias*.

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Before CPB, pleural fluid analysis including biochemical measurements such as protein, lactic dehydrogenase, and cholesterol levels was performed to classify the effusion as an exudate or transudate⁽⁶⁾; in addition, other measurements such as glucose, adenosine deaminase, and pH levels were performed, as were cell counts and cytological studies.

CPB was performed by different pulmonologists with 5 to 15 years of experience and by second- or third-year residents in pulmonary medicine of the emergency and inpatient departments. When CPB was performed by residents, these residents were always directed and supervised by the pulmonologist in charge of the patient. The diagnostic procedure was performed with a Cope⁽³⁾ or Abrams⁽⁴⁾ needle in patients with submassive or massive pleural effusion, in a hospitalization procedure room or in the emergency department. With the patient in a sitting position, his/her arms resting on a table, at shoulder level, the entry point was determined on the affected side. In general, the entry point was located between the posterior axillary line and the line of the inferior angle of the scapula, in the fifth intercostal space. With aseptic technique and local anesthesia (lidocaine 2%) of the skin, subcutaneous cellular tissue, intercostal muscle, and underlying region of the parietal pleura, a thoracentesis was performed to ensure that the pleural space had been entered; subsequently, a 3- to 5-mm incision was made with a scalpel blade on the skin and subcutaneous tissue to facilitate the insertion of the biopsy needle along and above the superior border of the inferior rib, so as to avoid damage to the intercostal neurovascular bundle.

The Abrams needle consists of three parts: an outer 11-gauge cannula (3 mm in outer diameter); an inner 13-gauge stylet that facilitates transparietal insertion; and a 13-gauge hooked needle for taking the biopsy.

When the stylet needle was withdrawn, there was an outflow of pleural fluid, which confirmed successful entry into the pleural cavity. With the cannula in the pleural space, the trocar needle was inserted through it into the pleural space, the notch of the trocar being positioned opposite the said needle grip. To collect a sample of parietal pleura, the said notch engaged the pleura, and with a rotating movement of the trocar needle, the required sample was cut off and taken. These steps were repeated as many times as the number of samples desired.

The Cope needle consists of four parts: an 11-gauge outer cannula 3 mm in diameter; a 13-gauge hooked biopsy trocar; a beveled trocar; and an inner stylet. After a syringe was attached to the hooked biopsy trocar, the inner stylet was inserted into the beveled trocar, and both were inserted through the outer cannula into the pleural space. The hooked biopsy trocar, to whose outer end a syringe had been attached, was inserted through the outer cannula into the pleural space. Entry into the pleural space was confirmed by aspiration of fluid into the syringe. The parietal pleura was hooked with the biopsy trocar, and, with a slight outward pulling motion, the biopsy was taken.

With either needle, between 4 and 8 samples were taken clockwise at 3, 6, and 9 o'clock, but never at 12 o'clock to avoid damage to the intercostal neurovascular bundle. The biopsies were placed in 3.7% formaldehyde solution for histopathological examination, which was performed by different pathologists from the pathology department with more than 10 years of experience in diagnosing pulmonary, pleural, and mediastinal diseases. Initially, the biopsies were analyzed morphologically, and, subsequently, they were evaluated immunohistochemically, with appropriate antibody panels for the diagnosis of different neoplastic and non-neoplastic diseases.

The identification of the cases in which CPB was performed was obtained from the records of the anatomical pathology department of the hospital. Information regarding each patient, such as general characteristics, history, clinical profile, radiological findings, and results of cytological and cytochemical study of pleural fluid, was obtained from the inpatient medical records.

When CPB results showed malignancy or tuberculosis, the biopsy was considered diagnostic, and that was the definitive diagnosis in the medical record. In cases of lymphocytic exudates with CPB histopathological findings of nonspecific inflammatory changes (nonspecific chronic inflammation or reactive mesothelial hyperplasia), a definitive diagnosis was established on the basis of other diagnostic procedures, which, for these cases, were the following: invasive procedures such as thoracoscopy, thoracotomy, fiberoptic bronchoscopy, adenosine deaminase levels, and/or microbiological tests for pyogenic bacteria and for *Mycobacterium tuberculosis*; or the clinical criterion and specific laboratory studies according to the case.

In all cases, CPB histopathological findings were compared with the definitive diagnosis made by the treating physician and 6-month follow-up data, on the basis of medical records.

Pleural tuberculosis was defined as the presence of at least one of the following: a finding of granulomas on pleural biopsy; a positive Ziehl-Neelsen staining of pleural fluid or biopsy material; a positive Löwenstein-Jensen culture of pleural fluid; a positive sputum smear microscopy; or an adenosine deaminase level of > 45 IU in a pleural exudate with a lymphocyte predominance of > 80%.

Parapneumonic pleural effusion was defined as the presence of a pleural exudate with a predominance of polymorphonuclear cells in addition to a clinical profile consistent with pneumonia; the case was treated with antibiotics, and there was improvement at discharge.

Statistical analysis

For the accuracy analysis of CPB, we used 2 × 2 contingency tables in which the results of the diagnostic test were compared with respect to the presence or absence of any intrathoracic malignant disease and with respect to the presence or absence of mesothelioma alone.

We calculated sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and pre-test and post-test probabilities.⁽⁷⁾

RESULTS

During the study period, 1,034 CPBs were performed in 1,034 patients with pleural effusion. The mean age of the patients was 57 ± 17 years, 615 (59.48%) were male, and 419 (40.52%) were female. Malignancy was identified in 466 (45.07%) of the patients, among whom lung adenocarcinoma and mesothelioma were the most common neoplasms, being found in 252 (24.37%) and 105 (10.16%), respectively (Table 1).

Of the 1034 CPBs, 171 (16.54%) were excluded from the accuracy analysis: 72 (6.96%) because of inadequate samples, given that no pleural tissue was obtained; and 99 (9.57%) because of lack of information about the case, since case follow-up until the establishment of a definitive diagnosis was impossible.

Among the final diagnoses of the 863 cases included in the accuracy analysis, the most common were lung adenocarcinoma, mesothelioma, and undifferentiated carcinoma (Table 2).

CPB results, by presence or absence of any intrathoracic malignant disease and by presence or absence of mesothelioma, as well as results for the diagnostic test performance indicators for each case, are described in 2 × 2 contingency tables (Tables 3 and 4).

Table 1. Histopathological results for 1,034 closed pleural biopsies.

Result	n (%)
Malignant neoplasm	
Lung adenocarcinoma	252 (24.37)
Mesothelioma	105 (10.16)
Undifferentiated carcinoma	53 (5.12)
Small cell lung cancer	19 (1.84)
Giant cell lung cancer	6 (0.58)
Epidermoid carcinoma	5 (0.48)
Hodgkin and non-Hodgkin lymphoma	11 (1.06)
Other neoplasms ^a	15 (1.45)
Total	466 (45.07)
Infectious disease	
Tuberculosis	116 (11.22)
Parapneumonic pleural effusion	2 (0.19)
Total	118 (11.41)
Other results	
Nonspecific inflammation ^b	378 (36.56)
Inadequate biopsy sample (no pleural tissue) ^c	72 (6.96)
Total	450 (43.52)

^aOther neoplasms included sarcomas and metastasis from clear cell renal, breast, and ovarian cancer. ^bIt refers to findings of non-specific acute and chronic inflammation and reactive mesothelial hyperplasia. ^cThese biopsies were excluded from the accuracy analysis.

In 38/863 cases (4.40%), there were complications (3 cases had two complications): 30 cases had pneumothorax, of which 19 did not require pleural tube placement and 11 did; 6 patients developed a hematoma at the puncture site; 2 had vasovagal syncope; and 3 developed subcutaneous emphysema in the area surrounding the puncture site.

DISCUSSION

The results of this study describe, according to modern clinical epidemiology, the performance of CPB in cases of lymphocytic exudative pleural effusion of unknown etiology. This diagnostic test proved useful since it allowed the identification of 77% of the cases of pleural effusion due to any malignancy and 81% of those due to mesothelioma. Lung adenocarcinoma metastatic to the pleura and mesothelioma were the most commonly diagnosed neoplasms by this method. The specificity of the diagnostic test under study was high, since only 2% of the patients with other causes of pleural effusion had a positive result for malignancy and none had a positive result for mesothelioma. Likewise, in a patient with a positive CPB result for neoplastic disease, the actual probability of having a neoplasm was 99% and that of having a mesothelioma was 100%. However, in clinical practice, the confidence with which it is possible to rule out the probability of a thoracic neoplasm, given a normal result or a result with nonspecific inflammatory changes, is very important in a setting where the prevalence of the disease is high,

Table 2. Diagnoses of 863 cases with completed follow-up for identification of a definitive diagnosis, for accuracy analysis of closed pleural biopsy.

Result	n (%)
Malignant neoplasm	
Lung adenocarcinoma	317 (36.73)
Mesothelioma	130 (15.06)
Small cell lung cancer	26 (3.01)
Hodgkin and non-Hodgkin lymphoma	20 (2.32)
Undifferentiated carcinoma	41 (4.75)
Epidermoid carcinoma	15 (1.74)
Giant cell carcinoma	6 (0.70)
Other neoplasms ^a	32 (3.71)
Total	587 (68.02)
Infectious diseases	
Tuberculosis	141 (16.34)
Parapneumonic pleural effusion	50 (5.79)
Total	191 (22.13)
Other diseases	
Others ^b	70 (8.11)
IIdiopathic	15 (1.74)
Total	85 (9.85)

^aOther neoplasms included sarcomas; metastasis from clear cell renal, breast, and ovarian cancer; germ cell tumors; and papillary thyroid cancer. ^bOther non-neoplastic diseases included rheumatoid arthritis; systemic lupus erythematosus; renal, hepatic, and cardiogenic failure; pneumoconiosis; pachy pleuritis; and pulmonary thromboembolism.

Table 3. Closed pleural biopsy results, by presence or absence of any intrathoracic malignant disease, and accuracy analysis.^a

Biopsy result	Presence of malignancy	Absence of malignancy	Total
Diagnostic biopsy	450	5	455
Non-diagnostic biopsy	137	271	408
Total	587	276	863
Test performance indicator			
Sensitivity $a/(a + c) = 450/587$		77% (95% CI: 74-79)	
Specificity $d/(b + d) = 271/276$		98% (95% CI: 97-99)	
Positive predictive value $a/(a + b) = 450/455$		99% (95% CI: 98-100)	
Negative predictive value $d/(c + d) = 271/408$		66% (95% CI: 63-70)	
Positive likelihood ratio Sensitivity/(1 - specificity) = 77/2		38.5	
Negative likelihood ratio (1 - sensitivity)/specificity = 23/98		0.23	
Prevalence $(a + c)/(a + b + c + d) = 587/863$		68% (95% CI: 65-71.3)	
Pre-test probability Prevalence/(1 - prevalence) = 68/32		2.13	
Post-test probability Pre-test probability × positive likelihood ratio = 2.13 × 38.5		82	

a: true-positive results; b: false-positive results; c: false-negative results; and d: true-negative results.
^aMesothelioma is included.

Table 4. Closed pleural biopsy results, by presence or absence of mesothelioma, and accuracy analysis.

Biopsy result	Presence of mesothelioma	Absence of mesothelioma	Total
Diagnostic biopsy	105	0	105
Non-diagnostic biopsy	25	733	758
Total	130	733	863
Test performance indicator			
Sensitivity $a/(a + c) = 105/130$		81% (95% CI: 78-83)	
Specificity $d/(b + d) = 733/733$		100%	
Positive predictive value $a/(a + b) = 105/105$		100%	
Negative predictive value $d/(c + d) = 733/758$		97% (95% CI: 96-98)	
Positive likelihood ratio Sensitivity/(1 - specificity) = 81/99		82	
Negative likelihood ratio (1 - sensitivity)/specificity = 19/100		0.19	
Prevalence $(a + c)/(a + b + c + d) = 130/863$		15% (95% CI: 13-17)	
Pre-test probability Prevalence/(1 - prevalence) = 15/85		0.18	
Post-test probability Pre-test probability × positive likelihood ratio = 0.18 × 82		14.8	

a: true-positive results; b: false-positive results; c: false-negative results; and d: true-negative results.

as is our case, to such an extent that a negative result does not exclude the probability of a neoplasm in 34% of cases. The usefulness of this diagnostic procedure lies in the possibility of excluding malignancy in cases of lymphocytic exudative pleural effusion on the basis of a

biopsy result showing nonspecific chronic inflammation or reactive mesothelial hyperplasia. Our series and other published series report a high number of such results (20%-60%)⁽⁸⁻¹³⁾; in some such cases malignancy is subsequently confirmed by other methods, those

Table 5. Performance of different methods of obtaining pleural tissue samples for the diagnosis of intrathoracic malignancy-related pleural effusion.

Reference	Technique	Number of patients	Diagnostic performance	Frequency of complications*
Studies of diagnosis of malignant pleural effusion				
Poe et al., 1984 ^{(8)a}	CPB	211	Sn: 68% Sp: 99% PPV: 98% NPV: 77%	9.9%
Chakrabati et al., 2006 ⁽⁹⁾	CPB	75	Sn: 51% Sp: 100% PPV: 100% NPV: 100%	11%
Pereyra et al., 2013 ⁽¹⁰⁾	CPB	658	Sn: 33.9% Sp and PPV: 100% NPV: 71%	14.4%
Botana et al., 2013 ⁽¹¹⁾	CPB vs. US-guided CPB	67 114	Sn: 60% Sn: 77.4%	1/67 (1.5%) 3/114 (2.5%)
Maskell et al., 2013 ⁽¹⁾	CPB vs. CT-guided CPB Clinical trial	25 25	Sn: 47% vs. 87% Sp: 100% vs. 100% NPV: 44% vs. 80% PPV: 100% vs. 100%	CPB 1/25 CT 0
Son et al., 2014 ⁽¹²⁾	CPB vs. MT	36 31	55.6% 93.5 %	7/36 (19.4%) 0
Haridas et al., 2014 ⁽¹⁴⁾	Clinical trial MT vs. CPB	29 29	Sn: 86.2% Sn: 62.1 %	10.3% 17.2%
Metintas et al., 2010 ⁽¹⁶⁾	Clinical trial MT vs. CT-guided pleural biopsy	62 62	Sn: 94.1% Sn: 87.5%	11/62 14/62
Present study	CPB for any malignancy	863	Sn: 77% Sp: 98% PPV: 99% NPV: 66%	4.40%
Studies of diagnosis of mesothelioma				
Boutin et al., 1993 ⁽¹⁵⁾	RTLA vs. CPB	188 145	Sn: 98% Sn: 21%	4.8% ----
Heilo et al., 1999 ⁽¹³⁾	US-guided biopsy	70	Sn: 77% Sp: 88% PPV: 100% NPV: 57%	No severe complications
Adams et al., 2001 ⁽¹⁷⁾	US- or CT-guided biopsy	53	Sn: 86% Sp: 100%	2/53
Present study	CPB for mesothelioma	863	Sn: 81% Sp: 100% PPV: 100% NPV: 97%	4.40%

CPB: closed pleural biopsy; Sn: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; US: ultrasound; MT: medical thoracoscopy; and RTLA: rigid thoracoscopy under local anesthesia. ^aDiagnoses of malignancy and tuberculosis are included.

being false-negatives for malignancy. In the present study, 378 biopsies (36.56%) showed nonspecific inflammatory changes, and, in the accuracy analysis, 137/587 (23.34%) corresponded to false-negative results for malignancy.

The explanation for such false-negative results lies in the fact that neoplasms disseminate in patches in the pleura in cases of intrathoracic malignancy, the effusion is due to obstruction of pleural or mediastinal lymphatics, or the disease involves only the visceral

pleura. Among the neoplasms for which false-negative CPB results occurred most often were several varieties of intrathoracic sarcomas and neoplasms of mediastinal and metastatic extrathoracic origin, such as metastasis from clear cell renal, breast, and ovarian cancer, germ cell tumors, and papillary thyroid cancer.

On the basis of the positive likelihood ratio, a patient with a lymphocytic pleural exudate and a CPB result positive for malignancy will be 38.5 times more likely to have a malignant chest disease compared with a patient

with the same characteristics but with a negative CPB result. Finally, there was a large difference between pre- and post-test probability, 2.13 and 82, respectively, which suggests clinically important displacement. A similar trend was observed for mesothelioma.

Previous studies on the performance of CPB in diagnosing malignancy, whether addressing CPB alone or comparing it with image-guided or medical thoracoscopy-guided techniques, have demonstrated that CPB with Cope or Abrams needles allows the diagnosis of 21% to 62% of cases of neoplasm-related pleural effusion^(1,8-12,14,15) (Table 5). When pleural biopsy is performed under image guidance, whether ultrasound or computed tomography, it consistently shows better performance, with sensitivity between 77% and 87.5%,^(1,11,13,16,17) and when there is pleural thickening greater than 1 cm, sensitivity increases to 95%, a value similar to that achieved when biopsy is obtained with thoracoscopy.⁽¹⁶⁾ In general, specificity and positive predictive values are high for CPB and for that performed under image guidance. In our study, sensitivity for neoplastic disease (77%) was higher than that reported in previous studies and was within the range reported for image-guided pleural biopsy (Table 5), and, similar to previous studies, specificity and positive predictive value were high in the present study. This is probably due to the fact that the place where our study was conducted is a referral hospital for respiratory diseases and many of the cases present with advanced stages of the disease.

Medical thoracoscopy and video-assisted thoracoscopy are considered the gold-standard methods of obtaining biopsies in cases of neoplasm-related pleural effusion.⁽⁵⁾ For medical thoracoscopy, evidence shows sensitivity ranging from 86.2 to 93.5%^(12,14,16) (Table 5).

There have been few studies assessing the accuracy of CPB in diagnosing mesothelioma. One study compared the performance of CPB with that of surgical thoracoscopy and found sensitivity of 21% vs. 98%.⁽¹⁵⁾ When biopsy is performed under image guidance such as ultrasound or computed tomography, sensitivity increases to 77% and 86%, respectively^(13,17) (Table 5). The above results contrast with those of the present study, since the CPB performance indicator values for the diagnosis of mesothelioma were high and even similar to image-guided biopsy results.^(13,17) This performance can be explained in part by the fact that many of the cases had pleural thickening.

Our study confirms the safety of CPB and its accessibility even to pulmonologists in training. The frequency of complications was 4.40% (Table 5), similar to that reported in the literature⁽²⁾; on the other hand, we demonstrated the performance of CPB in a routine work setting, given that biopsy collection and histopathological analysis were performed independently by different health care workers.

At our institution, CPB is still part of the diagnostic algorithm of patients with lymphocytic exudative pleural effusion for identification of etiology, although we have video-assisted thoracoscopy, whose performance is much better than that of CPB and which in addition facilitates performing therapeutic procedures, such as pleurodesis to prevent effusion recurrence, concurrently with biopsy collection; however, video-assisted thoracoscopy takes more time and resources and may be a risk factor in patients with high anesthetic risk.

Medical thoracoscopy is not yet available at our institution, and image-guided pleural biopsy is not often performed because it requires equipment, whether ultrasound or computed tomography equipment, and trained personnel. Currently at our institution we are attempting to generalize the performance of CPB under image guidance, whether ultrasound or computed tomography, as well as to implement the use of medical thoracoscopy.

One of the limitations of the present study is that cytology results, culture results, and radiographic findings such as pleural thickening were not included in the analysis, being considered only in including cases in the study and in the definitive diagnosis. Another potential limitation is the number of cases excluded from the analysis, which can undoubtedly affect the test performance indicators; nevertheless, we consider that we have a good sample size that includes more than 80% of all cases reported during the study period and therefore estimate that the change in the test performance indicators would be modest and would not ostensibly affect the trend of results.

In conclusion, at the facility where the present study was conducted, CPB proved to be valid, accurate, and precise in establishing the diagnosis of intrathoracic malignancy in patients with pleural effusion. CPB is useful in clinical practice as a diagnostic test, because there is an important change from pre-test to post-test probability.

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