Predictors of Pleural Malignancy in Patients With Pleural Effusion Undergoing Thoracoscopy*

Jaume Ferrer, MD; Juan Roldán, MD; Joan Teixidor, MD; Esther Pallisa, MD; Ignasi Gich, MD; and Ferran Morell, MD

Study objectives: Thoracoscopic pleural biopsy is highly accurate in the diagnosis of pleural malignancy. However, no scientific evidence is currently available to guide the physician’s decision as to when and in which patients with pleural effusion thoracoscopy is indicated. The application of predictive criteria of malignancy might improve the indication of thoracoscopy in patients with undiagnosed pleural effusion.

Methods: Prospective study of 93 patients referred for thoracoscopy at a tertiary hospital. Clinical variables were obtained prior to thoracoscopy by clinical history and review of previous data, patient interview, and physical examination. Radiologic variables were obtained by evaluation of chest radiograph and chest CT images by two independent readers. After thoracoscopy, all patients without a diagnosis were sent for long-term follow-up.

Results: Thoracoscopy demonstrated 94% sensitivity and 100% specificity in the diagnosis of pleural malignancy. Variables, which in a multivariate model are associated with pleural malignancy, include a symptomatic period > 1 month, absence of fever, blood-tinged pleural fluid, and chest CT scan findings suggestive of malignancy. Receiver operating characteristic analysis showed that the use of these four criteria offered adequate classification in 95% of patients. Twenty-eight patients had all four criteria, and all had malignancy; 21 patients had at most one criterion, and none had malignancy.

Conclusion: Clinical and radiologic criteria of patients with pleural effusion permit different risk levels for pleural malignancy to be distinguished. Consequently, application of the four proposed criteria permits better indication of thoracoscopy in patients with undiagnosed pleural effusion.

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Key words: cancer; pleural effusion; thoracoscopy

Abbreviation: ROC = receiver operating characteristic

Thoracoscopy, an established method in the diagnosis of pleural diseases, is highly sensitive for detecting pleural neoplasia with negative pleural fluid cytology and in the diagnosis of tuberculosis.6 The possibility of visualizing the pleural cavity and obtaining directed biopsy specimens7–9 accounts for
the high performance of thoracoscopy in the diagnosis of pleural neoplasia, > 90%. However, its precise indication in the workup of patients with pleural effusion remains controversial. In fact, in approximately half of the patients undergoing thoracoscopy, pleural biopsy does not demonstrate malignancy. Since nonmalignant pleural disease may be diagnosed by noninvasive methods, the indication of thoracoscopy in patients with pleural effusion should be optimized.

The 2000 American Thoracic Society statement on management of malignant pleural effusions states that indications for performing thoracoscopy include “the evaluation of exudative effusions of unknown cause,” among others, and that “in cases of undiagnosed exudative effusions with a high clinical suspicion for malignancy, some clinicians may proceed directly to thoracoscopy if the facilities for medical thoracoscopy are available.” Using clinical suspicion of malignancy to decide whether to perform thoracoscopy seems reasonable if the series of patients with undiagnosed pleural effusion are examined. In this series, malignancy was strongly suspected in the initial evaluation of patients in whom neoplasm was later detected; and, alternatively, when malignancy was not initially suspected, it was detected in only 5% of the patients who were followed up. However, what does “high clinical suspicion of malignancy” mean, and how can it be used in the workup of patients with undiagnosed pleural effusion? Patients with malignant pleural effusion present clinical differences compared with those with benign effusions; however, the predictive value of malignancy of clinical variables has scarcely been studied. In a study of patients with chronic pleural effusion in whom a reduced number of variables was analyzed, blood-tinged pleural fluid was the single variable with the strongest positive predictability of malignancy. Although it is therefore possible that clinical criteria may help physicians to improve the indication of thoracoscopy in patients with idiopathic pleural effusion, more data are required to confirm this possibility.

In the present study, a wide range of clinical and radiologic variables were used to predict malignancy in patients with pleural effusion referred for thoracoscopy. The hypothesis tested was that clinical predictors of malignancy permit a better indication of thoracoscopy in patients with undiagnosed pleural effusion.

Materials and Methods

All patients with pleural effusion consecutively referred for thoracoscopy to the Department of Thoracic Surgery between June 1993 and August 2001 were studied. The patients had been studied previously in respiratory and internal medicine departments on the decision of the attending physician, who indicated thoracoscopy. In all cases, this previous study included at least one thoracentesis with pleural fluid study (determination of glucose, proteins, lactate dehydrogenase, adenosine deaminase, mycobacterial and cytologic examination, with total and differential counts and detection of neoplastic cells), chest radiograph, and chest CT scan.

Prior to thoracoscopy, patients were prospectively evaluated by one of the authors to obtain the clinical variables. Two readers unaware of the clinical history evaluated the radiologic images, and classification was obtained by consensus.

Thoracoscopy was performed with a standardized technique. The macroscopic appearance of the pleura (pathologic/nonpathologic), days of hospitalization, and complications were recorded. Pleural samples were shipped for histologic study and cultured in Lowenstein-Jensen media for mycobacterial detection.

Diagnostic Criteria

Pleural effusion with neoplastic cells in pleural fluid and/or neoplastic infiltration in a pleural tissue biopsy sample was considered neoplastic. The diagnosis of malignant mesothelioma was made by histologic examination, histochemical techniques (positive periodic acid-Schiff diastase stain), and monoclonal antibodies (negative carcinoembryonic antigen and positive calretinin). Paramalignant effusion was defined as that occurring in a patient with neoplasia but with no evidence of malignancy in fluid or pleural tissue. Pleural effusion with no evidence of malignancy in a patient with a history of asbestos exposure and in whom an alternative diagnosis was ruled out in a 3-year follow-up was considered a benign asbestos pleural effusion. The diagnoses of tuberculosis and amyloidosis were based on the presence of caseating granulomas and amyloid in pleural tissue, respectively. Pleural effusion of unknown etiology after all diagnostic procedures was defined as idiopathic.

Clinical and Radiologic Variables

The following clinical variables were defined: sex, age, smoking, and asbestos exposure. Symptomatic variables were dyspnea, chest pain, and toxic syndrome, defined as the presence of anorexia, weakness, and weight loss. The symptomatic period was considered as acute-subacute if symptom duration was < 30 days, and chronic if longer. Fever was defined as body temperature > 37°C at the first evaluation. Red pleural fluid was considered as blood tinged.

Radiologic evaluation of pleural effusion included the extension measured in the chest radiograph as the ratio between height of the effusion and height of the affected hemithorax and expressed as a percentage. An effusion ≥ 75% was considered to be massive. The presence of pulmonary or pleural masses, pulmonary atelectasis, or adenopathies on plain chest radiograph and chest CT was considered suggestive of malignancy.

Follow-up

Patients with malignancy were referred to the Department of Oncology for treatment and control. Patients with idiopathic or suspected benign asbestos pleural effusions were referred to the outpatient department for follow-up control by one of the authors of the study. Those who did not attend for control were questioned by telephone.
Statistics

The relationship between all variables studied and diagnosis of pleural malignancy was evaluated initially by univariate analysis. \( \chi^2 \) test was used for categorical variables, and Student t test was used for continuous variables.

According to the result of univariate analysis, a multivariate approximation was made by binary logistic regression analysis. Variables in the model were chosen by the forward conditional elimination procedure. Goodness of fit of the logistic regression model was evaluated with the Hosmer-Lemeshow test. Finally, the corresponding receiver operating characteristic (ROC) curve was obtained.

In all cases, the significance level was considered to be 5% (\( \alpha = 0.05 \)) and the approach used was bilateral. All analyses were performed with statistical software (SPSS, version 11.5; SPSS; Chicago, IL), and the study was approved by the ethics committee of our center.

Results

During the study period, 93 patients with pleural effusion were referred for diagnostic thoracoscopy. Thoracoscopy was performed in 86 patients with pleural effusion of unknown etiology and in 7 patients with malignant cells in pleural fluid. Demographic, clinical, and radiologic characteristics of the patients are shown in Table 1. In accordance with Light's criteria, the pleural fluid was an exudate in 92 cases and a transudate in a patient with heart failure-induced pleural effusion. One patient with heart failure and another patient with liver disease had exudates, although both had been treated with diuretics prior to thoracentesis. A pleural biopsy with an Abrams needle, which proved to be nondiagnostic, was performed in 28 patients. Neoplasia was diagnosed in 11 patients by bronchoscopy, in 1 patient by gastroscopy, in 1 patient by splenectomy, and in 1 patient by transthoracic puncture.

Thoracoscopy Results

Fifty-one of the 54 patients with malignant pleural disease received a diagnosis by thoracoscopy, which represents 94.3% diagnostic sensitivity and 90.9% in the case of malignant mesothelioma. Specificity for both groups was 100%, with a positive predictive value of 100% and negative predictive value of 93% for malignancy in general, and 97.3% for mesothelioma. No patients with paramalignant pleural effusion presented evidence of pleural malignancy during follow-up.

Mean hospital stay of patients was 7.8 days (range, 4 to 16 days). Following thoracoscopy, five patients had fever and three patients had persistent chest pain; all had pleural neoplasia. Pleural infection and sepsis after thoracoscopy developed in a 69-year-old female patient with systemic lupus erythematosus receiving corticoid treatment and with massive right pleural effusion, and she died 2 days later.

Stepwise Diagnosis and Follow-up

The diagnostic workup and final diagnoses in the 93 patients are shown in Figure 1. Diagnosis was made in 76 of the 93 patients (83.8%) after thoracoscopy. Six of the 17 patients discharged with the diagnosis of idiopathic pleural effusion presented neoplasia during follow-up. Of these, three were pleural: epithelial malignant mesothelioma was diagnosed in two patients by thoracotomy 4 months and 6 months after thoracoscopy, respectively; and the other patient was readmitted 41 days after thoracoscopy for pain at the surgical site, and a mass was detected in the chest wall at the orifice of the thoracoscopy. A biopsy of the mass was indicative of adenocarcinoma. Colon neoplasia was diagnosed in two patients 34 months and 55 months after thoracoscopy, respectively, and lung cancer was diagnosed in the other patient 40 months after thoracoscopy. Seven asbestos-exposed patients received a diagnosis of benign asbestos-induced pleural effusion after a mean control time of 1,999.9 days (range, 966 to 3,132 days). All had good evolution. Eleven patients remained without a diagnosis after a mean follow-up of 1,462.7 days (range, 370 to 2,416 days). All had

| Table 1—Risk Factors for Pleural Malignancy Detected at Thoracoscopy* |
|-----------------------------|------------------|------------------|------------------|
| Variables†                 | Benign (n = 43)  | Malignant (n = 50) | p Value         |
| Chronic symptomatic period | 23 (53.4)        | 45 (90)          | < 0.001         |
| Toxic syndrome             | 11 (25.6)        | 29 (58)          | 0.002           |
| Fever                      | 15 (34.9)        | 3 (6)            | 0.001           |
| Chest pain                 | 17 (39.5)        | 34 (68)          | 0.007           |
| Massive pleural effusion   | 6 (13.9)         | 20 (40)          | < 0.001         |
| Blood-tinged pleural effusion | 8 (18.6)    | 35 (70)          | < 0.001         |

*Data are expressed as No. (%).
†Other variables analyzed, such as sex, age, smoking, asbestos exposure, and dyspnea showed no differences.
good evolution except one patient who did not attend the control visit and died at 370 days of unknown causes. Final diagnoses are described in Table 2.

Insufflated talc pleurodesis, at a dose of 2 to 5 g, was performed in conjunction with thoracoscopy in 36 of 54 patients with pleural malignancy. The oncology department of our center evaluated patients with malignant pleural effusion for a therapeutic decision. Among them, 38 patients underwent chemotherapy, while 16 patients with poor general status were sent home for palliative treatment.

**Comparative Analysis**

Comparison between patients with and without neoplasia yielded significant differences in a number of variables (Table 1), whereas biochemical data or the percentage of cells in pleural fluid were similar in both groups. Adenosine deaminase levels in pleural fluid were high (43 U/L) in five patients, four of whom had malignant mesothelioma, and one patient had pleural tuberculosis. Pleural fluid pH could be determined in 63 patients: 27 patients with benign disease, 20 patients with pleural metastasis, and 16 patients with malignant mesothelioma. Mean pH was lower in patients with pleural neoplasia (7.33 ± 0.14) than in those with benign disease (7.41 ± 0.14) [p = 0.013]. Patients with malignant mesothelioma had a nearly significant higher asbestos exposure than patients with benign pleural disease (p = 0.052), although no differences were observed between malignant and benign disease in general, or between mesothelioma and metastasis.

**Multivariate Analysis**

Multivariate analysis was carried out to determine the risk factors associated with the diagnosis of malignancy on thoracoscopy. The histologic result of the thoracoscopic pleural biopsy was considered to be the dependent variable and demographic, clinical, and radiologic data were independent variables.

ROC analysis showed chest CT scan to be the best criterion for classifying patients as having benign or malignant disease. However, the best classification was achieved when the four criteria (chest CT suggestive of malignancy, chronic symptomatic period, blood-tinged pleural fluid, and absence of fever) were combined (Table 3). These associations are maintained if the seven patients with malignant cells in pleural fluid are excluded and only patients with undiagnosed pleural effusions are considered.

Twenty-one patients (22.6%) had one or no criteria, and all had benign pleural disease; 28 patients (30.1%) had four criteria, and all received a diagnosis of pleural neoplasia. The proportion of pleural malignancy among patients with two criteria and three criteria was 5 of 21 patients (23.8%) and 17 of 23 patients (73.9%), respectively.

**Table 2—Final Diagnosis of Pleural Effusion in 93 Patients**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural malignancy</td>
<td>53</td>
</tr>
<tr>
<td>Malignant mesothelioma</td>
<td>22</td>
</tr>
<tr>
<td>Metastatic</td>
<td>31</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>22</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>4</td>
</tr>
<tr>
<td>Others*</td>
<td>5</td>
</tr>
<tr>
<td>Extrapleural malignancy</td>
<td>10</td>
</tr>
<tr>
<td>Paramalignant pleural effusion†</td>
<td>7</td>
</tr>
<tr>
<td>Malignancy detected in long-term follow-up‡</td>
<td>3</td>
</tr>
<tr>
<td>Benign</td>
<td>30</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>11</td>
</tr>
<tr>
<td>Asbestos</td>
<td>7</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>3</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>1</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td>1</td>
</tr>
<tr>
<td>Others§</td>
<td>7</td>
</tr>
</tbody>
</table>

*a Lung large-cell carcinoma (n = 1), breast carcinoma not otherwise specified (n = 2), lung small-cell carcinoma (n = 1), malignant thymoma (n = 1).
†Adenocarcinoma (n = 3) [(breast (n = 1), stomach (n = 1), and cervix (n = 1))], lung carcinoma (n = 3) [squamous-cell carcinoma (n = 2), and lung large-cell carcinoma (n = 1)] and lymphoma (n = 1).
‡Colon adenocarcinoma (n = 2), and squamous lung cancer (n = 1).
§Congestive heart failure (n = 2), liver transplantation (n = 1), liver disease (n = 1), Dressler syndrome (n = 1), amyloidosis (n = 1), kidney transplantation (n = 1).
Table 3—Predictors of Malignancy Detected at Thoracoscopy*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>ROC (95% Confidence Interval)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic period</td>
<td>90.0</td>
<td>86.0</td>
<td>7.8 (2.6–23.5)</td>
<td>0.95 (0.91–0.99)</td>
<td>0.001</td>
</tr>
<tr>
<td>Absence of fever</td>
<td>94.0</td>
<td>70.0</td>
<td>0.12 (0.03–0.45)</td>
<td>0.64 (0.53–0.76)</td>
<td>0.001</td>
</tr>
<tr>
<td>Blood-tinged pleural effusion</td>
<td>70.0</td>
<td>81.4</td>
<td>10.2 (3.8–27.1)</td>
<td>0.76 (0.66–0.86)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chest CT suggestive of malignancy</td>
<td>92.0</td>
<td>81.4</td>
<td>50.3 (14.0–180.6)</td>
<td>0.87 (0.79–0.95)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>70.0</td>
<td>86.0</td>
<td></td>
<td>0.88 (0.82–0.95)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>All criteria</td>
<td>92.0</td>
<td>86.0</td>
<td></td>
<td>0.95 (0.91–0.99)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Only combinations of variables with the best diagnostic yield are shown.

**DISCUSSION**

Neoplasia is the main diagnosis detectable on thoracoscopy in patients with pleural effusion and negative, noninvasive study findings. However, whether clinical and radiologic data can predict pleural malignancy detectable by thoracoscopy has not been determined to date. Our data show the combination of chest CT suggestive of malignancy, symptomatic period of > 30 days, blood-tinged pleural fluid, and absence of fever to be the variables that, in a multivariate model, are associated with malignancy detectable on thoracoscopy.

The usefulness of thoracoscopy in the diagnosis of malignant pleural involvement was confirmed in this study. False-negative results were limited to 1 of 31 patients with pleural metastasis and 2 of 21 patients with malignant mesothelioma. The greater diagnostic difficulty in malignant mesothelioma is well known and is attributed to the possibility that the neoplastic invasion is produced submesothelially. However, we also found that in 45% of patients undergoing thoracoscopy, pleural biopsy failed to show malignancy, and the majority of these patients eventually received a diagnosis of benign disease. These data confirm those reported by other authors and underline the need to improve the indication of an invasive technique such as thoracoscopy. Our results show that the application of clinical and radiologic criteria of pleural malignancy may permit better indication of thoracoscopy in the study of pleural effusion. First, no patients with one or no criterion had pleural neoplasia. This concurs with the results of a previous study showing that the majority of patients with idiopathic pleural effusion and no clinical suspicion of malignancy had good evolution after a long-term follow-up. This suggests that a conservative approach may be adopted and thoracoscopy not performed in the subgroup of patients with one or none of the described criteria. In contrast, malignancy was detected by thoracoscopy in all patients who fulfilled the four criteria and in 74% of those with three criteria. Patients fulfilling three or four criteria are probably very similar to those reported in previous idiopathic pleural effusion series. In patients in whom neoplasia was diagnosed during follow-up, but in whom malignancy had initially been clinically suspected, thoracoscopy is the technique of choice given its great sensitivity in the detection of pleural malignancy, as confirmed in the present study. In the patients with two criteria, 24% had neoplasia, and the indication of thoracoscopy in this group is therefore more doubtful. In our opinion, the need to reach a definitive diagnosis is another reason why these patients should undergo thoracoscopy, although the percentage of patients undergoing the procedure with a benign result will be high. In short, therefore, the criteria we propose might improve the indication of thoracoscopy according to the probability of pleural malignancy.

One important aspect is the applicability of the results of this study. All patients referred for diagnostic thoracoscopy, in the majority of cases for undiagnosed pleural effusion, were included consecutively. Therefore, we do not believe there was a selection bias. However, the number of thorascopies requested was low, and therefore a long period of time was required to complete the inclusion. A possible explanation would be that, at our center, pleural effusion in the majority of patients is diagnosed by cytologic examination of the pleural fluid. Finally, we believe that the variables predictive of malignancy we propose are applicable to any group of patients with undiagnosed pleural effusion, who are those in whom thoracoscopy should be considered. Moreover, we assume that the malignancy criteria applied in this study can be feasibly introduced into clinical practice. A symptomatic period > 1 month, absence of fever, and blood-tinged pleural fluid are easily obtained from the clinical evaluation of the patient, with no additional test or cost.

Chest CT scan proved to be the variable with the greatest positive predictive value of pleural malignancy in our study, way beyond that of plain chest radiography. An alteration in chest CT scanning afforded correct diagnosis in 46 of 50 patients, and all but one of the false-positive results were paramalignant pleural effusions with pulmonary neoplastic lesions. Since the recruitment period of this study, CT scanning has been applied as a guide for Tru-Cut needle pleural biopsies.
Minimally Invasive Techniques

In a randomized study in 46 pleural effusion patients, CT-guided Tru-Cut needle pleural biopsy yielded 87% diagnostic sensitivity of neoplasia and 75% in cases without pleural thickening, superior in both cases to biopsy with an Abrams needle. Thus, after thoracoscopy, CT-guided pleural biopsy appears to be the most sensitive technique for neoplasia detection, and the clinician must elect the most adequate in each case. For example, thoracoscopy permits, in addition to biopsy, pleurodesis, while CT-guided pleural biopsy would be preferable in patients with poor general status in whom thoracoscopy cannot be performed. Although comparative studies between the two techniques are not yet available, it may be affirmed that CT scanning is essential in the diagnostic evaluation of the patient with undiagnosed pleural effusion, both to optimize the indication of thoracoscopy and as a guide for Tru-Cut needle pleural biopsy.

Blood-tinged pleural fluid and chronic period of symptoms were previously found to be associated with pleural malignancy. However, most data considered to be suggestive of malignancy in clinical practice, such as advanced age, chest pain, dyspnea, constitutional syndrome, or massive effusion, have not shown a predictive value. In our study, most of these variables did not predict pleural neoplasia on multivariate analysis; therefore, we believe that, although many physicians follow some of these criteria as a part of a “common sense” in clinical practice, an effort should be made to decide on the use of thoracoscopy based on scientifically validated criteria.

The frequency of asbestos exposure was higher in patients with malignant mesothelioma than in those with benign disease, as was to be expected. However, in general, no association was observed between asbestos exposure and pleural neoplasia. The explanation for this is likely due to the presence of eight cases of benign asbestos-induced pleural effusion among the benign diseases.

In conclusion, the results of this study show that the indication of thoracoscopy can be improved if noninvasive clinical and radiologic predictors of pleural neoplasia are used. Of note is the outstanding predictive value of chest CT scanning, which renders its use advisable in patients with idiopathic pleural effusion. However, the usefulness of the proposed criteria needs to be confirmed in further studies before being incorporated into clinical practice.

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REFERENCES


