Prognostic Factors in Patients Presenting with Pleural Effusion Revealing Malignancy

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Key Words

Thoracoscopy · Prognosis · Survival · Malignant pleural effusion · Factor

Abstract

Background: The survival of patients with malignant pleural effusion is considered generally poor. Most of the studies reporting results of prognostic factors are retrospective, using pleural thoracentesis for diagnosis. The objectives of our study were to reveal possible prognostic factors in patients initially presenting with undiagnosed pleural effusion proven to be malignant by diagnostic thoracoscopy. **Methods:** Ninety consecutive patients, 48 of whom were male (53%), with a median age of 69 years (range 37–93) and a performance status (PS) of 0/1 (63%) and with initially undiagnosed pleural effusion that was proven to be malignant by thoracoscopy were evaluated. Survival time was defined as the time from thoracoscopic diagnosis to death or the last follow-up. A regression analysis was used to determine significant clinical and biological prognostic factors. **Results:** Lung carcinoma (44.4%), breast carcinoma (24.4%), and mesothelioma (12.2%) were the most frequent tumors diagnosed. The median overall survival was 11 months (range

0.5–55). The survival of the patients was related to the following factors: histology of the primary tumor ($p = 0.008$), PS ($p < 0.001$), white blood cells ($p = 0.018$), and the blood neutrophil-to-lymphocyte (N/L) ratio ($p = 0.002$). Multiple regression showed PS, histology, and the N/L ratio. **Conclusion:** The factors affecting survival in our patients were PS, primary tumor histology, and the N/L ratio. These factors may help physicians select patients for treatment and/or interventional procedures.

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Introduction

Malignant pleural effusion is a common medical problem in patients with cancer [1, 2]. It usually occurs in patients with advanced neoplastic disease and it is associated with a reduced life expectancy [3, 4]. Breast and lung cancers are responsible for approximately 75% of malig-

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nant pleural effusions [5]. Patients with malignant pleural effusion are considered to have a poor prognosis, with their quality of life affected by symptoms related to recurrent pleural effusion such as dyspnea, cough, and pain. In such patients, simple therapeutic thoracentesis might be the only option, while interventional procedures such as thoracoscopy with talc poudrage or chest tube insertion for blind pleurodesis are considered only in patients with a prolonged life expectancy [1, 6].

Several efforts have been made in the past to predict survival in patients with malignant pleural effusion. Most of the published reports have used clinical data [performance status (PS), cancer histology, and primary site] and biochemical parameters from pleural fluid examinations, such as pH, lactate dehydrogenase (LDH), and glucose [7–10]. These investigations have also suggested that the extent of pleural lesions detected during thoracoscopy is closely related to both glucose and hydrogen ion concentrations in pleural fluid, and that the duration of survival is inversely related to the extent of carcinomatous involvement of the pleura [10, 11]. Clinicians treating patients with malignant pleural effusion often rely on these increasingly controversial physiologic variables. In addition, they rely on their subjective assessment of the patient's potential for prolonged survival despite pleural involvement from the underlying malignancy.

Given the conflicting results regarding the prognostic value of pleural fluid pH, glucose levels, and anatomic measures of the extent of pleural carcinomatosis, we performed a study of different variables potentially indicative of the prognosis of patients with malignant pleural effusion who underwent thoracoscopy for diagnostic purposes. The purpose of this prospective study was to determine the contribution of each of these variables to predicting survival in patients initially presenting with malignant pleural effusion who underwent thoracoscopy for diagnosis of their primary tumor (treatment-naïve patients).

Patients and Methods

This is a prospective study of 90 patients with malignant pleural effusion out of 147 consecutive patients (61.2%) who underwent diagnostic thoracoscopy from March 2006 to December 2011. All 90 patients had undergone thoracoscopy for diagnostic purpose as their pleural effusion was the initial condition of their underlying malignant disease; therefore, they were treatment-naïve patients. The number of males was 48 (53.3%). The median age was 69 years (range 37–93). Patients' characteristics are presented in table 1. Patients gave informed consent and the Internal Review Board of our hospital approved this study. All patients underwent single port of

Table 1. Characteristics of the study population (n = 90)

Characteristic	Value
Gender, n (%)	
Males	48 (53.3)
Females	42 (46.7)
Median age (range), years	69 (37–93)
Median pleural glucose level (range), mg/dl	98 (37–223)
Median pleural pH (range)	7.41 (7.21–8.00)
Median pleural LDH level (range), U/l	587.5 (120–2,058)
PS, n (%)	
0	39 (43.3)
1	18 (20)
2	25 (27.7)
3	8 (9)
Median WBC (range), n/μl	8,450 (4,200–18,800)
Neutrophils	5,700 (2,570–16,620)
Lymphocytes	1,710 (560–3,240)
Diagnosis, n (%)	
NSCLC	34 (37.8)
SCLC	6 (6.6)
Breast cancer	22 (24.4)
Mesothelioma	11 (12.2)
Gastrointestinal cancer	4 (4.4)
Head-neck cancer	3 (3.3)
Ovarian cancer	3 (3.3)
Genitourinary cancer	2 (2.2)
Lymphoma	2 (2.2)
Unknown	3 (3.3)
Type of intervention, n (%)	
Diagnostic thoracoscopy	52 (57.8)
Talc pleurodesis	38 (42.2)
Mean pleural drainage time (range), days	3 (1–7)
Side of thoracoscopy, n (%)	
Left	49 (54.4)
Right	41 (45.6)

entry thoracoscopy under local anesthesia, with spontaneous ventilation, in the endoscopy suite [6, 12].

Pleurodesis was performed during a second thoracoscopy by insufflating 4 g sterile asbestos-free talc (Steritalc®; Novatech, France) into the patients' pleural space only after histological confirmation (on-site evaluation is not available in our settings) of metastatic disease, after a full case-by-case evaluation and discussion of the possible benefits according to the origin of the primary tumor and the efficacy of the therapy. The chest tube (20-french gauge) was removed after lung reexpansion in the case of diagnostic procedures, while in the case of pleurodesis it was removed when less than 100 ml pleural fluid was drained over a 24-hour period [6, 12].

Survival was studied in relation to other clinical parameters such as gender, the histology of the primary tumor, PS according to the ECOG score, and the type of intervention (talc pleurodesis vs. diagnostic thoracoscopy), as well as in relation to biological pa-

Fig. 1. Overall survival of our patients (n = 90).

rameters such as peripheral blood white cells (WBC), neutrophils, lymphocytes, the neutrophil-to-lymphocyte (N/L) ratio, pleural fluid pH, LDH, and glucose. Survival was measured from the time of diagnostic thoracoscopy to the date of death or the last follow up. This study was conducted in such a way that living patients could have at least a 3-year follow-up. All biological tests were carried out 1 day prior to the intervention.

Statistical Analysis

The Kaplan-Meier method was employed to determine the relationships between patient survival and other potential clinical or biological parameters such as gender, histology of the primary tumor, side of thoracoscopy, and mode of intervention (diagnostic vs. talc poudrage). A univariate analysis was performed to analyze the prognostic contribution of continuous variables such as age and blood and pleural fluid parameters. A Cox proportional hazards model was used to assess the independent prognostic value of each covariate selected by the univariate regression analysis [4]. $p < 0.05$ was considered statistically significant. All analyses were performed using StatView™ 4.5 statistical software (Abacus Concepts Inc., Berkeley, Calif., USA).

Results

Our patients' overall median survival was 11 months (range 0.5–55) (fig. 1). The Kaplan-Meier analysis showed that survival was significantly related ($p < 0.001$) to ECOG PS (fig. 2a). Patients with ECOG PS 0 had the best median survival (24 months), while patients with a score of 1, 2, or 3 had a median survival of 9, 5, or 1.5 months, respectively. Survival was also significantly related ($p = 0.008$) to the type of primary tumor (table 2). Patients with lymphoma had the best median survival (26 months), and patients with ovary and breast carcinomas had the second best survival (18 and 15 months, respectively) (table 2). Patients with non-small cell lung cancer (NSCLC)

and small cell lung cancer (SCLC) had a survival time of 9.5 and 6 months, respectively, while mesothelioma patients had an 8-month survival time (table 2). Other parameters examined, such as gender ($p = 0.33$), age >70 years ($p = 0.2$), type of intervention (diagnostic thoracoscopy vs. talc poudrage) ($p = 0.14$), and side of thoracoscopy ($p = 0.62$), did not affect survival. However, there was a trend towards better survival in patients who underwent thoracoscopic talc pleurodesis (median = 14 months) compared to those without pleurodesis (median = 8.5 months) (fig. 2b).

Univariate analysis (table 3) showed poor survival with increasing WBC ($p = 0.0016$, $r^2 = 0.058$), increasing blood neutrophils ($p = 0.018$, $r^2 = 0.055$), decreasing blood lymphocytes ($p = 0.015$, $r^2 = 0.14$), and increasing blood N/L ratios ($p = 0.0093$, $r^2 = 0.066$). Patients with $\text{WBC} < 13,000/\text{mm}^3$ (fig. 2c) and those with N/L ratios < 3 (fig. 2d) showed significantly better survival ($p = 0.001$ and $p = 0.002$, respectively). The simple regression analysis was unable to show any significant relationship between survival and pleural fluid pH, glucose, proteins, and LDH (table 3). When we stratified our patients by primary tumor in order to study the relation between pleural pH and survival, we were unable to reveal any impact of pleural pH (mesotheliomas: $R^2 = 0.17$, $p = 0.64$; metastatic carcinomas: $R^2 = 0.16$, $p = 0.37$, and lung carcinomas: $R^2 = 0.15$, $p = 0.54$).

Cox proportional hazards analysis showed that ECOG PS, histology of the primary tumor, and N/L ratio were independent factors affecting patient survival ($p = 0.020$, $p = 0.022$ and $p = 0.03$, respectively).

Discussion

This study was designed to evaluate potential prognostic variables in patients presenting with initially undiagnosed pleural effusion diagnosed as malignant after diagnostic thoracoscopy. We found that the primary tumor, the ECOG PS, WBC, and the N/L ratio were predictors of survival in this patient population. No pleural fluid parameter tested showed any association with survival in our patient population.

PS is an indisputable prognostic factor in cancer patients. Indeed, our results are consistent with other reports which found that PS was a significant predictor variable in patients with recurrent symptomatic malignant effusions undergoing thoracoscopic pleurodesis [4, 13]. Despite the presence of a pleural effusion, there is a strong correlation between the performance scale score

Fig. 2. Patient survival according to the studied parameters: ECOG PS (a), mode of intervention (diagnostic thoracoscopy vs. talc poudrage) (b), WBC (c), and the N/L ratio (d).

Table 2. Survival according to primary tumor (overall $p = 0.008$)

Type of malignancy	Median survival (range), months
Lymphoma	26 (24–28)
Ovary	18 (3–20)
Breast	15 (2–33)
Gastrointestinal	13.5 (1–27)
Head-neck	12 (12–13)
Genitourinary	11.5 (8–15)
NSCLC	9.5 (1–39)
Mesothelioma	8 (2–55)
SCLC	6 (2–9)
Unknown	1 (0.5–7)
Overall	11 (0.5–55)

Table 3. Simple regression analysis for age, blood, and pleural fluid variables in relation to survival ($n = 90$)

Parameter	R ²	SE	t value	p value
Age	0.032	0.106	-1.7	0.09
WBC	0.072	0.003	-2.5	0.012
Blood neutrophils	0.064	0.004	-2.44	0.016
Blood lymphocytes	0.14	0.003	2.54	0.015
Blood N/L ratio	0.063	0.48	-2.4	0.017
Pleural pH	0.047	11.6	-1.5	0.13
Pleural glucose	0.001	0.37	-0.16	0.87
Pleural proteins	0.032	1.7	1.6	0.11
Pleural LDH	0.002	0.003	0.33	0.73

and the survival of patients with lung cancer, lymphoma, and solid tumors [14–16].

In our study, the histology of the primary tumor was an independent prognostic factor. In all of our study patients, the primary tumor was diagnosed via thoracoscopic biopsy after referral for an undiagnosed pleural effusion. As shown in table 1, our patients presented

overall with a good PS [PS 0/1, $n = 57$ (63.3%); PS 2/3, $n = 33$ (37.7%)]. Also, as the patients in our series were primarily diagnosed by thoracoscopy, they were treatment naive and therefore more likely to do better, especially those with chemosensitive tumors such as breast and ovary tumors, carcinomas, and lymphomas. Although generally the occurrence of pleural effusion is

believed to be indicative of a poor prognosis in cancer patients [1, 3, 4], it is logical to consider differences depending on the primary tumor [10, 17] as the overall survival and time to progression vary according to the behavior of each tumor in response to treatment. Indeed, most published series include patients with a pleural effusion presenting when the disease has progressed, relapsed, and/or is resistant to any treatment [4, 13]; that is not the case in our series, which includes only patients whose disease was diagnosed through the occurrence of pleural effusion.

Increased WBC and blood neutrophils, decreased lymphocytes, and an increased N/L ratio were statistically significantly correlated with poor survival in our univariate analysis. Only the N/L ratio was an independent factor predicting survival. Increased WBC with an increased neutrophil count have been identified as an independent predictor of death in patients with advanced NSCLC [18, 19]. A high neutrophil count has been reported as an adverse marker of prognosis in metastatic melanoma [20] and renal cell carcinoma [21], while a low lymphocyte count has been reported as a marker of mortality in pancreatic and breast cancer [22]. The causes of lymphopenia in cancer patients may vary. It may result in part from the destruction of lymphocytes by the tumor, and/or from impaired differentiation of lymphocyte progenitors [23]. Peripheral blood lymphopenia is a recognized predictor of poor survival in patients with advanced cancer, attributed to the fundamental role of lymphocytes in cell-mediated immunity with the destruction of host cancer cells [24]. An increased N/L ratio is an important indicator of an adverse prognosis in colorectal [25, 26] and gastric [27] cancers as in the case of our patients. Interestingly, in early-stage NSCLC an increased preoperative N/L ratio is an independent predictor of poor survival after complete resection of the tumor, and it is a potential biomarker to stratify patients with stage I disease with a high risk of death [28].

Thoracoscopic talc poudrage is the local treatment of choice in this patient population. The earlier it is performed, the better the results we expect are, with maintenance of the patient's PS and quality of life [29, 30]. Talc pleurodesis was not a factor for better survival in our patients with malignant pleural effusion. Talc has been implicated in patients with prolonged survival after pleurodesis. Recent studies showed that talc may act directly on cancer cells by inducing apoptosis or it may inhibit neoangiogenesis [31]. Since our patient population was newly diagnosed (treatment-naïve patients), this finding might be due to the fact that survival may be re-

lated to treatment response as has also been reported in other studies [3, 4].

We found no statistically significant correlation of survival with pleural fluid pH, glucose, LDH, or the number of pleural fluid WBC. Controversy exists regarding whether pleural biological parameters are associated with survival in patients with malignant pleural effusion; some authors believe that low pleural pH and glucose levels are related to poor survival [8, 9], while others believe these values do not help predict patient outcomes [4, 32, 33]. The selection of patients with old and/or already known pleural effusions may explain these findings as the older the effusion is, the lower the pleural pH and glucose levels are. These patients have probably already consumed their survival at the time of evaluation by presenting a tumor relapse or resistance to chemotherapy. Another issue is differences in survival according to the pleural pH of patients with mesothelioma compared to other primaries [17]. We were unable to show any relation between pleural pH and survival after stratification of our patients by primary tumor. A possible explanation for this discrepancy is that we had confirmed diagnoses of mesothelioma by thoracoscopic biopsy, while others had diagnosis conformation by simple thoracentesis [17]. In agreement with our findings, a meta-analysis clearly showed that there is no relation between pleural pH and the survival of patients with malignant pleural effusions [34].

Gender was not a prognostic factor in our study. Indeed, despite our 25 female patients with breast and ovary carcinoma, of the remaining 17 female patients, 10 patients presented with NSCLC and 3 patients had mesothelioma. Patients with NSCLC presenting with metastatic pleural effusion have a poor median survival of 8.5 months [35], and they have been reclassified lately by the IASLC as having stage M1a disease [36]. Mesothelioma is also a highly aggressive tumor with a poor median survival [37].

In our study, histology of the primary tumor, ECOG PS, and the blood N/L ratio were found to be predictors of survival in patients with malignant pleural effusion as the initial manifestation necessitating thoracoscopy to reveal the primary tumor. These factors may help physicians select patients for treatment and/or interventional procedures.

Financial Disclosure and Conflicts of Interest

The authors have no conflicts to disclose.

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