Thoracoscopic Assessment of Pleural Tumor Burden in Patients with Malignant Pleural Effusion

Prognostic and Therapeutic Implications

Lama Sakr, MD,† Fabien Maldonado, MD,†‡ Laurent Greillier, MD,† Hervé Dutau, MD,† Anderson Loundou, PhD,§ and Philippe Astoul, MD, PhD†*

Background: Malignant pleural effusion (MPE) is encountered at an advanced stage of disease progression and often heralds a poor prognosis. The most reliable predictive factor of survival in such patients is the primary tumor. Thoracoscopy is often performed for accurate diagnosis and/or thoracoscopic talc insufflation as a therapeutic modality. It remains unknown whether pleural tumor burden, as visualized on thoracoscopy, has potential prognostic value. The objective of this study was to determine the prognostic accuracy of pleural tumor extent and localization (parietal, visceral, or diaphragmatic involvement), as assessed during medical thoracoscopy.

Methods: Medical records of all patients who underwent thoracoscopy for suspicion of MPE between 2001 and 2008 at a tertiary care referral hospital were reviewed. Patients were included if pleural metastatic invasion was confirmed on tissue biopsy and survival status ascertained.

Results: Four hundred twenty-one patients underwent diagnostic or therapeutic medical thoracoscopy at our referral center. Among them, 122 had confirmed metastatic pleural spread, but survival data were lacking in 15. Primary tumor consisted of non-mall cell lung cancer in 56, breast cancer in 23, melanoma in eight, and other malignancies in 20. Median survival of the entire population was 9.4 months. On univariate analysis, the following variables were significantly associated with reduced median overall survival: pleural metastatic melanoma, age less than 60 years, bloody MPE, extensive pleural adhesions, and widespread visceral pleural nodules ($p < 0.05$). On multivariate analysis, only melanoma as a primary tumor, pleural fluid appearance and extent of pleural adhesions remained independent and significant predictors of survival.

Conclusion: No significant association was found between the extent or localization of pleural tumor burden and overall survival.

*Division of Pulmonary Diseases, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada; †Division of Thoracic Oncology, Pleural Diseases and Interventional Pulmonology, Hôpital Sainte-Marguerite, AP-HM, Université de la Méditerrannée, Marseille, France; ‡Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota; and §Department of Public Health and Biostatistics, Université de la Méditerrannée, Marseille, France.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Philippe Astoul, MD, PhD, Department of Thoracic Onology, Hôpital Sainte-Marguerite, 270, Bd de Ste-Marguerite, 13274 Marseille Cedex 09, France. E-mail: pastoul@ap-hm.fr

ISSN: 1556-0864/11/0603-0592

Key Words: Pleural effusion, Malignant, Thoracoscopy, Prognosis.

(*J Thorac Oncol.* 2011;6: 592–597)

Malignant pleural effusion (MPE) is frequently encountered in patients with a variety of underlying malignancies, at an advanced stage of disease progression. It heralds a poor prognosis, with a median survival of 3[1–3] to 9[4] months from the time of diagnosis, with the exception of breast and ovarian carcinoma.[5] Associated symptoms may consist of significant dyspnea, poor exercise tolerance, and impaired quality of life. Thoracoscopy allows a prompt and accurate diagnosis, in addition to providing effective symptomatic management with talc insufflation. The latter is a highly effective procedure, achieving successful long-term pleurodesis in more than 80% of cases.[6–8] Before talc insufflation, careful assessment of pleural carcinomatosis is usually achieved. Interestingly, it remains unknown whether pleural tumor burden—as assessed during thoracoscopy—has potential prognostic value.

It is generally believed that the most important predictive factor of survival in patients with MPE is the primary tumor.[2,9] Karnofsky Performance Scale has been also proven reliable in predicting prognosis, as a Karnofsky Performance Scale score [metqu] 70 at presentation was associated with better overall survival in patients with recurrent symptomatic MPE.[1] Other variables, such as pleural fluid (PF) pH and glucose concentration, have been reported by some authors as reliable prognostic factors, as low levels were indicative of poor survival[10–12]; however, such association was not proven in subsequent research,[1,13,14] including a most recent prospectively designed study.[1]

Some other potential prognostic factors deserve further analysis. The extent of pleural carcinomatosis (EPC) observed during thoracoscopy has been initially shown to correlate closely but inversely with survival in patients with MPE.[11] Nevertheless, subsequent studies failed to prove such a correlation.[1,12] A locally developed scoring system was used to grade the EPC in previous studies. Assessment of costoparietal, visceral, and diaphragmatic pleura on thoracoscopic examination was done using a scale of 0 to 3 for each pleural surface; the sum of individual scores, ranging from 0

to 9, represented the final EPC score. Nevertheless, using such a global score might not have allowed accurate assessment of each individual pleural surface as a potential prognostic marker. It has been previously suggested that initial pleural metastases occur on the mediastinal and diaphragmatic pleura and that with disease progression, pleural invasion spreads cephalad and costal.[15] Therefore, it can be hypothesized that extent and specific localization of metastatic pleural involvement, as visualized on thoracoscopy, could affect survival time. Recently, in a retrospective analysis of 540 patients with MPE, pleural adhesion rating—assessed thoracoscopically—correlated positively with pleural tumor burden and inversely with median survival. Nevertheless, on multivariate analysis, only tumor burden—but not the extent of pleural adhesions—remained an independent prognostic factor.[16] Moreover, although bloody pleural effusions (BPEs) have been suggested to increase the probability of malignancy,[9,17] no data are available with regard to the prognostic importance of PF appearance in MPE. In addition, it is not known whether cytological yield of PF—obtained by thoracentesis before eventual thoracoscopy—has any potential prognostic value. If PF appearance and PF cytological yield prove to be significant prognostic factors, this might help avoid complex and invasive palliative therapeutic procedures.

The primary objective of this study was to reevaluate the prognostic accuracy of pleural tumor burden, by taking into account the extent, pattern, and specific localization (costoparietal, visceral, and diaphragmatic) of pleural malignant invasion, as assessed during medical thoracoscopy. Secondary objectives were to determine or reassess other morphologic and cytopathologic variables potentially indicative of prognosis: primary tumor, PF appearance and cytological yield, and the extent of pleural adhesions on thoracoscopic examination.

MATERIALS AND METHODS

Medical records of all patients who underwent medical thoracoscopy for suspicion of MPE between 2001 and 2008 at a French university hospital were reviewed. No ethical considerations were raised. Patients were included if pleural metastatic invasion was confirmed on pleural tissue biopsy obtained at thoracoscopy. Patients with malignant pleural mesothelioma (MPM) were excluded from the study. Eligible subjects were also excluded if the date of death was missing and the patient could not be confirmed alive by direct or indirect source of information (through family members or a recent doctor's appointment).

Collected data included demographics (age and gender), primary tumor origin, PF cytology on a most recent sample obtained by thoracentesis before thoracoscopy, PF appearance, thoracoscopic findings (grade of adhesions, extent, pattern, and localization of pleural metastatic spread with separate evaluation of costoparietal, visceral, and diaphragmatic pleural surfaces), and date of death or the most recent date at which the patient was confirmed alive.

Before thoracoscopy, patients were evaluated by an interventional pulmonologist and an anesthesiologist, to assess indication for diagnostic and/or therapeutic thoracoscopy (thoracoscopic talc insufflation [TTI]) and to ensure safety of the procedure, taking into account each patient's overall functional status and comorbid illnesses. Patients deemed fit enough to undergo medical thoracoscopy were selected. Subjects were either in- or outpatients known to our medical center, or referrals from outside our university hospital. Thoracoscopy was performed under general anesthesia, with patients in a lateral decubitus position, lying on the nonaffected side. Patients were intubated and maintained on spontaneous ventilation. Evacuation of PF was followed by careful examination of the pleural cavity, and multiple biopsies, using an optical biopsy forceps (Wolf, Knittelgen, Germany), were then performed on tumoral and inflammatory areas over the costoparietal pleura. TTI was subsequently achieved in all patients. Finally, a 28-Fr chest tube was introduced and directed toward the lung apex, where it was left in place for 48 hours.

A detailed description of thoracoscopic findings was recorded by the operating physician in a dedicated report. PF appearance was reported as bloody or nonbloody. Adhesions within the pleural cavity were classified as (1) no adhesions, (2) isolated adhesions allowing normal or near-normal thoracoscopic examination, and (3) more extensive adhesions precluding complete and optimal visualization of the pleural cavity. Visceral, costoparietal, and diaphragmatic pleura were separately assessed for tumoral invasion and more specifically for the pattern of tumoral spread (nodules, pleural thickening, or pleural lymphangitis). Nodules were subsequently quantified as isolated (reported as "unique nodule" or "few nodules") or multiple. Pleural lymphangitis was noted when reticular formations were visualized on the pleural surface during thoracoscopy. Patient survival status or date of death was confirmed by careful search of medical records, telephone calls to the patient or his/her family, contact with patient's treating physician, or by consultation of civil records at city hall. Patient survival was calculated from the time of thoracoscopy.

Statistical Analysis

The Kaplan-Meier method was used to determine the relationship between patient survival and pleural tumor burden (extent, pattern, and localization), in addition to other potential prognostic factors (age, gender, primary tumor, PF appearance and cytological yield, and the extent of adhesions). The 95% confidence interval was calculated, and log-rank test was used for comparison. To analyze the independent prognostic contribution of each variable, a Cox regression analysis was performed. Results were considered statistically significant at p less than 0.05. All analyses were performed with statistical software (SPSS for Windows, release 15.0, SPSS, Chicago, IL).

RESULTS

Between 2001 and 2008, 421 patients underwent diagnostic and/or therapeutic medical thoracoscopy at our referral tertiary care hospital. Among those, 122 patients had metastatic pleural spread, as confirmed by thoracoscopic pleural biopsy. Fifteen were excluded, as their survival status or exact date of death could not be ascertained. One hundred seven patients (mean age, 61 years; 50 men and 57 women)

were included in the final analysis. Primary tumor consisted of non-small cell lung cancer in 56 patients, melanoma in eight, breast carcinoma in 23, and other malignancies in 20 patients (Table 1). Pleural effusion was right sided in 57 patients (53%) and hemorrhagic in 61 (57%). Pleural adhesions were absent in 64 patients (60%), limited in eight (7%), and extensive in 35 (33%). Invasion of parietal pleura was found in the great majority of patients (105/107, 98%), whereas visceral pleural involvement was observed in 87/107 (81%). Diaphragmatic pleura were deemed malignant in 60 of 107 patients and normal in two. Data with respect to diaphragmatic pleural involvement were missing in 45 patients. Mediastinal pleural involvement was rarely reported. Most often, mediastinal pleura is not visualized on medical thoracoscopy; therefore, we did not account for mediastinal pleural invasion in our assessment of pleural carcinomatosis. The pattern and extent of pleural metastatic spread are described in detail in Table 2. PF cytology—assessed on thoracentesis before thoracoscopy—was positive in 78 patients and negative in 19. PF cytology results were not available in 10 patients.

Median survival of the entire study population was 9.4 months (Figure 1). Median survival values derived from the Kaplan-Meier analysis for each of the potential prognostic factors are listed in Table 2. Pleural metastatic melanoma, age less than 60 years, BPE, and extensive pleural adhesions were all reliable predictive factors on univariate analysis, as they were all associated with significantly reduced median overall survival ($p < 0.05$). When pleural tumor burden was further categorized, visceral pleural nodules ("multiple" category) were associated with significantly lower median survival. For unexplained reasons, parietal pleural nodules ("few" category) and diaphragmatic pleural lymphangitis were associated with better prognosis on univariate analysis. Such correlation did not remain significant on multivariate analysis of survival. No difference in overall survival was found between patients with cytologically positive and negative pleural effusions.

Using the multivariate model of survival, only melanoma as the primary tumor, PF appearance and extent of pleural adhesions remained as independent and significant predictors of survival ($p = 0.03$, 0.02, and 0.03, respectively) (Table 3).

TABLE 1. Tumor Type in Patients with Malignant Pleural Effusion

Tumor Types	*n* (%)
Lung	
Adenocarcinoma	47
Squamous	6
Squamous + adenocarcinoma	1
Small cell	3
Large cell neuroendocrine	1
Undifferentiated	1
Melanoma	8
Breast	23
Ovary	4
Kidney	4
Prostate	2
Gynecological	1
Pancreas	1
Gastrointestinal	1
Esophagus	1
Thyroid (medullary)	1
Undifferentiated	1
Adenocarcinoma (unknown origin)	1

DISCUSSION

The primary objective of this study was to assess the prognostic accuracy of pleural tumor burden in patients who undergo thoracoscopy for MPE. Secondary objectives were to determine the contribution of additional morphologic and clinicopathologic parameters at predicting survival.

As stated earlier, patients with MPM were excluded from the study. In fact, MPM is a rare and aggressive malignancy, with a distinct profile and biological behavior. The epidemiological background, natural history, staging system, therapeutic modalities, and prognosis are widely different from those of primary lung cancer or other primary carcinomas metastatic to the pleura. Boutin et al. have previously shown that MPM—in contrast to metastatic pleural spread—arises in the parietal and diaphragmatic pleura and later spreads to the visceral pleura. In their prospective study, patients with early disease involving only the ipsilateral parietal pleura (T1a) had a median survival of 32 months, whereas those with slightly more advanced tumor involving all pleural surfaces, including the visceral pleural (T1b), had a median survival of 7 months.[18] Such findings contributed to the elaboration of a new international staging system for MPM.[19] Therefore, given the distinct features of this malignant entity, we chose to exclude patients with MPM from our study.

In contrast to previous studies, pleural tumor burden prognostic accuracy was assessed by separately considering the malignant involvement of each pleural surface. It is worth noting that mediastinal pleura are not often visualized on standard medical thoracoscopy, and therefore, related data could not be obtained. Although our scoring system was not previously validated, we believed that it might provide a more precise description of the pattern and localization of pleural malignant invasion. Nevertheless, no significant association was found between the extent, pattern, or localization of pleural carcinomatosis and overall survival. This is in agreement with the findings of Burrows et al. and Sanchez-Armengol and Rodriguez-Panadero,[1,12] using a broader locally developed scoring system for assessment of the EPC.

On the other hand, although metastatic pleural melanoma accounted for only 8% of our cohort, it was associated with significantly reduced median overall survival. The latter might suggest that the extent or pattern of pleural metastatic involvement in itself is not a prognostic factor; rather, a MPE is perhaps simply indicative of advanced disease stage, and survival could be mainly determined by the primary tumor and its inherent characteristics, namely its degree of aggression and its response to chemotherapeutic treatments. Interestingly, outcome was not statistically different between the larger and clinically more important groups of metastatic pleural lung and breast carcinomas, in contrast to previous

TABLE 2. Variables Predicting Overall Survival in Patients with Malignant Pleural Effusion (Univariate Analysis)

Variables	Value	*n* (%)	Median Survival (d)[a]	95% CI	Hazard Ratio[b]	95% CI	*p*[c]
Primary tumor	NSCLC	56	297	196–398	1		
	Melanoma	8	42	0–115	2.3	1.08–4.89	0.03
	Breast	23	424	387–461	0.66	0.38–1.14	0.14
	Other	20	128	0–345	1.3	0.76–2.23	0.34
Sex	Male	50	260	103–417	1		
	Female	57	317	177–457	0.81	0.54–1.23	0.32
Age (yr)	<60	51	217	85–349	1		
	≥60	56	382	219–545	0.64	0.42–0.96	0.03
Effusion side	Left	50	251	174–328	1		
	Right	57	338	202–474	1.11	0.73–1.67	0.63
PF cytology on thoracentesis	Negative	19	220	0–472	1		
	Positive	78	252	167–337	0.82	0.48–1.40	0.46
PF appearance	Nonbloody	46	471	258–684	1		
	Bloody	61	215	82–348	2.18	1.41–3.36	<0.001
Grade of adhesions	No adhesions	64	405	323–487	1		
	Limited adhesions	8	127	0–636	0.92	0.40–2.15	0.85
	Large adhesions	35	118	61–175	2.4	1.52–3.77	<0.001
Parietal pleural nodules	No nodules	20	142	0–412	1		
	Nodules	87	317	208–426	0.74	0.44–1.23	0.24
Parietal pleural nodules	No nodules	20	142	0–412	1		
	Few nodules	5	617	480–754	0.23	0.07–0.80	0.02
	Multiple nodules	82	265	150–380	0.8	0.48–1.33	0.38
Parietal pleural pachypleuritis	No pachypleuritis	67	342	208–476	1		
	Pachypleuritis	40	215	65–365	1.02	0.67–1.56	0.93
Parietal pleural lymphangitis	No lymphangitis	69	260	191–329	1		
	Lymphangitis	38	342	38–646	0.77	0.50–1.18	0.24
Visceral pleural invasion	No invasion	17	530	342–718	1		
	Invasion	87	260	180–340	1.81	0.98–3.34	0.06
Visceral pleural nodules	No nodules	46	400	274–526	1		
	Nodules	58	217	106–328	1.43	0.94–2.20	0.1
Visceral pleural nodules	No nodules	46	400	274–526	1		
	Few nodules	14	342	0–744	0.88	0.46–1.70	0.71
	Multiple nodules	44	163	65–261	1.8	1.14–2.85	0.01
Visceral pleura pachypleuritis	No pachypleuritis	69	317	147–487	1		
	Pachypleuritis	35	260	181–339	1.24	0.80–1.91	0.34
Visceral pleura lymphangitis	No lymphangitis	82	338	244–432	1		
	Lymphangitis	22	158	50–266	1.33	0.81–2.20	0.26
Diaphragmatic pleural nodules	No nodules	7	158	35–281	1		
	Nodules	55	361	227–495	0.78	0.35–1.73	0.54
Diaphragmatic pleural pachypleuritis	No pachypleuritis	53	382	294–470	1		
	Pachypleuritis	9	185	7–363	0.72	0.32–1.63	0.44
Diaphragmatic pleural lymphangitis	No lymphangitis	51	340	238–442	1		
	Lymphangitis	11	729	439–1019	0.46	0.23–0.92	0.03

[a] Kaplan-Meier survival estimates.
[b] Cox proportional hazards model.
[c] Log-rank (Mantel-Cox) *p* value.
CI, confidence interval; NSCLC, non-small cell lung cancer; PF, pleural fluid.

reports. A relatively small number of patients in each category, and therefore, a poor statistical power could have accounted for our findings.

Curiously, PF appearance was significantly correlated with overall survival. A bloody MPE was independently associated with poor prognosis. A previous study has shown that a BPE slightly increases the risk of underlying malignancy and that MPEs were bloody in 11% of cases.[17] Nevertheless, no data were previously available with respect to the prognostic importance of a bloody malignant PE. The latter usually develops after direct tumor invasion of blood vessels, occlusion of venules, tumor-induced angiogenesis, or

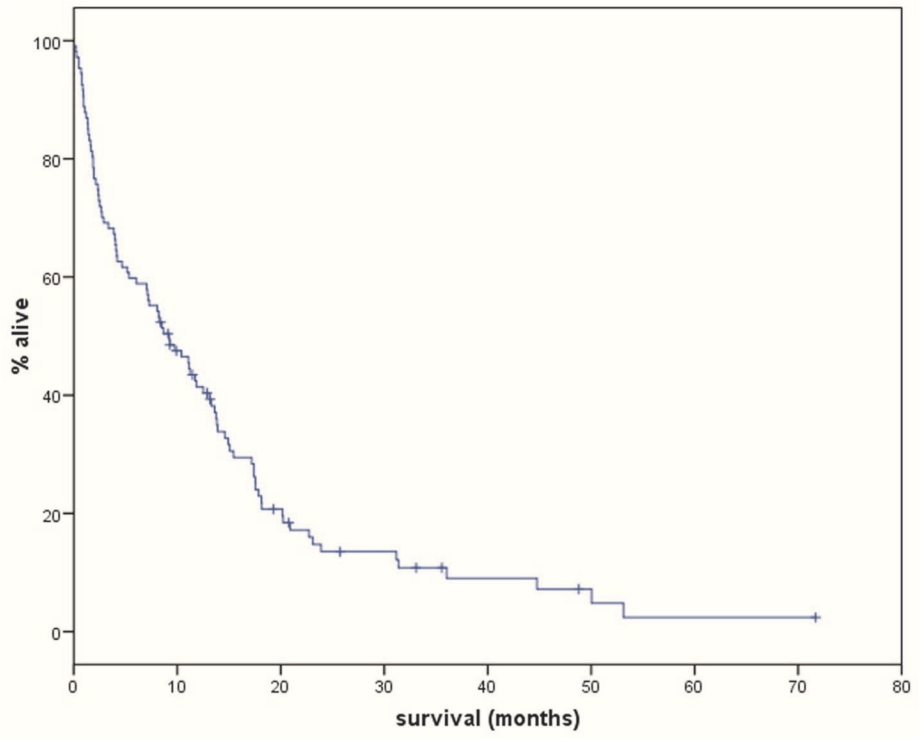

FIGURE 1. Kaplan-Meier curve showing median overall survival of the study population. Median survival of the entire group was 9.4 months.

TABLE 3. Variables Predicting Overall Survival in Patients with Malignant Pleural Effusion (Multivariate Analysis)

Variables	Hazard Ratio	95% CI	*p*
Primary tumor			0.04
NSCLC	1	—	—
Melanoma	2.84	1.20–6.75	0.02
Breast	0.73	0.38–1.41	0.36
Others	0.81	0.42–1.54	0.51
Age	0.76	0.47–1.25	0.28
Sex	1.03	0.60–1.76	0.93
PF appearance	1.89	1.10–3.28	0.02
Grade of adhesions			0.02
No adhesions	1	—	—
Limited adhesions	0.86	0.33–2.28	0.76
Large adhesions	2.2	1.23–3.94	0.01
Parietal pleural nodules			0.07
No nodules	1	—	—
Few nodules	0.22	0.06–0.84	0.03
Multiple nodules	0.93	0.46–1.86	0.83
Visceral pleural invasion	0.77	0.34–1.78	0.55
Visceral pleural nodules	0.65	0.35–1.23	0.18
Diaphragmatic pleural lymphangitis	0.51	0.23–1.15	0.10

NSCLC, non-small cell lung cancer; PF, pleural fluid; CI, confidence interval.

increased capillary permeability due to vasoactive cytokines and chemokines.[20,21] Vascular endothelial growth factor (VEGF) is a potent growth factor for endothelial cells and is believed to be a key mediator in the formation of MPE. In fact, it has been shown that MPE contained significantly higher levels of VEGF than effusions of inflammatory etiology.[22] Moreover, hemorrhagic effusions have shown significantly higher VEGF levels than nonhemorrhagic effusions.[22] In a recent prospective study, a significant positive correlation was found between the number of red blood cells and VEGF values in MPE; in addition, high VEGF levels in PF was a significant negative predictor of patient survival.[23]

Moreover, the extent of pleural adhesions correlated with lower survival expectancy, in accordance with the findings of Bielsa et al.[16] Nevertheless, in contrast to the latter study, such correlation remained statistically significant on multivariate analysis. Pleural adhesions are thought to develop in the pleural space in response to several inflammatory stimuli, including infection, malignancy and trauma.[24] Pleural inflammation is associated with an influx of a large number of cytokines and inflammatory cells, which initiate a cascade of cellular processes ultimately leading to collagen synthesis, tissue remodeling, and pleural fibrosis. Tumor necrosis factor-α and transforming growth factor-β are examples of mediators strongly implicated in the pathogenesis of pleural inflammation and fibrosis. As a result of cytokine-induced pleural injury and increased microvascular permeability, a coagulation cascade is initiated, and components of both the fibrinolytic system and inhibitors of the fibrinolytic system are produced.[25,26] Plasminogen, as well as plasminogen activators and plasminogen activator inhibitors (PAI-1 and PAI-2), are readily detectable in inflammatory PFs.[26] Whether the extent of underlying intrapleural inflammatory and procoagulation responses could induce or reflect a systemic hypercoaguable state, which might lead to fatal thromboembolic disease, thereby accounting for worse short-term survival, deserves further study.

In this study, there was no significant difference in survival duration between patients with cytologically positive and negative pleural effusions, as assessed on thoracentesis before thoracoscopic examination. As described previously, pleural malignant involvement in all our patients was ultimately confirmed on pleural tissue biopsy. Therefore, PF cytological yield is not a reliable prognostic marker; rather, a negative cytology—in the absence of plausible alternative diagnoses (i.e., infection)—warrants further investigation.

Our study has several potential limitations. Because of the retrospective design of our study, some data (i.e., diaphragmatic pleural invasion) were not always available. Our study population was also relatively small, preventing reliable assessment of potential prognostic markers in specific tumor types. In addition, the scoring system used for grading pleural tumor burden and the extent of adhesions requires further validation. It is also worth noting that some findings, such as PF appearance, are partly subjective, and a potential bias could have, therefore, affected our results. Moreover, tumor response to chemotherapy, although previously shown to affect short-term survival in such patients, was not accounted for in this study. Many patients were treated and followed up outside our university hospital setting and were most often referred to us solely for thoracoscopic management of recurrent and symptomatic MPEs. Therefore, rigorous follow-up data regarding response to systemic therapy were not available. In addition, primary tumor types were widely variable; therapeutic modalities and, more specifically, chemotherapeutic agents are therefore expected to be significantly diverse, further complicating the assessment of tumor response to treatment, and its contribution to overall survival. As metastatic stage was ascertained in all patients, we did not feel the need to collect further data with regard to the extent of disease at the primary site or the presence of metastatic disease beyond the pleural space. Whether such information might have affected outcome could not be determined. Moreover, the success or failure of pleurodesis after TTI could not be assessed after patient discharge from hospital, as most patients were subsequently followed up outside our tertiary care setting. Nevertheless, recent data show no correlation between postpleurodesis lung expansion and clinical outcome—including survival—in patients with recurrent MPE.[27] Finally, all patients who were included in this study were medically fit to undergo diagnostic and therapeutic thoracoscopy under general anesthesia; obviously, this does not apply to all patients who present with a MPE.

In conclusion, the extent, pattern, and specific localization of pleural carcinomatosis do not seem to portend a significant prognostic value in patients with MPE. Nevertheless, other variables, namely melanoma as the primary tumor, PF appearance, and the extent of pleural adhesions proved to be important predictive survival factors.

REFERENCES

1. Burrows CM, Mathews WC, Colt HG. Predicting survival in patients with recurrent symptomatic malignant pleural effusions. *Chest* 2000; 117:73–78.
2. Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of survival for patients with malignant pleural effusions. *Chest* 2000;117: 79–86.
3. Jiménez D, Diaz G, Gil D, et al. Etiology and prognostic significance of massive pleural effusions. *Respir Med* 2005;99:1183–1187.
4. Martinez-Moragon E, Aparicio J, Sanchis J, et al. Malignant pleural effusion: prognostic factors for survival and response to chemical pleurodesis in a series of 120 cases. *Respiration* 1998;65:108–113.
5. Ruckdeschel JC. Management of malignant pleural effusions. *Semin Oncol* 1995;22:58–63.
6. Viallat JR, Rey F, Astoul P, et al. Thoracoscopic talc poudrage pleurodesis for malignant effusions. A review of 360 cases. *Chest* 1996;110: 1387–1393.
7. Dresler CM, Olak J, Herndon JE, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest* 2005;127:909–915.
8. de Campos JRM, Vargas FS, de Campos Werebe E, et al. Thoracoscopy talc poudrage: a 15-year experience. *Chest* 2001;119:801–806.
9. Light RW. Pleural Diseases, 5th Ed. Philadelphia: Williams & Wilkins, 2007.
10. Sahn SA, Good JT. Pleural fluid pH in malignant effusions. *Ann Intern Med* 1988;108:345–349.
11. Rodriguez-Panadero F, Lopez-Mejias J. Survival time of patients with pleural metastatic carcinoma predicted by glucose and pH studies. *Chest* 1989;95:320–324.
12. Sanchez-Armengol A, Rodriguez-Panadero F. Survival and talc pleurodesis in metastatic pleural carcinoma, revisited: report of 125 cases. *Chest* 1993;104:1482–1485.
13. Foresti V, Scolari N, Villa A, et al. Malignant pleural effusions: meaning of pleural-fluid pH determination. *Oncology* 1990;47:62–64.
14. Aelony Y, King RR, Boutin C. Thoracoscopic talc poudrage in malignant pleural effusions: effective pleurodesis despite low pleural pH. *Chest* 1998;113:1007–1012.
15. Sahn S. Malignancy metastatic to the pleura. *Clin Chest Med* 1998;19: 351–361.
16. Bielsa S, Martín-Juan J, Porce JM, et al. Diagnostic and prognostic implications of pleural adhesions in malignant effusions. *J Thorac Oncol* 2008;3:1251–1256.
17. Villena V, López-Encuentra A, García-Luján R, et al. Clinical implications of appearance of pleural fluid at thoracentesis. *Chest* 2004;125: 156–159.
18. Boutin C, Rey F, Gouvernet J, et al. Thoracoscopy in pleural malignant mesothelioma: a prospective study of 188 consecutive patients: II. Prognosis and staging. *Cancer* 1993;72:394–404.
19. Rusch VW. The International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. *Chest* 1995;108:1122–1128.
20. Meyer PC. Metastatic carcinoma of the pleura. *Thorax* 1966;21:437.
21. Spriggs AI, Boddington MM. Malignant effusions. In The Cytology of Effusions, 2nd Ed. New York: Grune and Stratton, 1968. Pp. 21–31.
22. Ishimoto O, Saijo Y, Narumi K, et al. High level of vascular endothelial growth factor in hemorrhagic pleural effusion of cancer. *Oncology* 2002;63:70–75.
23. Hsu IL, Su WC, Yan JJ, et al. Angiogenetic biomarkers in non-small cell lung cancer with malignant pleural effusion: correlations with patient survival and pleural effusion control. *Lung Cancer* 2009;65:371–376.
24. Mason AC, Miller BH, Krasna MJ, et al. Accuracy of CT for the detection of pleural adhesions: correlation with videoassisted thoracoscopic surgery. *Chest* 1999;115:423–427.
25. Antony VB, Sahn SA, Mossman B, et al. Pleural cell biology in health and disease. *Am Rev Respir Dis* 1992;145:1236–1239.
26. Philip-Joët F, Alessi MC, Philip-Joët C, et al. Fibrinolytic and inflammatory processes in pleural effusions. *Eur Respir J* 1995;8:1352–1356.
27. Terra RM, Junqueira JJM, Teixeira LR, et al. Is full postpleurodesis lung expansion a determinant of a successful outcome after talc pleurodesis? *Chest* 2009;136:361–368.

