Prognostic Factors for Survival after Surgical Palliation of Malignant Pleural Effusion

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Introduction: To investigate prognostic factors for patient survival after surgical palliation of malignant pleural effusion (MPE).

Method: We reviewed 278 consecutive nonoverseas patients (108 men, median age: 60 years [range 26–89]) undergoing 310 surgical procedures for palliation of MPE over a 72-month period. There were 195 thoracoscopic talc pleurodesis, 39 pleuroperitoneal shunts, 38 pleurodesis by an intercostal drain, 29 pleural biopsies alone, and nine long-term drains. Referring physicians provided survival data. The significance of prognostic factors was examined with the log-rank test (Kaplan-Meier), those significant entered a Cox logistic multivariate regression analysis.

Results: Follow-up was complete until death (following 264 procedures) and for a median 648 days (range 173–2135) for surviving patients. Overall median postoperative survival was 211 days (95% confidence interval: 169–253). Survival was not significantly different for tumor type or method of palliation. In univarate analysis, preoperative leucocytosis, hypoxemia, raised alanine transaminase, body mass index below 18 and hypoalbuminemia were associated with a significantly reduced postoperative survival. In multivariate analysis, leucocytosis ($p < 0.0001$), hypoxemia ($p = 0.014$), and hypoalbuminemia ($p < 0.0001$) maintained significance.

Conclusions: The survival reported demonstrates the necessity of an active approach to palliation of MPE. The identification of prognostic factors will assist the choice of palliative technique. In addition, an appreciation of the influence of selection on survival after surgical palliation of malignant pleural mesothelioma, especially that of unforeseen prognostic factors, is useful when evaluating the results of aggressive treatment such as chemoradiotherapy and radical surgery for these diseases.

Key Words: Malignant pleural effusion, Mesothelioma, Albumin, Prognosis, Pleurodesis.

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Recurrent pleural effusions are common in patients with advanced malignant disease.[1] A wide range of interventions are available to diagnose, control, and palliate the symptoms,[2] palliative measures which have been shown to be effective.[3–5] There are few identified prognostic factors available, especially before surgery, to help the surgeon to select the appropriate modality for palliation. This study seeks to analyze factors associated with long-term survival after palliation of malignant pleural effusion (MPE).

METHODS

We reviewed all nonoverseas patients admitted to our unit for management of MPE during a 72-month period (January 1999–December 2004). Data on features available preoperatively were collected to allow analysis of prognostic factors which may influence survival. Data collected included basic demographics, arterial blood gas analysis, blood biochemistry and hematology, and body mass index (BMI) on the day before surgery. The influence of the site of the primary tumor, sometimes not available until after surgery, was also assessed. Referring physicians and oncologists were contacted to obtain survival data.

The method of palliation of effusion depended on the patient's fitness for general anesthesia and the intraoperative findings. In patients judged unfit for general anesthesia, an intercostal drain was inserted under local anesthetic. Once the lung had reexpanded and drainage reduced, tetracycline or talc slurry was injected into the pleural cavity by the drain.

Patients treated under general anesthetic underwent an initial bronchoscopy to exclude central airway obstruction, and double-lumen tube intubation was performed to allow single-lung ventilation. Although recent developments in cross-sectional imaging allow good visualization of tumor in the central airways, we believe, the information gathered, importance of giving the affected lung every chance of expanding and the training opportunity afforded by routine bronchoscopy outweigh the cost in terms of time and resources. With the patient in the lateral decubitus position, a single port was fashioned to allow inspection of the pleural space with the video-assisted thoracoscope. After appropriate samples of the effusion were obtained for cytologic examination and culture, multiple large pleural biopsies were taken from any abnormal areas and if the pleura were uniform from a number of representative areas including the posteroinferior costal pleura. If no preoperative diagnosis was available,

these were subject to frozen section histopathological examination. We would take biopsies of the pleura even in the presence of a previous cytologic diagnosis of MPE. Cytology is limited in the diagnosis of malignant pleural mesothelioma (MPM), and it is not always possible to perform immunohistochemistry on a cytology specimen, which may be helpful in guiding treatment.

If mediastinal shift and lung reinflation were deemed adequate to allow apposition of the pleural surfaces over most of the hemithorax, then pleurodesis was attempted by insufflation of 10 g of sterile talc. If this was not feasible, usually because the lung was trapped by thickening of the visceral pleura, then a pleuroperitoneal shunt was inserted as described previously.[3] In cases where the effusion was infected, a portion of rib was excised and a long-term intercostal drain inserted. Where the pleural biopsy was inconclusive on frozen section analysis or the pleural space was obliterated by tumor, no procedure other than biopsy was performed at this initial examination.

The relationship of factors to survival after palliative treatment of their MPE was analyzed using the log-rank test (Kaplan-Meier method). To perform this test, continuous variables had to be dichotomized. Alkaline phosphatase, white cell count, and alanine transaminase were dichotomized using the upper end of the normal range in our laboratory, whereas for hemoglobin and serum albumin, the lower end of the normal range was used. Age was split at 70 years to select out the elderly. As most patients are hypoxic before this procedure, arterial hypoxemia was dichotomized at the cohort's median value of 9.5 kPa. Serum creatinine was split at 100 because using the normal range would have left a very small abnormal group and using the median a very large one. BMI <18 and weight loss of $>10\%$ are commonly used when assessing nutritional status.[6] Factors with a significant association then entered a multivariate analysis using Cox proportional hazard method. p values of 0.05 or less were considered significant.

RESULTS

Two hundred seventy-eight consecutive nonoverseas patients (108 men, median age: 60 years [range 26–89]) underwent 310 procedures for palliation of MPE over 72 months. Two procedures were performed in 32 patients; 24 were bilateral (eight presenting with synchronous effusions and 16 metachronous), and eight underwent two unilateral procedures. The commonest causes were carcinoma of the breast, malignant pleural mesothelioma, carcinoma of the lung, and ovarian carcinoma (Table 1). Data on prior management of the effusion were available in 216 procedures (69%); 30 (14%) had no intervention before referral to our department, 67 (31%) a single intervention (aspiration or drainage), and 119 (55%) multiple interventions (including attempted pleurodesis in 14) before referral. The serum albumin concentration of those patients who underwent none or one aspiration of the pleural space before surgical palliation (mean, 34.3 g/liter [standard deviation 5.8]) was significantly higher than those who underwent two or more procedures (mean, 29.9 g/liter [standard deviation 7.0]) ($p = 0.0003$, t test). Smoking data were available on 180 patients, and those patients shown to be hypoxemic on arterial blood gas analysis were less likely to be current smokers (3 of 89 versus 25 of 180 [$p = 0.009$]) and less likely to have ever smoked (41 of 89 versus 107 of 180 [$p = 0.05$]) than those who were not hypoxemia. The procedures performed were 195 thoracoscopic talc pleurodeses (62.5%), 39 pleuroperitoneal shunts (12.5%), 38 pleurodesis by an intercostal drain (12.2%), 29 pleural biopsies (9.3%), and nine long-term drains (2.9%).

TABLE 1. Underlying Malignancy Associated with MPE

	Patients, *n* (%)	Procedures, *n* (%)
Breast cancer	81 (28.9)	101 (32.4)
Malignant pleural mesothelioma	77 (27.5)	79 (25.3)
Lung cancer	37 (13.2)	39 (12.5)
Ovarian cancer	25 (8.9)	31 (9.9)
Adenocarcinoma of unknown origin	19 (6.8)	19 (6.1)
Malignant melanoma	13 (4.6)	13 (4.2)
Lymphoma	5 (1.8)	7 (2.2)
Renal cell carcinoma	6 (2.1)	6 (1.9)
Sarcoma	5 (1.8)	5 (1.6)
Pancreatic cancer	3 (1.1)	4 (1.3)
Endometrial cancer of the uterus	2 (0.71)	2 (0.64)
Myeloma	1 (0.36)	2 (0.64)
Colon cancer	1 (0.36)	1 (0.32)
Squamous cancer of the tongue	1 (0.36)	1 (0.32)
Thyroid cancer	1 (0.36)	1 (0.32)
Thymic carcinoma	1 (0.36)	1 (0.32)

MPE, malignant pleural effusion.

The in-hospital mortality after the palliative procedures was nine patients (2.9%) (pulmonary embolus, three; respiratory failure, two; hepatic failure, two; myocardial infarction, one; and ischemic lower limb, one). There were nine admissions to intensive care for invasive ventilation, multiple inotropes, or hemofiltration and 24 prolonged admissions to the surgical high dependency unit for single inotropes or noninvasive ventilation.

Follow-up data were obtained for all patients. Follow-up was complete until death (following 264 procedures) and for a median 648 days (range 173–2135) for surviving patients. Overall median postoperative survival was 211 days (95% confidence interval [CI]: 169–253), Figure 1 and Table 2. Malignant pleural mesothelioma and breast cancer showed a trend toward increased survival over other primary sites, although this was not statistically significant (Table 3 and Figure 2).

When survival was analyzed by palliative procedure (Table 4), there was no statistically significant difference. The 29 patients who underwent pleural biopsy only were predominantly those in whom either pleural thickening was predominant and there was very little pleural fluid or those in whom there was no palliative benefit gained when their effusion had previously been drained but surgery was felt to be the only method of obtaining a diagnosis. There was a trend to reduced survival in these patients which may be due to them being in a later stage of the disease process as the pleural

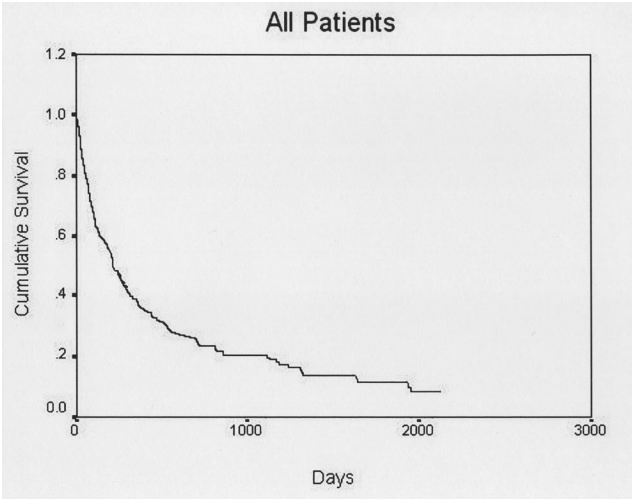

FIGURE 1. Kaplan-Meier survival curve for all patients from the day of palliative procedure.

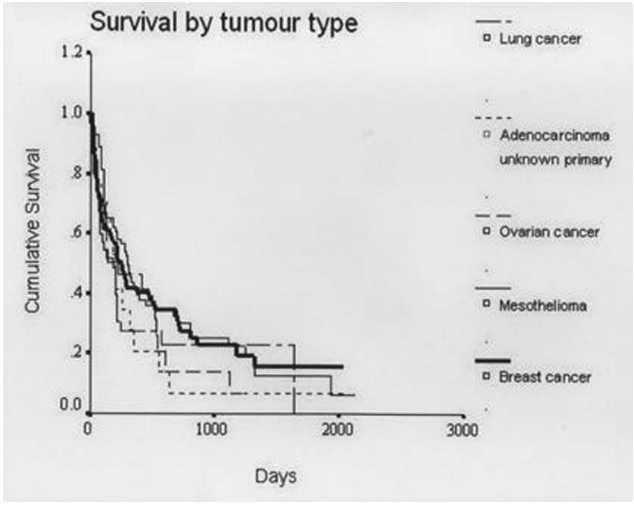

FIGURE 2. Kaplan-Meier survival curve for patients with the commonest five pleural malignancies.

TABLE 2. Numbers at Risk for All Patients by Time from Procedure (Figure 1)

Time (d)	0	500	1000	1500	2000
Number at risk	312	70	29	14	4

TABLE 3. Survival by Tumor Type

Tumor	*N*	Median Survival (d)	95% CI	*p*
Breast cancer	100	258	185–331	0.546
Malignant pleural mesothelioma	79	297	236–358	
Ovarian cancer	31	130	72–188	
Adenocarcinoma of unknown primary	19	123	62–184	
Lung cancer	39	138	10–266	

CI, confidence interval.

TABLE 4. Survival by Procedure

Procedure	*n*	Median Survival (d)	95% CI	*p*
VATS and talc pleurodesis	195	211	148–274	0.5589
VATS and biopsy alone	29	165	0–379	
VATS and insertion of pleuroperitoneal Shunt	39	207	122–292	
VATS and insertion long-term drain	9	312	0–744	
Pleurodesis by drain inserted on the ward	38	250	169–331	

CI, confidence interval; VATS, video-assisted thorascopic surgery.

space becomes obliterated by tumor. The median survival of those patients who underwent a bedside talc pleurodesis is longer than those recorded for the other procedures. It is within the 95% CIs of all the postprocedure survivals and not statistically significantly different. Although these patients may have had significant comorbidities, making anesthesia hazardous, their pleural disease was generally early as their lung reexpanded on drainage allowing a talc slurry pleurodesis. Only 3 of the 51 patients with a preoperative leucocytosis had a macroscopic empyema at surgery. No peritoneal deposits were observed in those patients palliated with a pleuroperitoneal shunt in keeping with previously reported data.[3]

Univariate analysis of factors affecting postprocedural survival showed leucocytosis (Figure 3), hypoxemia (Figure 4), raised alanine transaminase, BMI <18, and hypoalbuminemia (Figure 5) were associated with a significantly reduced postoperative survival (Table 5). On multivariate analysis, leucocytosis ($p < 0.0001$), hypoxemia ($p = 0.014$), and hypoalbuminemia ($p < 0.0001$) maintained significance (Table 4). Sex, age, weight loss $>10\%$, anemia, creatinine >100, and raised alkaline phosphatase were not significant factors affecting survival. The presence of none, some, or all three factors which maintain independent significant associations with poor postoperative survival stratifies the patient population into three distinct groups (Table 6 and Figure 6). The median survival of patients with all three poor prognostic factors present preoperatively is significantly less than those with none (42 versus 702 days [$p < 0.00001$]).

The 79 patients with MPM were followed up for a median 1114 days postsurgery during which there were 64 deaths. The median survival was 297 days (95% CI: 234–360), Figure 7 and Table 7. The presence of the three prognostic factors stratified the patients survival (Figure 8), although the difference was not significant ($p = 0.06$). Median survival with no factors present ($n = 15$) was 438 days (95% CI: 0–909), one or two factors ($n = 39$) 215 days (95% CI: 109–321), and all three factors ($n = 3$) 65 days (95% CI: 17–113 days).

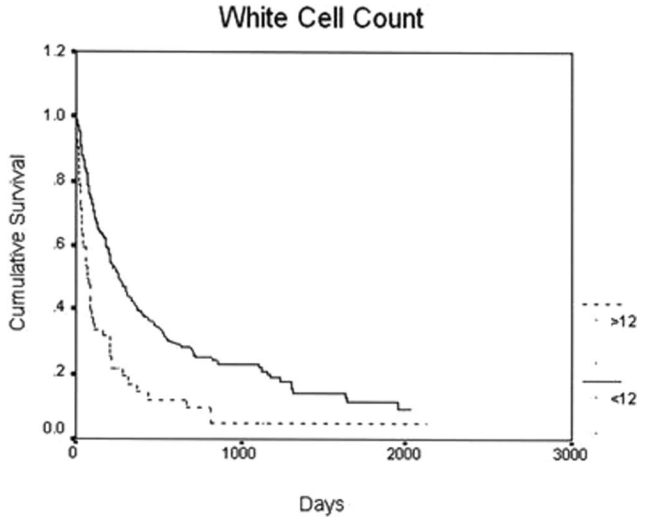

FIGURE 3. Kaplan-Meier survival curve comparing patients with a white cell count $\leq 12 \times 10^9$/liter or $>12 \times 10^9$/liter.

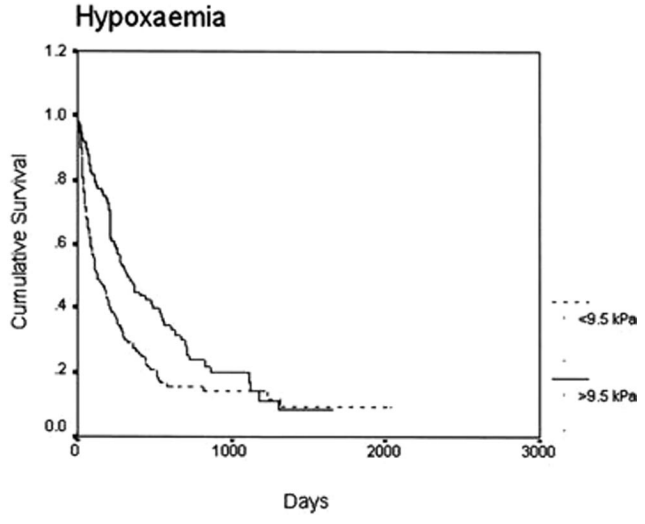

FIGURE 4. Kaplan-Meier survival curve comparing patients with a partial pressure of oxygen (Pao_2) $\leq$9.5 kPa or $>$9.5 kPa.

DISCUSSION

The survival to be expected after palliation of MPE is an important factor in selecting the appropriate method of treatment. All surgical techniques carry some risk of death and morbidity for the patient[7] and have significant cost implications for the health service.[8] The median survival of our patients was 211 days, and therefore, an active approach to palliating MPE is justified. We present a study that has determined three factors—hypoalbuminemia, hypoxia, and leucocytosis—which are easily obtained before intervention and may help to predict patients' prognosis afterward. We found patients with all three adverse prognostic factors had a median survival of 42 days (compared with 702 days for patients with none). Therefore, it would be reasonable to palliate these patients with multiple pleural aspirations or the use of an indwelling pleural catheter inserted under local anesthetic. General anesthesia and surgical approaches, such as talc pleurodesis and pleuroperitoneal shunting, with their attendant risks and longer period of hospitalization should be reserved for patients with better prospects of survival.

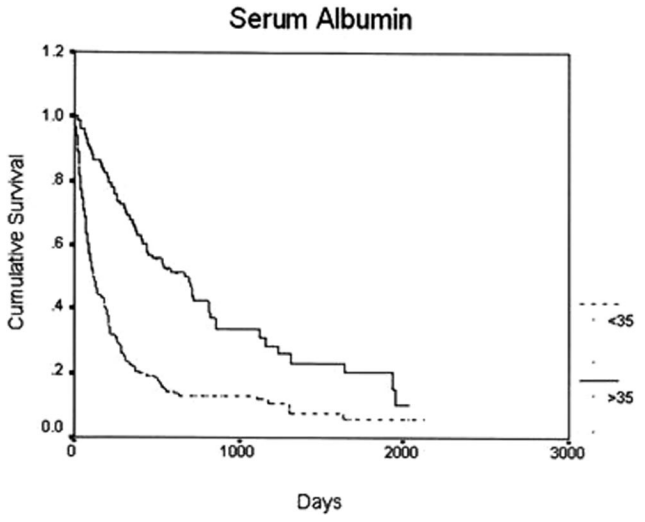

FIGURE 5. Kaplan-Meier survival curve comparing patients with a serum albumin $\leq$35 g/liter or $>$35 g/liter.

Of the three factors significantly associated with poor survival, hypoalbuminemia is the most commonly recognized across all medical and surgical specialties. A number of large studies have demonstrated its significant, severity dependant relationship with early mortality, morbidity, intensive care stay, and hospital stay in both medical and surgical patients.[9,10] Because of its long half-life (14–20 days), albumin is recognized as a surrogate marker of nutritional status, although in our study other measures of nutritional status, weight loss $>$10%, and BMI $<$18 did not have a significant association with poor survival. Although the protein concentration in pleural effusions was not routinely measured during palliative procedures at our institution, MPE is usually a protein-rich exudate. The majority of our patients had undergone multiple pleural aspirations and drainage procedures before referral, and we have shown these patients to have lower serum albumin levels. Serum albumin is also influenced by systemic inflammation and has been used as a prognostic marker in advanced colorectal[11] and non-small cell lung cancer.[12] Bernard et al.[7] reported serum albumin to be associated with poor 3-month survival in their series of patients undergoing surgical palliation of MPE although this did not achieve significance on multivariate analysis. Serum albumin measurement is cheap and easy to obtain before surgery. Hypoxia is common in patients with MPE but is probably more common in those patients with a poor respiratory reserve, larger effusions, and those associated with lymphangitis or extensive nodal disease. Leucocytosis in a patient with a pleural effusion, especially if they have had previous intervention raises the possibility of malignant empyema. This is known to have a poor prognosis because the infection prevents the optimum use of chemotherapy, and the presence of pleural malignancy makes eradication of infec-

TABLE 5. Univariate Analysis of Survival by Preoperative Factors (Kaplan-Meier Method, Log-Rank Test) and Multivariate Analysis of Survival (Cox Regression)

	Univariate Analysis				Multivariate Analysis		
Factors	***n***	**Median Survival (d)**	**95% CI**	***p***	**Hazard Ratio**	**95% CI**	***p***
Sex							
Female	197	210	166–254	0.277			
Male	115	184	122–246				
Age (y)							
>70	80	201	118–284	0.257			
<70	230	210	161–259				
More than 10% weight loss							
No	247	210	164–256	0.621			
Yes	63	199	115–283				
Hemoglobin (g/dl)							
>11	248	220	184–256	0.118			
<11	62	105	77–133				
Creatinine (μmol/liter)							
>100	38	258	141–375	0.929			
<100	271	206	171–241				
Body mass index (kg/m^2)							
>18	269	220	184–256	0.002	1.632	0.883–3.015	0.118
<18	23	82	49–115				
Alkaline phosphatase (IU/liter)							
<250	204	211	172–250	0.098			
>250	92	109	57–161				
White cell count ($\times 10^9$/liter)							
>12	53	68	36–100	<0.00001	0.495	0.337–0.727	<0.0001
<12	254	259	207–311				
Pao_2 (kPa)							
>9.5	98	317	220–414	0.0015	0.678	0.497–0.924	0.014
<9.5	131	130	75–185				
Albumin (g/liter)							
>35	104	667	449–885	<0.00001	0.414	0.291–0.588	<0.0001
<35	202	114	87–141				
Alanine aminotransferase (IU/liter)							
<41	246	250	199–301	0.0007	0.690	0.449–1.061	0.091
>41	50	69	36–102				

CI, confidence interval.

TABLE 6. Survival by Presence of None, One or Two of Three, or All Three Factors Significantly Associated with Poor Survival (Log-Rank Test, Kaplan-Meier Method) (Figure 2)

No. of Factors	***n***	**Median Survival (d)**	**95% CI**	***p***
None	39	702	473–931	<0.00001
One or two	74	200	111–289	
Three	23	42	23–61	

CI, confidence interval.

tion with antibiotics difficult. Decortication has a prohibitively high mortality.[7] Leucocytosis could also be a manifestation of systemic inflammatory response to the burden of tumor. White blood cell count is easily and routinely measured before surgery.

There have been case reports[13] and small series[14] of patients surviving for prolonged periods after palliative procedures for MPM. In fact, Aelony and Yao[14] report a series of 26 patients who underwent talc pleurodesis for MPM, 21 of which had no further oncological treatment, with a median survival of 19.4 months. Unfortunately, outside of these reports, the survival of patients with MPM is poor. In the United Kingdom, median survival with best supportive care has been reported as 5.9[15] and 8.9 months.[16] Our institution previously reported a median survival of 10.1 months for 36 patients palliated with a pleuroperitoneal shunt.[3] Hence, the report of a median survival of 19 months in a series of 183 patients undergoing trimodality therapy[17] and 35 months in 51 patients receiving extra pleural pneumonectomy and adjuvant chemotherapy[16] has stimulated interest in investigating a radical approach to treatment.[18] The part played by selec-

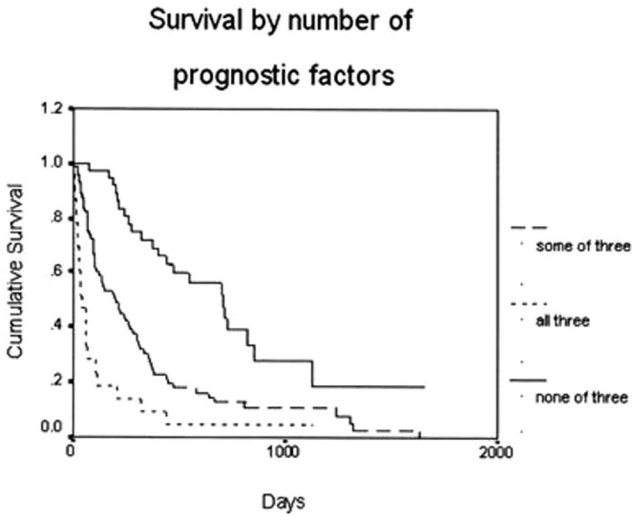

FIGURE 6. Kaplan-Meier survival curve comparing patients with none, one or two of three, or all three prognostic factors determined by multivariate analysis.

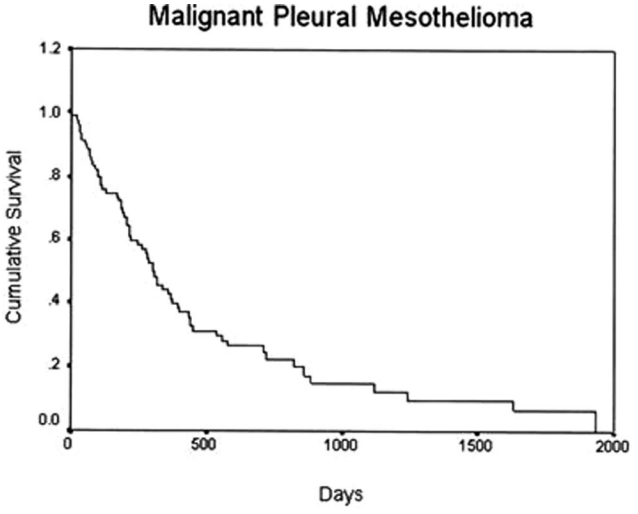

FIGURE 7. Kaplan-Meier survival curve for all patients with malignant pleural mesothelioma from the day of palliative procedure.

TABLE 7. Numbers at Risk with MPM by Time from Procedure (Figure 7)

Time (d)	0	250	500	750	1000
Number at risk	79	43	19	10	5

tion in the favorable results of such radical therapy is a concern. The median survival of 297 days for the 79 patients with mesothelioma in our series was achieved in a group with bulkier disease, more advanced disease, and impaired performance status than those selected for radical treatment. However, three hematological features were associated with widely differing prognoses, with median survival ranging from 65 days in the worst category to 483 days in the group

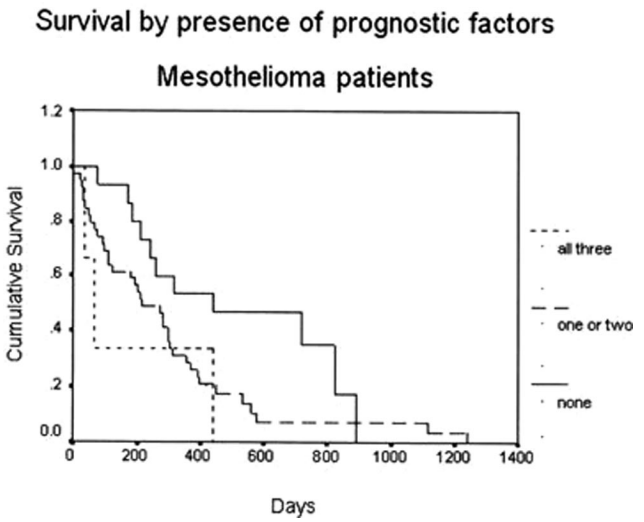

FIGURE 8. Kaplan-Meier survival curve comparing patients with malignant pleural mesothelioma with none, one or two of three, or all three prognostic factors determined by multivariate analysis.

with none of the adverse prognostic factors. The patients we report had only a relatively small palliative procedure with a median hospital stay of only 6 days. They were then able to return home and spend as much time as possible with their family and loved ones.

Our study is retrospective, and therefore, we can only claim a significant association between the factors we have identified and poor prognosis. The population we have studied is that referred to a thoracic surgical unit for consideration of palliation and is not disease specific. Tumor type did not significantly influence survival in our study, although this may be an effect of not having enough patients in each group as there was a trend toward better survival with breast cancer and MPM. We were unable to obtain complete information on the oncological treatment that patients had received outside our institution, and therefore, we cannot comment on whether these have any bearing on survival. This article was not designed to answer questions regarding the success of palliation, but we report eight patients (2.9%) underwent two procedures due to failure of their initial palliative procedure, seven for failure of video-assisted thorascopic surgery talc pleurodesis, and one for blocked pleuroperitoneal shunt. We recognize this may underestimate the number of procedural failures.

Performance status has been shown to be associated with prognosis in this group of patients,[19] but this was not routinely recorded at the time of admission to our unit. Retrospective analysis of performance status was felt to be too inaccurate and open to bias to be included in our data collection. Similarly, pleural fluid biochemistry (glucose and pH) have been shown by some,[20] but not all,[19] to be associated with patient survival. These tests were not routinely performed in our institution and, therefore, have not been included in our analysis. Finally, extent of disease, as reflected in tumor bulk or the number of metastatic sites, has

been shown to impact on survival in this group of patients,[7] but such data were not universally available on our patients, and therefore, this was not analyzed. The variables we have analyzed are those recorded in every patient's admission and the results of their routine laboratory studies. Therefore, we believe we have reduced the element of bias, which can taint retrospective studies.

We present data from a series of 278 patients undergoing 310 procedures to palliate MPE with complete follow-up for 3.5 years. We have identified three factors significantly associated with a poor prognosis. Hypoxia, hypoalbuminemia, and leucocytosis are easily measured by the routine investigations usually undertaken before such surgery, and the results could help patient counseling and the choice of the appropriate method of palliation for MPE.

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