# Prognostic Factors According to the Treatment Schedule in Malignant Pleural Mesothelioma

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**Objectives:** In this study, we aimed to investigate the factors affecting the survival of patients with malignant pleural mesothelioma (MPM) according to their treatment schedules, including those treated with best supportive care, chemotherapy, and multimodality therapy.

**Methods:** We evaluated 235 patients with MPM. The patients were classified into three groups according to their treatment schedules: the best supportive care group, the chemotherapy group, and the multimodality therapy group. Prognostic factors were determined for all patients and for the three groups by univariate and multivariate analyses. However, the effectiveness of treatment schedules as a prognostic factor was not evaluated in this study.

**Results:** After adjusting for therapy in a Cox model, a Karnofsky Performance Status (KPS) $\leq$70, a right side tumor, serum lactate dehydrogenase $>$500 IU$^{-1}$, a nonepithelial subtype, and stage 3 to 4 disease were determined by multivariate analyses to be unfavorable prognostic factors for all the patients. A KPS $\leq$70, serum lactate dehydrogenase $>$500 IU$^{-1}$, a nonepithelial subtype, and stage 3 to 4 disease were associated with a poor prognosis for the best supportive care group. The single unfavorable prognostic factor for the chemotherapy group was a KPS $\leq$70. A right side tumor and a nonepithelial subtype were associated with a poor prognosis for the multimodality therapy group.

**Conclusions:** The patients with an epithelial subtype, a good KPS, and an early-stage tumor had a good prognosis, even if they did not receive any treatment. The only prognostic factor for the chemotherapy group was KPS. The histologic subtype and stage of the tumor were not related to the prognosis in this group. A mixed subtype and a right side tumor were unfavorable prognostic factors for the multimodality therapy group. These findings may be useful in counseling patients and in planning further studies.

**Key Words:** Malignant pleural mesothelioma, Prognostic factors, Treatment schedule.

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Malignant pleural mesothelioma (MPM) is an uncommon tumor of the pleura that is usually associated with a poor prognosis. The incidence of MPM is still increasing throughout most of the world, and it is expected to rise in the coming decades.[1] Until recently, no particular therapies have been accepted as a standard of care due to the resistance of the tumor to treatment modalities. However, some authors suggest that the new chemotherapeutic agents and the therapeutic combination of surgery, chemotherapy, and radiotherapy have resulted in an increased survival for patients with MPM.[2–7]

The overall survival of patients with MPM varies among the different available treatment strategies. However, the treatment of patients with MPM depends on several parameters including performance status, medical comorbidities, pulmonary function, tumor stage, and age. These factors are also prognostic factors for MPM, and it is important to identify them. These prognostic factors allow the selection of patients more likely to benefit from more intensive treatment, and this more accurate patient selection contributes to better survival, with lower morbidity and mortality rates. Both the European Organization for Research and Treatment of Cancer and the Cancer and Leukemia Group B examined the effect of various pretreatment clinical characteristics on the survival of patients with MPM who received chemotherapy.[8,9] In the European Organization for Research and Treatment of Cancer study, poor prognosis was associated with a poor performance status, a high white blood cell (WBC) count, a probable/possible histologic diagnosis of mesothelioma, male gender, and having sarcomatous tissue as the histologic subtype.[8] The Cancer and Leukemia Group B showed that pleural involvement, serum lactate dehydrogenase (LDH) level $>$500 IU/L, poor performance status, chest pain, platelet count $>$400,000 $\mu$L$^{-1}$, nonepithelial histology, and age more than 75 years predict poor survival.[9]

Most prognosis analyses have evaluated all patients as a single group with no attention paid to treatment differences. However, different antitumoral treatments may influence prognosis. Additionally, the features of different treatment groups vary from one another. For example, patients who received multimodal treatment were younger, had a better performance status, and had mostly epithelial type tumors of an early stage.[5]

We hypothesized that the prognostic factors could be determined according to the different treatment schedules, including best supportive care, chemotherapy, and multimo-

dality therapy, thereby allowing a more suitable selection of patients for treatment and a more accurate estimation of prognosis. Thus, the morbidity, mortality, and cost due to treatment could subsequently be decreased and survival could be improved. In this study, we aimed to investigate the various pretreatment clinical and laboratory characteristics affecting the survival of patients with MPM according to their treatment schedules, including those treated with best supportive care, chemotherapy, and multimodality therapy in a single institution.

## PATIENTS AND METHODS

### Patients

Between January 1991 and June 2008, 274 patients with MPM were diagnosed in our clinic. After diagnosis, best supportive care, chemotherapy, or multimodality therapy was performed on the patients. There were 39 patients who were excluded for the analysis, including patients who had received prior therapy, pleurectomy decortication, or pleurectomy decortication plus chemotherapy. In addition, patients who were not followed up, died within 30 days after diagnosis, died due to reasons unrelated to MPM (treatment complication, pneumonia, pulmonary embolism, etc.) and those who received only one or two cycles of chemotherapy without measured response were excluded.

In this study, 235 patients were evaluated. Tumors from all patients were staged according to the International Union Against Cancer staging system. The patients were classified into three groups according to their treatment schedule: the best supportive care group (71 patients), the chemotherapy group (147 patients), and the multimodality therapy group (17 patients). Chemotherapy was given between 1990 and 1996 as cisplatin + mitomycin C + recombinant interferon alpha 2a, between 1996 and 2000 as cisplatin + mitomycin C + ifosfamide, between 2000 and 2005 as cisplatin + gemcitabine, and since 2005 as cisplatin + pemetrexed. Surgical resection consisted of extrapleural pneumonectomy with en bloc resection of the lung, parietal pleura, hemipericardium, and diaphragm. A systematic hilar and mediastinal lymphadenectomy was conducted. The diaphragm and pericardium were reconstructed using mesh. Adjuvant radiotherapy was delivered to the hemithorax, the thoracotomy incision, and at the sites of chest drains.

### Pretreatment Patient Characteristics

First, the prognostic factors were determined for all patients. These factors were then also determined for each treatment group, including the best supportive care group, the chemotherapy group, and the multimodality therapy group, by univariate and multivariate analyses. The following pretreatment characteristics were evaluated for prognostic importance: age ($<75/\geq 75$ years), gender, asbestos exposure (yes/no), smoking history, presence of chest pain, presence of dyspnea, weight loss in past 6 months (>5% loss of body weight/none or <5%), Karnofsky Performance Status (KPS) ($\leq 70/>70$), primary site of disease (right/left), platelet count ($\leq 400\ 000/>400{,}000\ \mu L^{-1}$), WBC count ($\leq 10{,}000/>10{,}000\ \mu L^{-1}$), hemoglobin level ($<12.8/\geq 12.8$ g/dl), serum LDH level ($\leq 500/>500\ IU^{-1}$), histologic subtype, and stage. All prognostic indices were evaluated as categorical variables. Continuous variables were categorized into two groups. The cutoff points chosen were based on previous studies.[8,9] However, the median values were used as the cutoff point for both the hemoglobin level and the WBC count.

### Statistical Analysis

Characteristics of the patients according to their treatment schedule were compared using analysis of variance and $\chi^2$ test. Survival curves were estimated using the Kaplan-Meier method. Survival was measured from the date of diagnosis. All the patients were followed until death or for a minimum period of 1 year. Dates of death were verified through the National Population Registry System. Comparisons for survival were performed using log-rank tests. The proportional hazards regression model with stratification for the clinical trial was used for both univariate and multivariate analyses. Univariate analysis examined the prognostic importance of all factors. The Cox proportional hazard model was used to examine variables. A two-sided test was used at a 0.05 level of significance. A step-down/step-wise variable selection procedure was used to fit the multivariate model. Only parameters that had $p$ values $\leq 0.10$ in the univariate analysis used in the final model for multivariate analysis. The importance of a prognostic factor was assessed by the $p$ value of the Wald $\chi^2$ statistic, the relative risk (risk in patients in a given category, when compared with the reference one), and the 95% confidence interval. Statistical analyses were performed using SPSS statistical software.

## RESULTS

### Patient Demographics

Patient characteristics are summarized in Table 1. The mean age and mean KPS were found to be different among the three groups. The presence of weight loss at diagnosis and the tumor stage were also different between the multimodality therapy group and the other two groups but were not different between the best supportive care and the chemotherapy group. The overall median survival time of all patients was 10.0 months. The median survival times were 7.0, 11.5, and 21.0 months for the best supportive care group, the chemotherapy group, and the multimodality therapy group, respectively (Figure 1).

### Univariate Analysis Results

In univariate analysis, poor prognosis was associated with the presence of weight loss ($p = 0.031$; 9.0 versus 12.0 months), a poor KPS ($p < 0.0001$; 4.5 versus 12.0 months), a right site tumor ($p = 0.012$; 9.0 versus 12.0 months), a high WBC count ($p < 0.0001$; 6.0 versus 12.0 months), a high LDH level ($p = 0.002$; 7.0 versus 11.0 months), a nonepithelial histology ($p < 0.0001$; 7.0 versus 11.0 months), stage III to IV disease ($p < 0.0001$; 8.5 versus 14.0 months), and therapy with the best supportive care ($p < 0.0001$; 7.0, 11.5, and 21.0 months for the best supportive care, the chemotherapy, and the multimodality therapy group, respectively) for all the patients.

**TABLE 1.** Characteristics of the Patients According to Their Treatment Schedule*

| | Best Supportive Care Group | Chemotherapy Group | Multimodality Therapy Group | Test Value |
|---|---|---|---|---|
| No | 71 | 147 | 17 | |
| Mean age, years | 63.6 ± 11.0 (33–83) | 58.5 ± 11.1 (26–80) | 49.7 ± 10.7 (33–69) | F=12.27; ***p*<0.0001** |
| Male : Female | 36:35 | 75:72 | 10:7 | $\chi^2$=0.397; $p$=0.820 |
| Asbestos exposure, n (%) | 60 (84.5) | 132 (89.8) | 13 (76.5) | $\chi^2$=3.109; $p$=0.211 |
| Smoking history, n (%) | 29 (40.8) | 59 (40.1) | 9 (52.9) | $\chi^2$=1.039; $p$=0.595 |
| Weight loss, n (%) | 37 (52.1) | 61 (41.5) | 2 (11.8) | $\chi^2$=9.313; ***p*=0.009** |
| Chest pain, n (%) | 55 (77.5) | 119 (81.0) | 14 (82.4) | $\chi^2$=0.427; $p$=0.808 |
| Dyspnoea, n (%) | 58 (81.7) | 115 (78.2) | 13 (76.5) | $\chi^2$=0.427; $p$=0.808 |
| Mean Karnofsky Performance Status | 77.7 ± 10.6 (50–100) | 82.5 ± 7.8 (60–100) | 86.5 ± 7.0 (80–100) | F=10.34; ***p*<0.0001** |
| Primary site of disease, n (%) | | | | |
| Right | 46 (64.8) | 91 (61.9) | 6 (35.3) | $\chi^2$=5.431; $p$=0.066 |
| Left | 24 (33.8) | 56 (38.1) | 11 (64.7) | |
| Histologic subtype, n (%) | | | | |
| Epithelial | 46 (64.8) | 100 (68.0) | 13 (76.5) | $\chi^2$=5.24; $p$=0.513 |
| Mixed | 10 (14.1) | 25 (17.0) | 4 (23.5) | |
| Sarcomatous | 7 (9.9) | 9 (6.1) | 0 (0.0) | |
| Unidentified | 8 (11.3) | 13 (8.8) | 0 (0.0) | |
| Stage, n (%) | | | | |
| I | 24 (33.8) | 40 (27.2) | 12 (66.7) | $\chi^2$=16.60; ***p*=0.011** |
| II | 12 (16.9) | 17 (11.6) | 1 (5.6) | |
| III | 25 (35.2) | 61 (41.5) | 4 (22.2) | |
| IV | 9 (12.7) | 29 (19.7) | 0 (0.0) | |

* Variance analysis and chi-square test were used for statistical analysis.

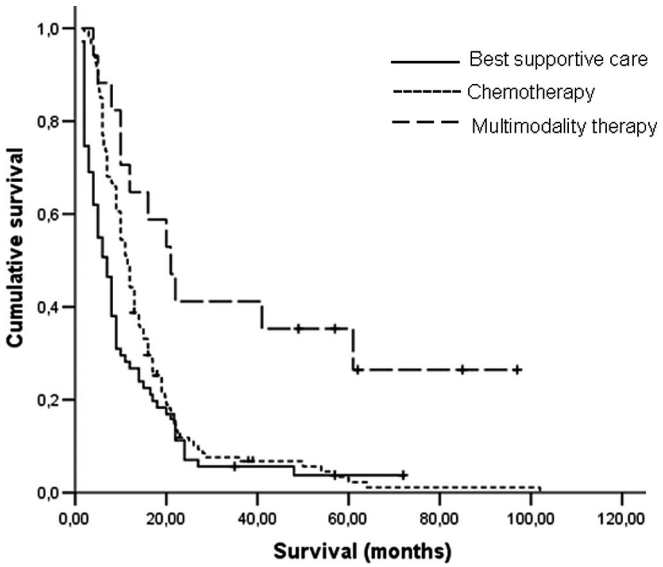


**FIGURE 1.** Kaplan–Meier survival curves for the best supportive care, the chemotherapy, and the multimodality therapy group.

In the best supportive care group, univariate analysis indicated that the presence of smoking history ($p = 0.049$; 5.0 versus 7.0 months), a poor KPS ($p < 0.0001$; 2.0 versus 9.0 months), a right site tumor ($p = 0.036$; 5.0 versus 9.0 months), a high WBC count ($p = 0.008$; 4.0 versus 8.0 months), low hemoglobin level ($p = 0.015$; 5.0 versus 8.0 months), a high LDH level ($p = 0.008$; 3.0 versus 8.0 months), a nonepithelial histology ($p = 0.011$; 5.0 versus 7.0 months), and stage III to IV disease ($p < 0.0001$; 5.0 versus 9.0 months) were significantly related to a poor prognosis. A poor KPS ($p < 0.0001$; 5.4 versus 13.0 months), a high platelet count ($p = 0.038$; 10.0 versus 12.0 months), a high WBC count ($p = 0.022$; 8.0 versus 12.0 months), a high-LDH level ($p = 0.027$; 9.0 versus 12.0 months), a nonepithelial histology ($p = 0.046$; 10.0 versus 12.0 months), and stage III to IV disease ($p = 0.010$; 10.0 versus 14.0 months) were related to a poor prognosis for the chemotherapy group. The presence of smoking history ($p = 0.022$; 10.0 versus 41 months), a right site tumor ($p = 0.016$; 8.0 versus 41.0 months), and a mixed subtype ($p = 0.035$; 10.0 versus 41.0 months) were associated with a poor prognosis in the multimodality therapy group.

## Multivariate Analysis Results

After adjusting for therapy in a Cox model, a KPS ≤70, a right side tumor, serum LDH >500 $IU^{-1}$, a nonepithelial subtype, stage III to IV disease were associated with a poor prognosis for all the patients (Table 2). A KPS ≤70, serum LDH >500 $IU^{-1}$, a nonepithelial subtype, and stage III to IV disease were related to a poor prognosis for the best supportive care group (Table 3). The unfavorable prognostic factor for the chemotherapy group was only a KPS ≤70 (Table 4). The statistician thought that stage has more clinical importance than smoking on MPM prognosis. Because of that stage was chosen instead of smoking history for multivariate model in the multimodality therapy group. The mixed subtype and a

 

**TABLE 2.** Multivariate Stepwise Logistic Regression Model for All of the Patients*

| Variable | Risk Ratio | 95% CI | *p* |
|---|---|---|---|
| Weight loss | | | |
| No | 1 | | |
| Yes | 1.051 | 0.772–1.429 | 0.753 |
| KPS | | | |
| >70 | 1 | | |
| ≤70 | 4.160 | 2.695–6.423 | <0.0001 |
| Primary site of disease | | | |
| Left | 1 | | |
| Right | 1.399 | 1.016–1.926 | 0.040 |
| WBC count, μl-1 | | | |
| ≤10 000 | 1 | | |
| >10 000 | 1.381 | 0.992–1.921 | 0.056 |
| LDH, IU-1 | | | |
| ≤500 | 1 | | |
| >500 | 1.530 | 1.078–2.172 | 0.017 |
| Histologic subtype | | | |
| Epithelial | 1 | | |
| Others | 1.574 | 1.109–2.235 | 0.011 |
| Stage | | | |
| I–II | 1 | | |
| III–IV | 1.661 | 1.199–2.300 | 0.002 |

* Multivariate analysis was used for statistical analysis.
WBC, white blood cell; LDH, lactate dehydrogenase.

**TABLE 3.** Multivariate Stepwise Logistic Regression Model for the Best Supportive Care Group*

| Variable | Risk Ratio | 95% CI | *p* |
|---|---|---|---|
| Smoking | | | |
| No | 1 | | |
| Yes | 1.491 | 0.854–2.606 | 0.160 |
| KPS | | | |
| >70 | 1 | | |
| ≤70 | 3.832 | 1.978–7.424 | <0.0001 |
| Primary site of disease | | | |
| Left | 1 | | |
| Right | 1.672 | 0.959–2.913 | 0.070 |
| WBC count, μl-1 | | | |
| ≤10 000 | 1 | | |
| >10 000 | 1.305 | 0.749–2.273 | 0.348 |
| Hemoglobin level, gdL-1 | | | |
| ≥12,8 | 1 | | |
| <12,8 | 1.422 | 0.815–2.483 | 0.215 |
| LDH, IU-1 | | | |
| ≤500 | 1 | | |
| >500 | 2.208 | 1.192–4.093 | 0.012 |
| Histologic subtype | | | |
| Epithelial | 1 | | |
| Others | 1.858 | 1.061–3.256 | 0.030 |
| Stage | | | |
| I–II | 1 | | |
| III–IV | 2.278 | 1.244–4.172 | 0.008 |

* Multivariate analysis was used for statistical analysis.
WBC, white blood cell; LDH, lactate dehydrogenase.

**TABLE 4.** Multivariate Stepwise Logistic Regression Model for the Chemotherapy Group*

| Variable | Risk Ratio | 95% CI | *p* |
|---|---|---|---|
| KPS | | | |
| >70 | 1 | | |
| ≤70 | 4.776 | 2.725–8.370 | <0.0001 |
| Histologic subtype | | | |
| Epithelial | 1 | | |
| Others | 1.031 | 0.686–1.549 | 0.884 |
| Platelet count, μl-1 | 1 | | |
| ≤400 000 | | | |
| >400 000 | 1.348 | 0.912–1.994 | 0.135 |
| WBC count, μl-1 | 1 | | |
| ≤10 000 | | | |
| >10 000 | 1.363 | 0.906–2.050 | 0.137 |
| LDH, IU-1 | 1 | | |
| ≤500 | | | |
| >500 | 1.513 | 0.998–2.296 | 0.051 |
| Stage | | | |
| I–II | 1 | | |
| III–IV | 1.357 | 0.912–2.020 | 0.132 |

* Multivariate analysis was used for statistical analysis.
WBC, white blood cell; LDH, lactate dehydrogenase.

**TABLE 5.** Multivariate Stepwise Logistic Regression Model for the Multimodality Therapy Group*

| Variable | Risk Ratio | 95% CI | *p* |
|---|---|---|---|
| Primary site of disease | | | |
| Left | 1 | | |
| Right | 4.531 | 1.233–16.647 | 0.023 |
| Histologic subtype | | | |
| Epithelial | 1 | | |
| Others | 4.545 | 1.018–20.290 | 0.047 |
| Stage | | | |
| I–II | 1 | | |
| III–IV | 1.561 | 0.310–7.852 | 0.589 |

* Multivariate analysis was used for statistical analysis.

right side tumor were associated with worse prognosis for the multimodality therapy group (Table 5).

## DISCUSSION

MPM is always a fatal malignancy. The overall survival of patients with MPM varies among different treatment schedules. The median survival of patients receiving best supportive care is 8 months[10–12] and those receiving chemotherapy is about 12 months,[2,3,12] whereas the survival of patients with multimodality treatment is 16 to 25 months.[4–7,13] The prognosis for MPM can be predicted by well-validated parameters. Additionally, the treatment strategy is determined in part by using known prognostic factors. Various patient characteristics have been examined for their potential effect on the survival of patients with MPM. Performance status,[8–10,14–16] histology,[4,6,8,9,14–19] stage,[6,10,17–19] age,[9,10,17,19] and gender[6,8,15] were identified as the most im-

portant predictors of prognosis in these studies. However, smoking history, asbestos exposure, chest pain, weight loss, laterality, LDH level, platelet count, WBC count, and hemoglobin level were less frequently observed as prognostic factors.

Our study evaluated the prognosis and prognostic factors for the survival of 235 patients with MPM undergoing varying treatments. We determined that the median survival time was 7.0, 11.5, and 21.0 months in the best supportive care group, the chemotherapy group, and the multimodality therapy group, respectively. Some factors such as KPS, stage, and age, which are considered before selecting the most suitable treatment, were different among the groups. Patients who received multimodality therapy were younger, their KPS was higher, and their stage was earlier when compared with the others. Patients who received chemotherapy were younger than those who received best supportive care, and their performance status was also better. Therefore, adjustments were made according to the treatment before analysis and then the prognostic factors were assessed for all the patients. We identified that a KPS $\leq$70, a right side tumor, serum LDH $>$500 $IU^{-1}$, a nonepithelial subtype, and stage III to IV disease were significant independent negative prognostic factors for all the patients. Subsequently, prognostic factors were identified according to each treatment schedule.

The prognostic importance of an epithelial type versus nonepithelial types has been often addressed, with a clear survival advantage for the patient with an epithelial type.[4,6,8,9,14–19] A good performance of the patient is also considered important as a prognostic and predictive factor.[8–10,14–16] Additionally, the prognostic significance of the stage has been shown in many studies.[6,10,17–19] These three factors have been used when planning clinical trials and identifying the most suitable patients for chemotherapy and radical surgery. We also identified the effect of these three factors on the survival of the patients who received the best supportive care. This analysis showed that patients with a better performance status, an epithelial type, and an early-stage tumor had better survival even when they received no therapy. However, the histology and stage were not related to prognosis in patients who received chemotherapy; only KPS was related to prognosis in these patients. Therefore, chemotherapy should be given to patients with the best performance status, regardless of their histologic subtype and stage. However, histology was related to prognosis in the multimodality therapy group. When the morbidity and mortality rates are considered, multimodality treatment should not be performed on mixed and sarcomatous subtypes.

In our study, the primary site of disease (laterality) was identified as a prognostic factor for all the patients and for the multimodality therapy group. The survival of patients with a left side tumor was better than for those with a right side tumor. A similar result was obtained in a comprehensive study that also included patients who received radical surgery.[6] Furthermore, authors in this study found that the survival of patients with asbestos exposure was worse.[6] In this study, although asbestos exposure was not identified as a prognostic factor, it could be a reason for the laterality of disease if different amounts of asbestos fiber reached the right or left pleura due to partial differences in the morphologic structures of the right and left lung. Christensen et al.[20] also found that patient survival was associated with asbestos fiber burden in MPM, where patients with either low or high asbestos burden had a higher risk of death compared with patients with a moderate fiber burden. However, more studies are necessary to further elucidate the ability of this variable to predict survival in MPM.

Laboratory characteristics have been included in many of the multivariate analyses for MPM and have indicated that low hemoglobin,[15] a high WBC count,[8,15,16] elevated platelets,[9,14] and elevated LDH[9,10] are inversely related to the survival rate. In this study, hemoglobin, WBC count, and platelet level were not related with the prognosis. However, the serum LDH level was identified as a prognostic factor for all the patients and for the best supportive care group. This parameter may be a marker of disease activity.

Although the mean patient age was different among the groups, age was not identified as a prognostic factor, which was contrary to some other studies.[9,10,17,19] The male:female ratio was similar due to the environmental asbestos exposure in our study. Men had a similar survival to women in this study, despite being associated with poor prognosis in some other studies.[6,8,15] Patients with MPM mostly present with symptoms such as chest pain, dyspnea, weight loss, anorexia, lethargy, and night sweat. Most of these symptoms are indicators of advanced disease. Weight loss was more frequent in patients who received best supportive care and chemotherapy than in those who received multimodality therapy. Additionally, these patients had advanced stage disease; however, weight loss was not identified as a prognostic factor.

There has been interest in finding a biomarker that has value in the prognosis of MPM. The relationship between numerous overexpressed molecular markers and prognosis has recently been reported in patients with MPM.[21–24] These markers will allow more targeted treatments. Studies are necessary to further elucidate the ability of these variables to predict survival in MPM.

In conclusion, we investigated the various pretreatment clinical and laboratory characteristics affecting the survival of patients with MPM according to their treatment schedules, including those treated with best supportive care, chemotherapy, and multimodality therapy. However, we did not evaluate treatment effectiveness as a prognostic factor. As has been observed in other studies, patients who had an epithelial subtype, a good KPS, and early-stage tumors had a better prognosis, even if they did not receive any treatment. The only prognostic factor for the chemotherapy group was KPS. The histologic subtype and stage of the tumor were not related to the prognosis in this group. A mixed subtype and a right side tumor were unfavorable prognostic factors for the multimodality therapy group. These findings may be useful in counseling patients and in planning further studies.

## REFERENCES

1. Robinson BWS, Musk AW, Lake AR. Malignant mesothelioma. *Lancet* 2005;366:397–408.
2. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of

 

pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003;21: 2636–2644.
3. van Meerbeeck JP, Gaafar R, Manegold C, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005;23:6881–6889.
4. Sugarbaker DJ, Flores RM, Jaklitsch MT, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. *J Thorac Cardiovasc Surg* 1999;117:54–65.
5. Batirel HF, Metintas M, Caglar HB, et al. Trimodality treatment of malignant pleural mesothelioma. *J Thorac Oncol* 2008;3:499–504.
6. Flores RM, Zakowski M, Venkatraman E, et al. Prognostic factors in the treatment of malignant pleural mesothelioma at a large tertiary referral center. *J Thorac Oncol* 2007;2:957–965.
7. Rea F, Marulli G, Bortolotti L, et al. Induction chemotherapy, extrapleural pneumonectomy (EPP) and adjuvant hemi-thoracic radiation in malignant pleural mesothelioma (MPM): feasibility and results. *Lung Cancer* 2007;57:89–95.
8. Curran D, Sahmoud T, Therasse P, van Meerbeeck J, Postmus PE, Giaccone G. Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer Experience. *J Clin Oncol* 1998;16:145–152.
9. Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. *Chest* 1998;113:723–731.
10. Metintas M, Metintas S, Ucgun I, et al. Prognostic factors in diffuse malignant pleural mesothelioma: effects of pretreatment clinical and laboratory characteristics. *Res Med* 2001;95:829–835.
11. Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the malignant pleural mesothelioma (MS01): a multicentre randomized trial. *Lancet* 2008;371:1685–1694.
12. Metintas M, Ak G, Erginel S, et al. A retrospective analysis of malignant pleural mesothelioma patients treated either with chemotherapy or best supportive care between 1990 and 2005: a single institution experience. *Lung cancer* 2007;55:379–387.
13. Schipper PH, Nichols FC, Thomse KM, et al. Malignant pleural mesothelioma: surgical management in 285 patients. *Ann Thorac Surg* 2008;85:257–264.
14. Borasio P, Berruti A, Bille A, et al. Malignant pleural mesothelioma: clinicopathologic and survival characteristics in a consecutive series of 394 patients. *Eur J Cardio-thorac Surg* 2008;33:307–313.
15. Edwards JG, Abrams KR, Leverment JN, Spyt TJ, Waller DA, O'Byrne KJ. Prognostic factors for malignant mesothelioma in 142 patients: validation of CALGB and EORTC prognostic scoring systems. *Thorax* 2000;55:731–735.
16. Fennell DA, Parmar A, Shamash J, et al. Statistical validation of the EORTC prognostic model for malignant pleural mesothelioma based on three consecutive phase II trials. *J Clin Oncol* 2005;23:184–189.
17. Gelder TV, Damhuis RAM, Hoogsteden HC. Prognostic factors and survival in malignant pleural mesothelioma. *Eur Respir J* 1994;7:1035–1038.
18. Boutin C, Rey F, Gouvernet J, Viallat JR, Astoul P, Ledoray V. Thoracoscopy in pleural malignant mesothelioma: a prospective study of 188 consecutive patients. *Cancer* 1993;72:394–404.
19. De pangher Manzini V, Brollo A, Franceschi S, De Matthaeis M, Talamini R, Bianchi C. Prognostic factors of malignant mesothelioma of the pleura. *Cancer* 1993;72:410–417.
20. Christensen BC, Godleski JJ, Roelofs CR, et al. Asbestos burden predicts survival in pleural mesothelioma. *Environ Health Perspect* 2008;116:723–726.
21. Roe OD, Creaney J, Lundgren S, et al. Mesothelin-related predictive and prognostic factors in malignant mesothelioma: a nested case-control study. *Lung Cancer* 2008;61:235–243.
22. Cappia S, Righi L, Mirabelli D, et al. Prognostic role of osteopontin expression in malignant pleural mesothelioma. *Am J Clin Pathol* 2008; 130:58–64.
23. Schneider J, Hoffmann H, Dienemann H, Herth FJ, Meister M, Muley T. Diagnostic and prognostic value of soluble mesothelin-related proteins in patients with malignant pleural mesothelioma in comparison with benign asbestosis and lung cancer. *J Thorac Oncol* 2008; 3:1317–1324.
24. Grigoriu BD, Scherpereel A, Devos P, et al. Utility of osteopontin and serum mesothelin in malignant pleural mesothelioma diagnosis and prognosis assessment. *Clin Cancer Res* 2007;13:2928–2935.