Prognostic Factors in the Treatment of Malignant Pleural Mesothelioma at a Large Tertiary Referral Center

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Introduction: Most studies describing the natural history and prognostic factors for malignant pleural mesothelioma antedate accurate pathologic diagnosis, staging by computed tomography, and a universal staging system. We conducted a large single-institution analysis to identify prognostic factors and assess the association of resection with outcome in a contemporary patient population.

Methods: Patients with biopsy-proven malignant pleural mesothelioma at our institution were identified and clinical data were obtained from an institutional database. Survival and prognostic factors were analyzed by the Kaplan-Meier method, log-rank test, and Cox proportional hazards analysis. A p value <0.05 was considered statistically significant.

Results: From 1990 to 2005, 945 patients were identified: 755 men, 190 women; median age, 66 years (range, 26–93). Extrapleural pneumonectomy was performed in 208 (22%), pleurectomy/decortication in 176 (19%). Operative mortality was 4% (16/384). Multimodality therapy including surgery was associated with a median survival of 20.1 months. Significant predictors of overall survival included histology, gender, smoking, asbestos exposure, laterality, surgical resection by extrapleural pneumonectomy or pleurectomy/decortication, American Joint Committee on Cancer stage, and symptoms. A Cox model demonstrated a hazard ratio of 1.4 without surgical resection when controlling for histology, stage, gender, asbestos exposure, smoking history, symptoms, and laterality ($p = 0.003$).

Conclusions: In addition to tumor histology and pathologic stage, predictors of survival include gender, asbestos exposure, smoking, symptoms, laterality, and clinical stage. Surgical resection in a multimodality setting was associated with improved survival.

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The treatment of malignant pleural mesothelioma (MPM) has evolved in the past 20 years. Although controversy still exists with regard to standard care, significant advances have been made in diagnosis, imaging, staging, patient selection, chemotherapy, surgical technique, and radiotherapy. Before 1990, pathologic diagnosis was less precise. Therefore, older series included adenocarcinomas and sarcomas inadvertently diagnosed as epithelioid and sarcomatoid mesotheliomas, respectively, leading to inaccurate survival information. Table 1 shows some of the largest and most relevant studies in MPM.[1–10]

Older data, including the surgical series reported by Butchart et al.,[3] used patient chest radiographs as the only imaging modality because computed tomography (CT) was not yet universally used until the late 1990s. In addition, patient selection for surgery was less accurate because cardiopulmonary function testing was not done as thoroughly as it is today. Finally, a universally accepted staging system was not developed until 1995.[11] However, the AJCC/UICC (American Joint Committee on Cancer/Union Internationale Contre le Cancer) staging system now allows grouping of similar stage patients into similar survival groups and for comparisons among different studies.

Current treatment practices are still highly individualized and range from radical resection with extrapleural pneumonectomy (EPP) to observation alone. Most surgical series are retrospective, not contemporary, and lack a nonsurgically treated comparison group. Only recently have chemotherapeutic agents such as pemetrexed and cisplatin demonstrated significant activity in this difficult to manage disease.[10] As chemotherapy developed during this period, the mortality of surgical resection with EPP decreased from the once prohibitive mortality of 31% to less than 5%, therefore, driving a reevaluation of surgical management, especially in a multimodality setting.

Significant improvements in areas of diagnosis, imaging, and treatment led us to undertake this study to identify a homogeneous group of MPM patients diagnosed by modern methods and staged according to the AJCC staging system to

TABLE 1. Time Periods, Numbers of Patients, and Median Survival in Large Studies of MPM

Study	Years	No. of Pts.	MS (mo)
Ruffie et al.[1]	1964–1985	332	7
Alberts et al.[2]	1965–1985	262	10
Butchart et al.[3]	1959–1972	29	6
Sugarbaker et al.[4]	1980–1997	183	17
Rusch and Venkatraman[5]	1983–1998	174	18
Herndon et al.[6]	1984–1994	337	7
Aziz et al.[7]	1989–1998	302	9, 14, 35[a]
Lee et al.[8]	1995–2000	32	18
Maggi et al.[9]	1998–2000	32	9.5, NR[b]
Vogelzang et al.[10]	1999–2001	456	9, 12[c]
Current study (Flores et al.)	1990–2005	945	13

MPM, malignant pleural mesothelioma; MS, median survival; NR, not reported.

[a] Patients with palliative treatment alone had an average survival of 9 months. Surgery by extrapleural pneumonectomy or pleurectomy/decortication had an average survival of 13 and 14 months, respectively. Radical surgery followed by postoperative chemotherapy had survival of 35 months.

[b] Eight of 27 medium-term survivors died with a medium survival of 9.5 months. Twenty-one patients are alive with a median follow-up of 12.5 months.

[c] Nine months for patients receiving cisplatin and 12 months for those receiving cisplatin and pemetrexed.

identify accepted prognostic factors, identify new ones, and evaluate the association of surgical resection with survival.

MATERIALS AND METHODS

After internal review board approval for development and analysis of this database, patients with biopsy-proven MPM from 1990 to 2005 at Memorial Sloan-Kettering Cancer Center were identified from the Department of Pathology database. Pathologic diagnosis was based on histology, immunohistochemical analysis, and, when indicated, electron microscopy. Clinical data were obtained from an institutional database and verified against source documents. Variables recorded included symptoms, gender, histologic subtype, laterality, stage, smoking history, asbestos exposure history, surgical procedure, and multimodality treatment. Staging was performed using the sixth edition of the AJCC staging manual.[11] Clinical stage was based on the reported interpretation of CT findings. Pathologic stage was based on the pathologist's evaluation of the resected specimen and the surgeon's intraoperative findings. All patients were followed until death or December 31, 2005 if still alive. Dates of death were verified through the Social Security Death Index. There were six foreign patients for whom follow-up data were unavailable.

Treatment Selection and Methods

Treatment selection was based primarily on tumor stage and the patient's overall medical condition, but also influenced by sequential clinical trials performed at Memorial Sloan-Kettering Cancer Center. Operative intervention was recommended to patients with tumor localized to the hemithorax by CT and adequate cardiopulmonary function by cardiac stress testing and pulmonary function testing. Routine mediastinoscopy and magnetic resonance imaging were not performed. Positron emission tomography has only recently been used for clinical staging. EPP was defined as an en bloc resection of the pleura, lung, ipsilateral diaphragm, and pericardium. Pleurectomy/decortication (P/D), which removed all gross tumor without removing underlying lung was performed in patients who had minimal visceral pleural tumor or poor pulmonary function. The decision to perform an EPP was based on intraoperative findings of a confluent visceral tumor not separable from the underlying lung and a partially or totally fused pleural space. The decision to perform chemotherapy or radiation was based on enroll-

TABLE 2. Patient Characteristics of 945 Patients

Median age: 66 yr (range, 26–93)
Men: 755 (80%)
Women: 190 (20%)
Symptoms
- Chest pain: 167 (18%)
- Dyspnea: 323 (34%)
- Cough: 92 (10%)
- Asymptomatic: 94 (10%)
- Unknown: 269 (29%)

Histology
- Epithelioid: 319 (34%)
- Mixed: 99 (10%)
- Sarcomatoid: 44 (5%)
- Unclassified: 483 (51%)

AJCC Stage	Pathologic	%	Clinical	%
I	22	2	99	11
II	85	9	173	18
III	227	24	141	15
IV	153	16	54	7
Unknown	458	48	478	49

Treatment	%
208 EPP	22
176 P/D	19
174 ET	18
387 Nonoperative	41

Smoking History	No. (%)
Current or former smoker	486 (52)
Never smoker	142 (15)
Unknown	317 (33)
Asbestos history	
Asbestos exposure	399 (43)
No asbestos exposure	190 (20)
Unknown	356 (37)
Laterality	
Right	520 (55)
Left	349 (37)
Bilateral	76 (8)

AJCC, American Joint Committee on Cancer; EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortication; ET, exploratory thoracotomy.

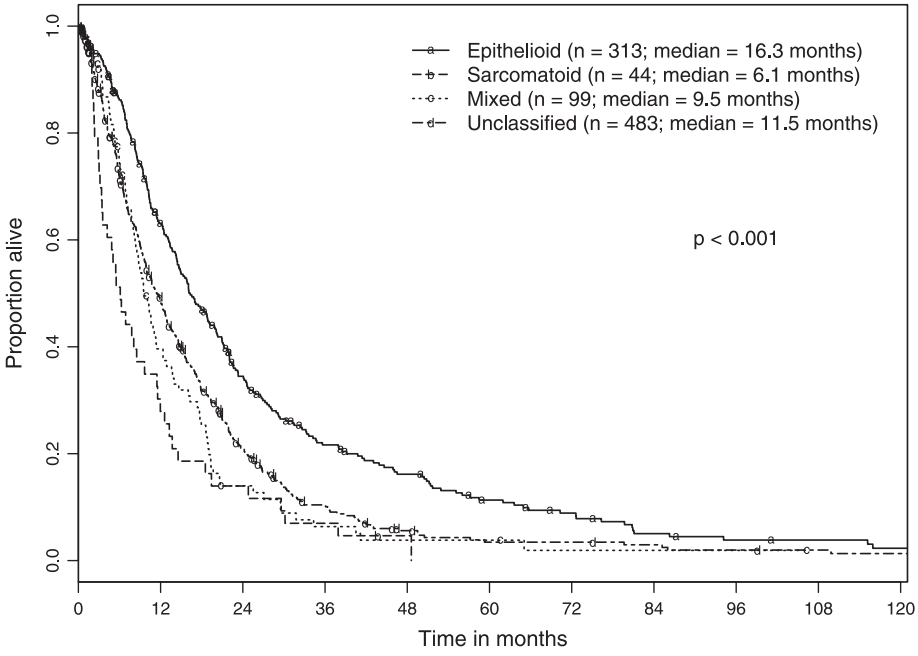

FIGURE 1. Overall survival by histology ($p < 0.001$).

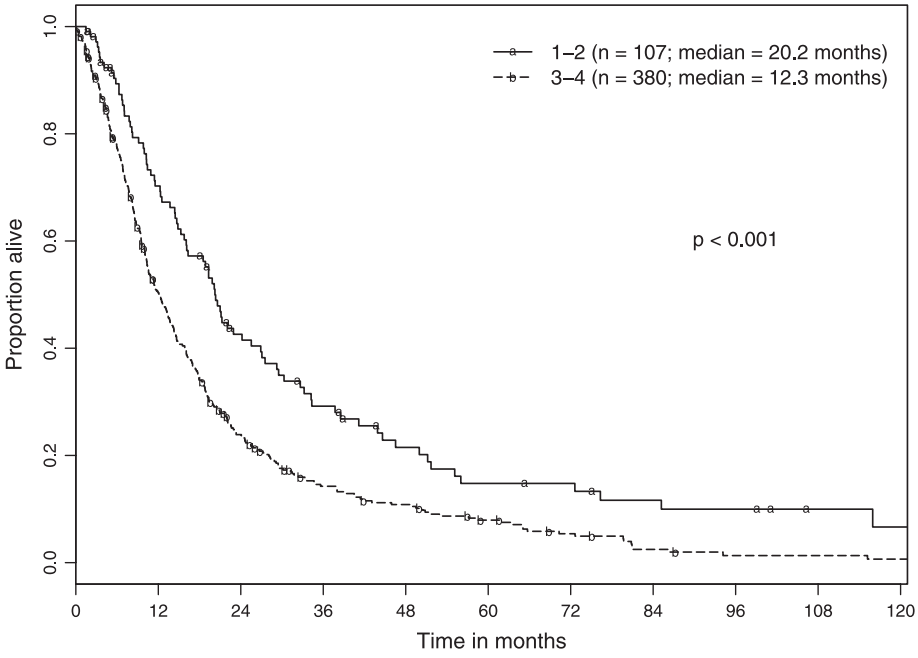

FIGURE 2. Survival by pathologic stages I–II versus 3–4 ($p < 0.001$).

ment in a clinical trial. When the patient could not participate in a clinical trial, treatment was usually administered according to protocol guidelines. The total radiation dose and method of administration were dependent on whether an EPP or a P/D had been performed.[12,13]

Statistical Methods

Operative mortality included all patients who died within 30 days of surgery or during the same hospitalization. Survival was calculated from the date of the initial diagnostic biopsy until date of death or date of last follow-up. Survival and prognostic factors were analyzed by the Kaplan-Meier method, and the log-rank test was used to assess statistical significance. A Cox proportional hazard analysis was used to assess the joint influences of predictors on survival. Missing variables were handled as separate groups. The initial model was performed including significant predictors of survival from Table 2. Insignificant variables were then dropped using a stepwise procedure, thus yielding the final model. A p value of <0.05 was considered statistically significant. The statistical package used was the R Development Core Team (2005, Vienna, Austria).

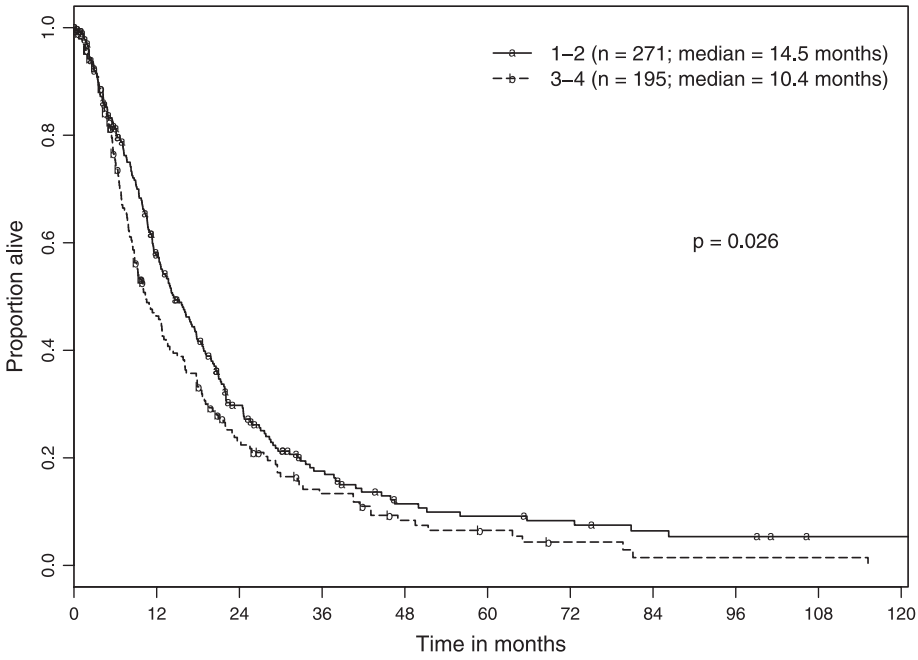

FIGURE 3. Survival by clinical stages 1–2 versus 3–4 ($p < 0.01$).

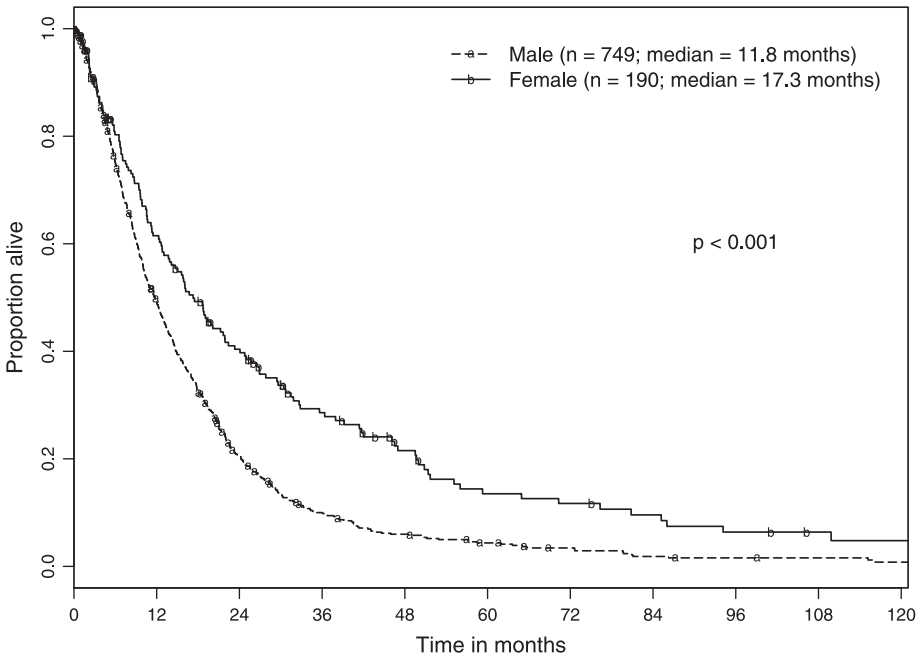

FIGURE 4. SURVIVAL BY GENDER ($P < 0.001$).

RESULTS

Demographic Information

A total of 945 patients were identified and clinical features are outlined in Table 2.

Multimodality Therapy with Surgical Resection

Of the 384 patients who had surgical resection, operative mortality was 11 (5%) for EPP and five (3%) for P/D. Overall operative mortality was 4% (16/384). Exploratory thoracotomy (ET) without resection had a zero operative mortality. For patients who had a macroscopic complete resection by EPP or P/D, the type of adjuvant or treatment varied according to several clinical trials performed over this period: surgical resection plus external beam radiation therapy, induction gemcitabine/cisplatin followed by EPP and external beam radiation therapy, induction pemetrexed/cisplatin followed by EPP and external beam radiation therapy, and several small trials of oral suberoylanilide hydroxamic acid and 10-propargyl-10-deazaaminopterin.

Of the 384 patients who had either an EPP or P/D, 207 received adjuvant therapy, including 130 who had radiation without chemotherapy, 35 who had chemotherapy without radiation, and 42 who received both chemotherapy and radiation.

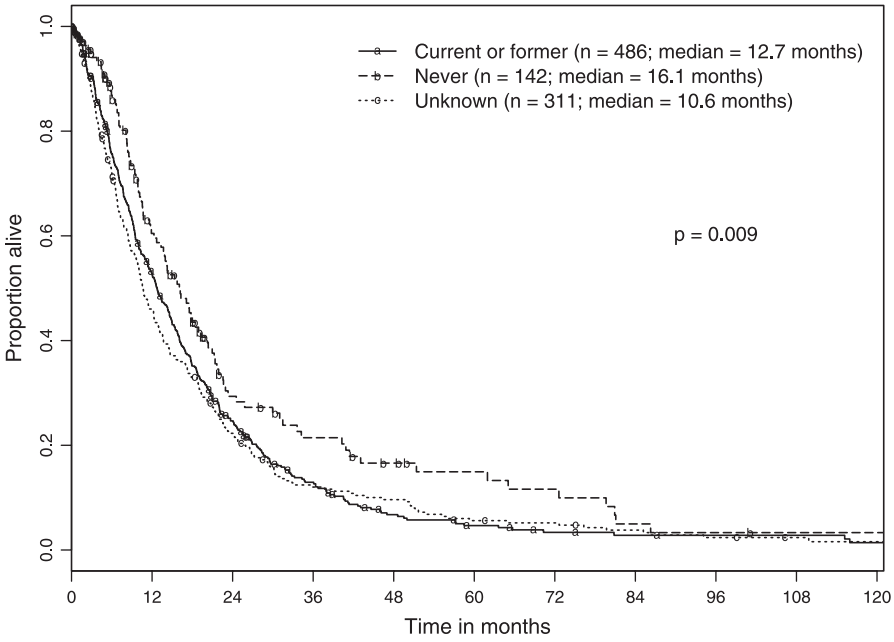

FIGURE 5. Survival by smoking history ($p = 0.002$).

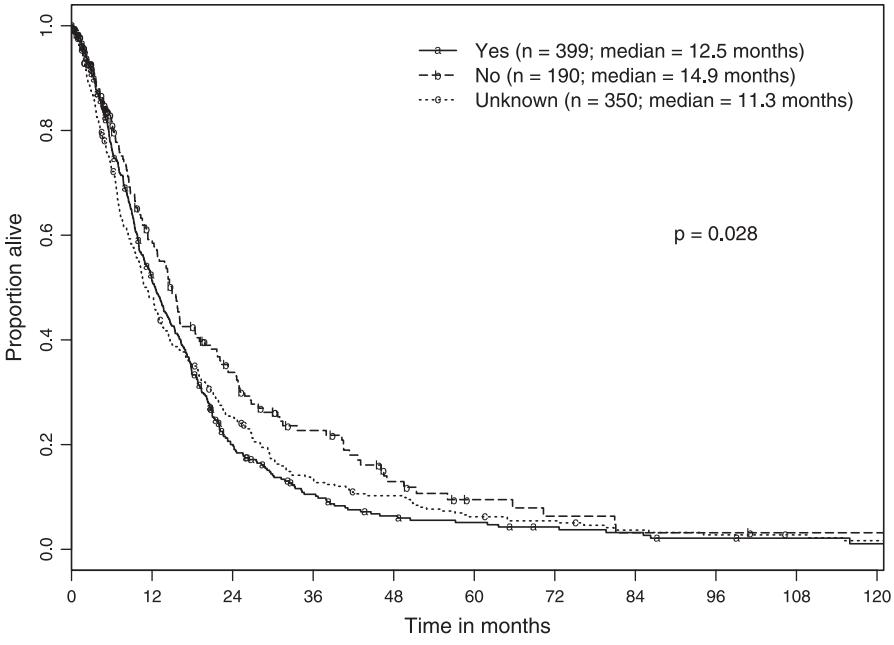

FIGURE 6. Survival by history of asbestos exposure ($p < 0.001$).

Therapy without Surgical Resection

A total of 561 patients did not have resection including 174 who underwent thoracotomy but had incomplete tumor resected at exploration. Of these, 61 received chemotherapy, 12 received palliative external beam radiotherapy, and 101 were treated with best supportive care.

In the group of 387 patients who did not undergo surgical exploration, 76 had evidence of stage IV disease, seven had sarcomatoid tumors, and 304 refused surgery or were deemed medically inoperable. Of these, 74 received chemotherapy, 296 had best supportive care, and 17 had no available treatment data.

Statistical Analysis

Kaplan-Meier survival analysis

Survival data were available for 939 patients and the median overall survival was 12.5 months. Univariate analysis showed that epithelioid histology was associated with the best survival and sarcomatoid with the worst survival (Figure 1). Tumors of unclassified histology had a survival midway between the epithelioid and nonepithelioid histologies. There were 483 patients with unclassified histology due to missing pathology slides that were unavailable for re-review because

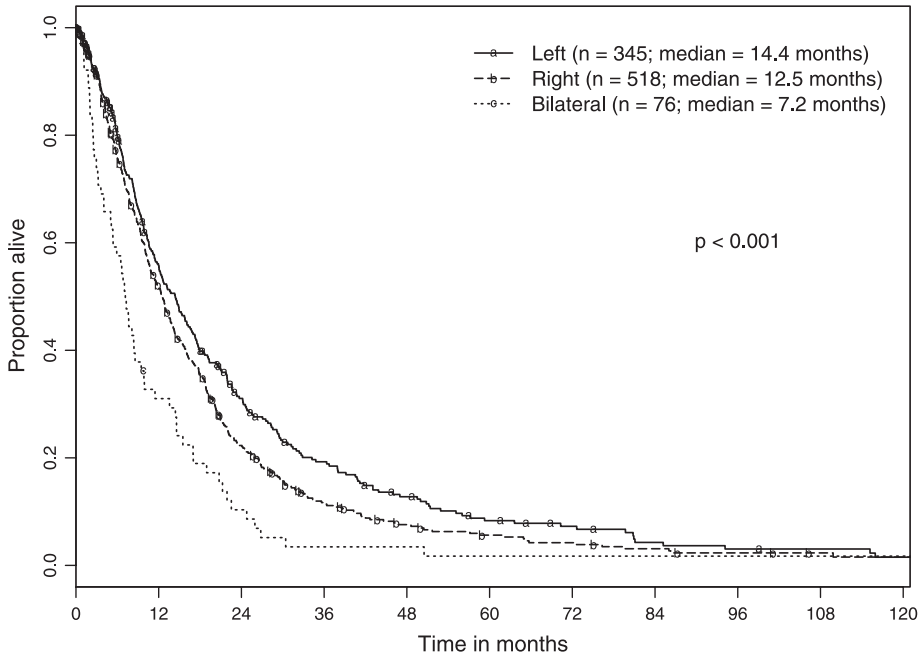

FIGURE 7. Survival by laterality ($p = 0.001$).

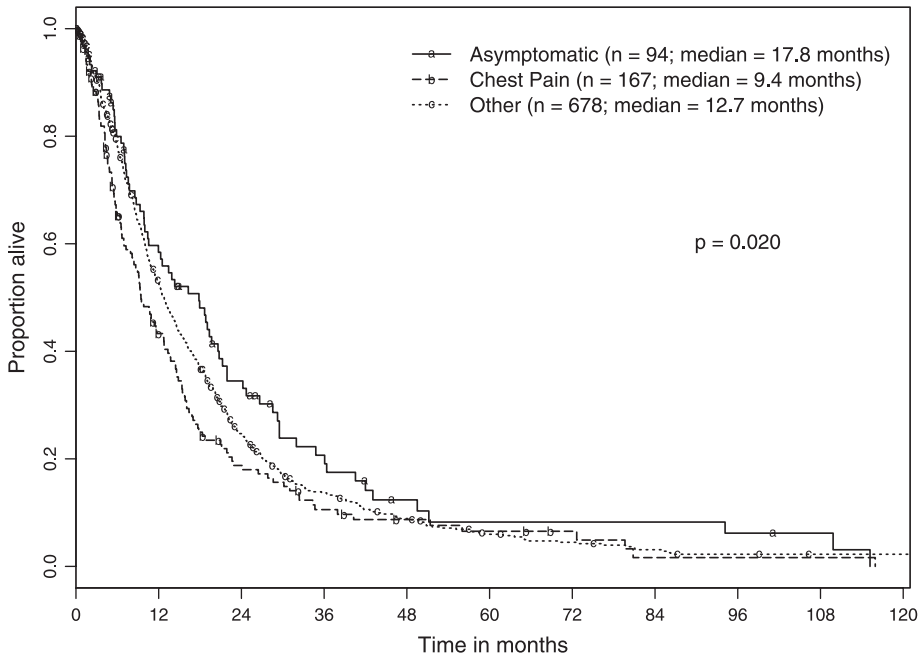

FIGURE 8. Survival by symptom presentation ($p = 0.02$).

they were from another institution or lost in storage. However, all patients had slides reviewed at least once at Memorial Sloan-Kettering Cancer Center.

Overall survival for patients with early (I–II) versus late (III–IV) stage tumors was significantly different (Figure 2). Although radiographic imaging is known to have limitations in the staging MPM, patients clinically staged by CT as early (stages I–II) versus late (stages III–IV) were found to have significantly different survivals as well (Figure 3). There were 478 patients with unknown clinical stage. All patients with available CT scans were staged clinically. We did not stage patients by chest radiograph alone because the presence of a pleural effusion could vary from a stage I to a stage IV and therefore lead to a staging bias.

Female gender, lack of a smoking history, lack of a history of asbestos exposure, and left-sided tumors were all associated with a better prognosis (Figures 4–7). The significance of tumor laterality was not a direct result of operative mortality because the operative mortality of right- and left-sided tumors was equal. Patients who presented with chest pain had a significantly worse median survival (9.4 months) than patients without chest pain (15 months, $p = 0.02$) (Figure 8).

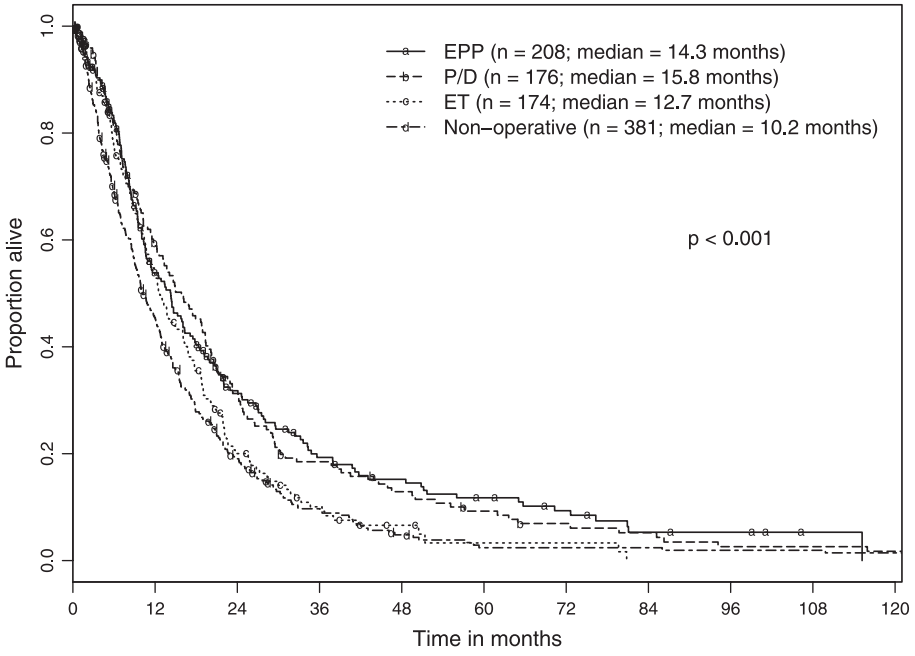

FIGURE 9. Survival by surgical resection, extrapleural pneumonectomy (EPP), and pleurectomy/decortication (P/D) versus ET (exploratory thoracotomy) and nonoperative ($p = 0.001$).

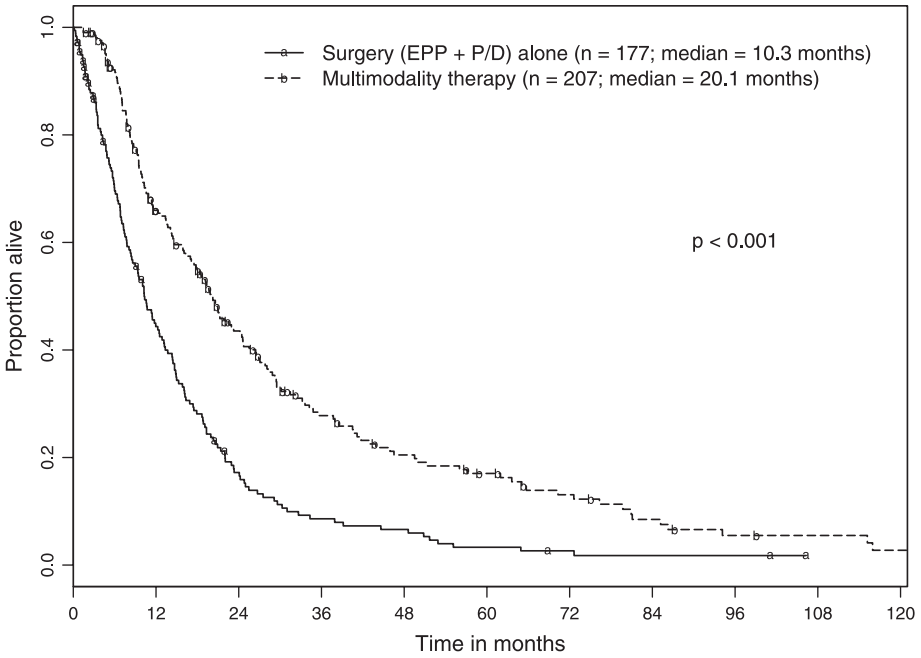

FIGURE 10. Survival by multimodality treatment versus surgical resection alone ($p = 0.001$). EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortication.

Patients who underwent surgical resection had significantly better survival than patients without surgical resection (Figure 9). However, the type of surgical resection (EPP versus P/D) did not significantly influence survival. The greatest survival difference was demonstrated in patients who underwent multimodality therapy with surgery compared with patients who underwent surgery alone (median survival, 20 versus 10 months) (Figure 10).

Cox Proportional Hazards Model

To minimize selection bias, we controlled for tumor stage in both the surgical and nonsurgical groups. Other variables included smoking, asbestos exposure, gender, pain, histology, and laterality. After all variables were dichotomized, the association of surgical resection with survival remained statistically significant with a hazard ratio of 0.75 (CI: 62, 91) and a p value of 0.003. (Table 3).

DISCUSSION

Recent advances in the multimodality management of MPM include more accurate methods of pathologic diagnosis, improved physiologic testing leading to better patient selection for surgery, lower operative mortality, improved

TABLE 3. Cox Proportional Hazards Model of 939 Patients

Variable	HR	CI	*p*
Surgical resection	0.75	0.62–0.91	0.003
Nonsmokers	0.77	0.61–0.97	0.023
No asbestos history	0.95	0.77–1.19	0.600
Female	0.63	0.51–0.77	<0.001
No pain	0.77	0.69–0.91	0.008
Epithelioid histology	0.59	0.46–0.71	<0.001
Left side	0.84	0.72–0.98	0.020
Stage (I + II)	0.84	0.68–1.05	0.100

local control with combined EPP and hemithoracic radiation, and better systemic therapies.[10,12–14] However, controversy still exists regarding stratification variables for clinical trials and the influence of surgical resection on survival. Unlike studies of more common malignancies that include thousands of patients, most large MPM studies contain only a few hundred, making it harder to identify reliable prognostic factors.

The largest and most comprehensive report by Ruffie et al.[1] was a multi-institutional, retrospective study of 332 MPM patients over a 20-year period. It provided a benchmark against which many modern studies are compared, although it lacks the technologic advances available today. Tumor histology and chest pain were identified as significant prognostic variables. Resection was performed in only 86 patients and was not associated with improved survival. Operative mortality was 13%.

Since then, operative mortality at high volume centers has decreased to 5%.[4,5] However, recent surgical series do not provide a perspective of how many patients are candidates for resection or of the outcome of patients managed nonsurgically. The methodology for this study was identical to that used in the Ruffie et al. study with the advantages of a much larger number of patients treated both surgically and nonsurgically and of improved contemporary approaches to diagnosis, staging, and treatment selection.

This study confirmed that most patients are male, have epithelioid tumors, and present with locally advanced disease. However, contrary to the perception that most patients present with clinically unresectable disease, more than half of the patients with MPM at our institution were candidates for resection.

Histology, pathologic stage, and symptoms are confirmed as significant predictors of survival and should continue to be used as stratification variables in clinical trials. Gender, smoking history, asbestos exposure, and laterality are significant predictors as well in this large series. These variables require validation in prospective studies but will help the design of prospective clinical trials. Based on the positive prognostic value of female gender in this study, future prospective studies should attempt to stratify patients by gender because a preponderance of females in any one study could result in falsely improved survival rates.

CT is known to be somewhat inaccurate as a method of clinical staging. However, our results show that CT correctly stratifies patients by early and late clinical stage disease and is, therefore, useful for patient stratification in future clinical trials. In conjunction with positron emission tomography, CT enables appropriate selection of initial treatment in MPM.[15,16]

Any retrospective study has limitations. As with the Ruffie et al. study, missing variables were handled in a manner to minimize bias. Although confounding variables were included in the Cox model, unknown confounders may be present that influence outcome as well. The criticism of recommending resection based solely on retrospective studies is the inherent presence of selection bias of the earlier staged patients and the lead-time bias that may account for the apparent improved survival. However, to date, no retrospective study comparing surgically and nonsurgically treated patients has ever demonstrated a statistically significant difference in survival between the two groups. Although no study can prove the benefit of surgery or of multimodality therapy outside the context of a prospective randomized trial, our data strongly suggest benefit from multimodality therapy and underscore the importance of a multidisciplinary team evaluation before the initiation of treatment. Finally, this study provides a modern benchmark against which future studies can be compared, using recent advances in diagnosis, staging, imaging, and treatment. The prognostic variables defined here will aid in the design of prospective clinical trials in MPM.

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