Annals of Surgical Oncology, 4(3):215–222
Published by Lippincott-Raven Publishers

Surgically Debulked Malignant Pleural Mesothelioma: Results and Prognostic Factors

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Background: We analyzed morbidity and mortality, sites of recurrence, and possible prognostic factors in 95 (78 male, 17 female) patients with MPM on phase I–III trials since 1990. A debulking resection to a requisite, residual tumor thickness of ≤5 mm was required for inclusion.

Methods: Preoperative tumor volumes were determined by three-dimensional reconstruction of chest computerized tomograms. Pleurectomy (n = 39) or extrapleural pneumonectomy (EPP; n = 39) was performed. Seventeen patients could not be debulked. Preoperative EPP platelet counts (404,000) and mean tumor volume (491 cm^3) were greater than that seen for pleurectomy (344,000, 114 cm^3).

Results: Median survival for all patients was 11.2 months, with that for pleurectomy 14.5 months, that for EPP 9.4 months, and that for unresectable patients 5.0 months. Arrhythmia (n = 14; 15%) was the most common complication, and there were two deaths related to surgery (2.0%). Tumor volume of >100 ml, biphasic histology, male sex, and elevated platelet count were associated with decreased survival ($p < 0.05$). Both EPP and pleurectomy had equivalent recurrence rates (27 of 39 [69%] and 31 of 39 [79%], respectively); however, 17 of 27 EPP recurrences as opposed to 28 of 31 pleurectomy recurrences were locoregional ($p_2 = 0.013$).

Conclusions: Debulking resections for MPM can be performed with low operative mortality. Size and platelet count are important preoperative prognostic parameters for MPM. Patients with poor prognostic indicators should probably enter nonsurgical, innovative trials where toxicity or response to therapy can be evaluated.

Key Words: Mesothelioma—Surgery—Prognostic factors—Debulking.

The exact role of surgery in the management of malignant pleural mesothelioma (MPM) remains undefined due to a number of factors. The high associated mortality and morbidity rates in the 1970s and 1980s and the inability to prevent subsequent local thoracic recurrences resulted in a generalized feeling of despair with regard to any benefit of surgical treatment except in the rare cases of stage I tumors. The lack of a uniform staging system of merit made the interpretation of different surgical series impossible with regard to long-term survival. It is only recently that a complete revision of the staging system that subcategorizes the disease with regard to anatomic specifics as well as the T, N, M classification has been accomplished (1). Therefore, renewed interest has developed in examining the role of surgery in this disease and in determining the preoperative prognostic factors that may portend a poor outcome. This article reports our experience since 1990 with the operative management of malignant pleural mesothelioma as part of a treatment package under phase

Received March 22, 1996; accepted July 29, 1996.

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Presented at the 49th Annual Cancer Symposium of The Society of Surgical Oncology, Atlanta, Georgia, March 21–24, 1996.

I and II protocols at our institution. The goals were to attempt to (a) document current morbidity and mortality rates for pleurectomy/decortication and extrapleural pneumonectomy as part of a maximal cytoreductive effort, (b) report recurrence patterns and survival after these operations, and (c) define preoperative/postoperative parameters that may define poor risk patients for surgical cytoreduction of disease.

METHODS AND PATIENT POPULATION

Patients with malignant pleural mesotheliomas studied in this report were enrolled in intramural NCI/NIH phase I or II protocols between February 1990 and April 1995. These protocols involved surgery with intraoperative photodynamic therapy or surgery and postoperative immunochemotherapy. The majority of patients received varying doses of phototherapy under the phase I trial; therefore, no conclusions can be made regarding phototherapy efficacy. Patients were eligible if they had histologically documented malignant mesothelioma that was confined to a hemithorax. All experimental protocols were approved by the Institutional Review Board of the National Cancer Institute. All patients were required to understand and sign informed consent forms before participation.

All patients had preoperative complete blood counts, serum chemistries, 24-h creatinine clearance, hepatic panel and urinalysis and computerized tomograms of the chest that showed varying degrees of chest wall, pleural, and parenchymal involvement by tumor. In addition, preoperative head and abdominal computerized tomograms, as well as bone scans, were performed, all of which showed no evidence of disease outside the confines of the hemithorax. Routine pulmonary function testing was performed to verify that the patients could have thoracic exploration and resection; in selected instances, quantitative ventilation–perfusion scanning was performed to verify tolerance to pneumonectomy.

Operations performed

The goal of the operation was a subtotal extirpation of all gross malignant disease (debulking). The maximum remaining thickness of malignancy at any intrathoracic site was to be ≤ 0.5 cm. There could be multiple discontinuous sites of disease with these satisfactory dimensions (diffuse studding) or one large area (plaquelike). This could be accomplished via either pleurectomy or extrapleural pneumonectomy (EPP). Patients who did not fulfill criteria for maximal debulking were classified as unresectable.

Patients were surgically staged using the new International Mesothelioma Interest Group staging system (1) using the surgeon's (H.I.P.) personal observations and operative and postoperative pathology reports.

Tumor volume measurement

Volume of tumor preoperatively was objectively quantitated using the Voxel Scope II three-dimensional (3-D) imaging work station (Picar International, Highland Heights, OH) (2) in 60 of the 95 patients, of whom 57 had complete tumor status assessment by surgery, and 51 had lymph nodal samplings. For each patient the tapes of the computerized tomographic examinations were loaded into the memory of the system, and serial images of each study were depicted on the screen. One individual outlined the borders of the solid tumor using the mouse, with discrimination of solid tumor from fluid based on differences in tissue density. The system then calculated the 3-D volume in cubic centimeters of total solid tumor burden or of any desired subset or fraction.

Follow-up studies

Follow-up computerized tomograms of the chest and upper abdomen were performed every 3 months along with physical examination, complete blood counts, and serum chemistries. Tumor volumes were recorded prospectively, and the presence of recurrent disease was documented by biopsy if possible. Patients with recurrent disease were offered treatment under other phase I protocols at the NCI or discharged to their referring physician.

Statistical methods

Survival time and time to progression were calculated from date of diagnosis until death, progression, or last follow-up as appropriate. The probability of survival or progression was calculated using the Kaplan-Meier method (3), and the significance of the difference between pairs of Kaplan-Meier curves was calculated using the Mantel-Haenszel procedure (4). The Cox proportional hazards model was used to identify which factors were jointly significant in the association with survival (5). The factors analyzed included asbestos exposure, performance status, age, interval from symptoms to diagnosis, interval from diagnosis to operation, preoperative pain, sex, histo-

TABLE 1. *Preoperative MPM patient characteristics*

	Extrapleural pneumonectomy	Pleurectomy	Unresectable
Mean years of age (range)	57 (30–72)	59 (34–77)	60 (41–70)
Sex	6 F/33 M	8 F/31 M	3 F/14 M
Race	38 W/1 B	38 W/1 B	17 W
Asbestos exposure (%)	28/39 (72)	27/39 (69)	13/17 (76)
Mean months from diagnosis to treatment	3.2	3.3	4.3
ECOG performance status	1: 39/39 (100%)	1: 38/39 (97%) 2: 1/39 (3%)	1: 14/17 (82%) 2: 1/17 (6%) 3: 2/17 (12%)
Symptoms (%)			
Dyspnea	29/39 (74%)	23/39 (59%)	13/17 (76%)
Pain	15/39 (38%)	20/39 (51%)	11/17 (65%)

logic type of MPM, pretreatment platelet counts, type of operative procedure, and size (in cm^3) pretreatment. Postoperative adjuvant therapy, given to a minority of patients, was not evaluated since its efficacy is being determined in an ongoing randomized Phase III trial. The resulting model parameters (b_i) were converted to relative risks by computing exp(b_i), where exp(a) = 2.7183[a] (6). The 95% confidence interval for the relative risk was computed as [exp (b_{iL}), exp (b_{iH})], where $b_{iL} = b_i - 1.96$ [estimated SE (b_i) and $b_{iH} = b_i + 1.96$ [estimated SE (b_i)]. The relative risk indicates the risk associated with dying or progressing while being in a greater risk category compared with that of being in a lower risk category. All p values are two sided. Jonckheere's test for trend (7) was used to determine the trends in preoperative tumor volumes among patients who underwent EPP or pleurectomy according to their surgically assessed T status (n = 57) using the new International Mesothelioma Interest Group staging system (1).

RESULTS

Patient and tumor demographics

During the 62-month interval, 95 patients underwent thoracotomy. The study population was composed of 78 men and 17 women. Patient characteristics for all three groups are provided in Table 1, and there were no significant differences between patients who underwent EPP or pleurectomy, or who were unresectable. The relevant preoperative laboratory and functional parameters, as well as tumor demographics, are provided in Table 2. There was a trend toward higher platelet counts in the EPP and unresectable groups compared with the pleurectomy group ($p_2 = 0.087$, EPP vs. pleurectomy, and $p_2 =$

TABLE 2. *Laboratory parameters and tumor characteristics*

	Extrapleural pneumonectomy	Pleurectomy	Unresectable
Platelet count (×1000)	404	344	434
Pulmonary function tests			
FEV_1	2.27 L/min (68%)	2.46 L/min (80%)	1.91 L/min (64%)[a]
FVC	2.92 L (65%)	3.28 L (76%)	2.55 L (62%)[a]
DLCO	69% of predicted	76% of predicted	71% of predicted
Histology			
Epithelial	27	33	13
Sarcomatoid	2	4	1
Biphasic	10	2	3
Tumor volume (ml)	491 (51–856)[a]	114 (4–397)	304 (101–568)

[a] $p2 < 0.005$ vs. pleurectomy.

TABLE 3. *Operative and postoperative parameters in patients having surgery for MPM*

	Extrapleural pneumonectomy	Pleurectomy	Unresectable
Operative time (min) (range)	325 (80–630)	272 (105–530)	126 (50–480)
Estimated blood loss (ml) (range)	2,314 (600–4,800)	1,315 (300–2,700)	2,082 (50–8,000)
Days in ICU (range)	5 (2–23)	4 (2–9)	8 (1–88)
Postoperative hospitalization duration (days) (range)	12 (6–39)	9 (5–14)	13 (0–88)

0.0545, unresectable vs. pleurectomy), but the data did not reach statistical significance. Patients having an EPP had significantly greater tumor burdens than did the pleurectomy group. Only three patients in the unresectable group had tumor volume measurements taken before operation. Epithelial mesothelioma was the most common histologic type in the series (77%). Fifteen patients (16%) had biphasic histology, whereas seven (7%) were sarcomatoid.

Specifics of the operative procedure and postoperative course are seen in Table 3. There was a trend ($p_2 = 0.06$) toward longer operative times for EPP compared with pleurectomy. These operative times in both groups also included the time for delivery of intraoperative phototherapy in selected patients. Blood loss was significantly greater for the EPP and unresectable groups compared with the pleurectomy group ($p_2 < 0.001$). Intensive care unit and postoperative durations were similar between the three groups.

Morbidity

Sixty-one of the 95 patients were complication free (64%). The most common complication postoperatively was supraventricular tachyarrythmias (EPP, 14 of 39; pleurectomy, two of 39; 17% overall). Bronchopleural fistulae occurred in seven of 39 EPP patients, all on the right side. Only one patient, who had had mediastinal irradiation for Hodgkin's disease, developed a fistula during the immediate postoperative period. The other fistulae, diagnosed by changes in the air fluid level with or without symptoms, were diagnosed on days 40, 41, 69, 70, 400, and 420 postoperatively. Management included open thoracostomy alone (n = 2), fibrin glue instillation via bronchoscopy (n = 1), or serratus flap transposition with (n = 3) or without (n = 1) open thoracostomy. All patients became asymptomatic after fistula management. The duration of chest tubes in the pleurectomy group was 3.6 days (range 2–8). Other complications included postoperative pancreatitis (n = 4), phototherapy-related esophageal–pleural fistula (n = 2) (8), postoperative hemorrhage (n = 2), diaphragmatic herniation necessitating repair (n = 1), temporary left radial nerve palsy (n = 1), and wound dehiscence (n = 1).

Mortality

There were two surgically related deaths (2%). One occurred intraoperatively due to uncontrollable hemorrhage from the superior vena cava, and the other occurred in an unresectable patient who had postoperative bleeding and sustained an intraoperative myocardial infarction. He was ventilator dependent when he died from progressive malignant ascites 87 days after exploratory surgery. Four patients in the series did not die from mesothelioma (three from suicide, one from food aspiration).

Survival and recurrence of tumor

Median potential follow-up at the time of analysis was 33.7 months for the entire group of 95 patients. The overall survival for the entire group is seen in Fig. 1. Median survival for all patients was 11.2 months.

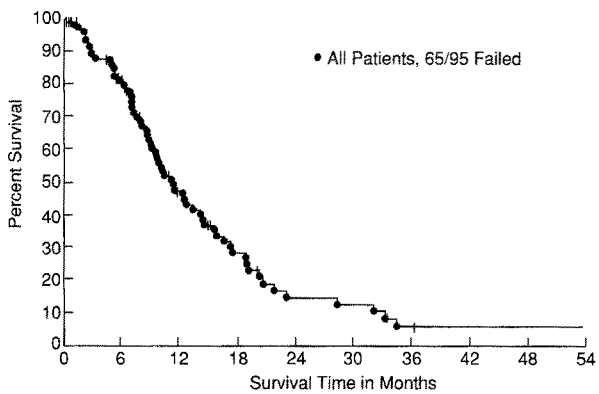

FIG. 1. Overall survival (all causes of death) for the entire group of 95 patients with MPM who were explored for cytoreductive surgery to 5 mm.

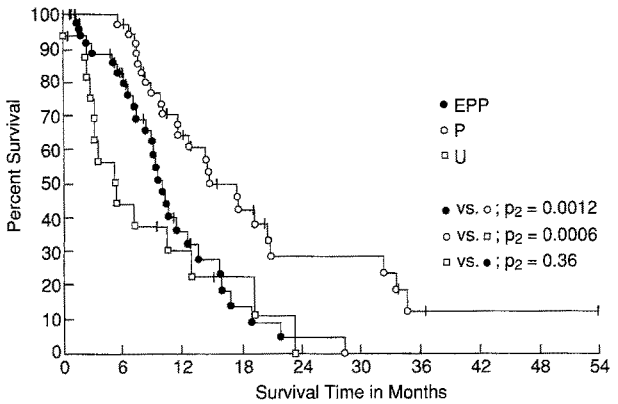

FIG. 2. Overall survival (all causes of death) for the EPP, P, and U groups. Patients having pleurectomy had significantly longer survivals.

Median survival for patients undergoing pleurectomy was 14.5 months, for those undergoing EPP 9.4 months, and for unresectable patients 5.0 months (Fig. 2). Patients undergoing pleurectomy had significantly enhanced survival over those undergoing EPP (p_2 = 0.012) and unresectable patients (p_2 = 0.006). No difference was seen between survival times of unresectable patients and those undergoing EPP. The median progression-free survival for debulkable patients was 7.2 months, and there was no difference in the progression-free survival between patients having extrapleural pneumonectomy or pleurectomy (EPP 7.0 months; pleurectomy 7.4 months). We classified the first sites of recurrence or progressive disease as Rusch et al. has described (9). Briefly, diaphragm, chest wall, mediastinum, pleura, and ipsilateral lung were classified as locally recurrent disease, whereas nodes, contralateral chest, abdomen, and other were considered as distant disease. Despite equal times to recurrence, there was a distinct difference in the pattern of recurrences, with a significantly greater number of patients failing systemically in the EPP group first compared with pleurectomy (p_2 = 0.013 by χ^2 analysis) (Table 4).

TABLE 4. *Sites of first recurrence or progression for patients having cytoreduction of MPM to 5 mm*

	Extrapleural pneumonectomy (n = 39)	Pleurectomy (n = 39)
Local only	15 (38%)	27 (69%)
Distant only	10 (25%)	3 (8%)
Local plus distant	2 (5%)	1 (3%)

TABLE 5. *Correlation of preoperative size with postoperative surgical T status*

Group	Tumor volume (ml) Mean	No.	Median	Jonckheere p value
T_1	3.9	2	3.9	
T_2	124.8	23	97	0.00011
T_3	385.2	32	274	

As depicted in Table 5, there was a significant trend for preoperative volume status to reflect the T status.

Prognostic factors

Of the factors analyzed to determined whether they had any impact on overall or progression-free survival, the following were not found to correlate with survival: age, performance status, asbestos exposure, preoperative pain, of length of interval from symptoms to diagnosis or from diagnosis to thoracotomy. Although 33 of 65 patients who were sampled had either N1 or N2 intranodal MPM, survival did not correlate with nodal involvement (p_2 = 0.58). In univariate analyses, tumor volume (Figs. 3 and 4) and platelet counts (Figs. 5 and 6) were predictive of overall survival in all three groups of patients and progression-free survival in the EPP and pleurectomy groups. High platelet counts (>462,000/mm^3) and tumor volume of >100 cm^3 were associated with decreased survival. For the EPP and pleurectomy patients, a biphasic histology was associated with a decreased overall survival time compared with the patients having epithelial or sarcomatoid mesotheliomas (p_2 = 0.028). In a multivariate analysis, tumor volume of >100 cm^3, biphasic histology, male sex,

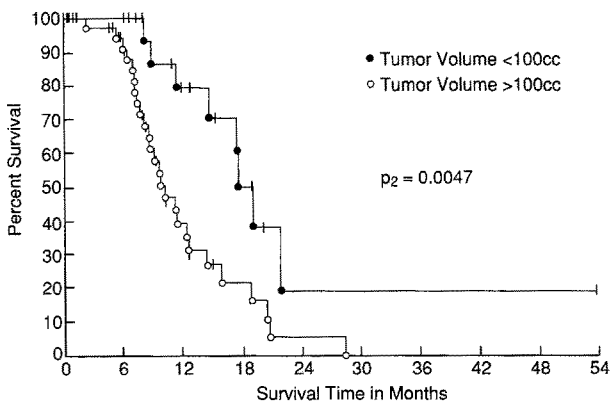

FIG. 3. Survival of patients with MPM debulked to 5 mm stratified by preoperative tumor volume. Patients with small tumor volumes had longer survival.

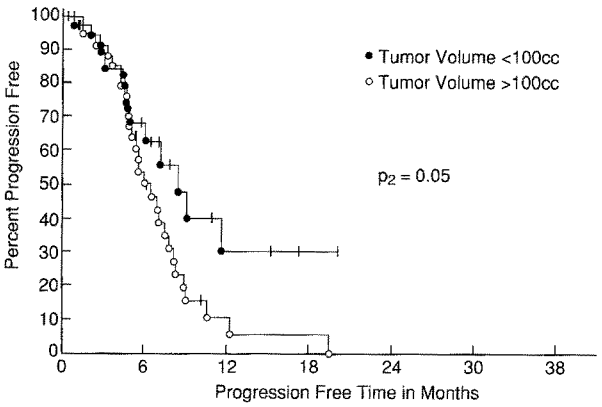

FIG. 4. Time to recurrence or progression in patients with MPM debulked to 5 mm stratified by preoperative tumor volume. Patients with larger tumor volumes recurred earlier than did those with smaller tumor volumes.

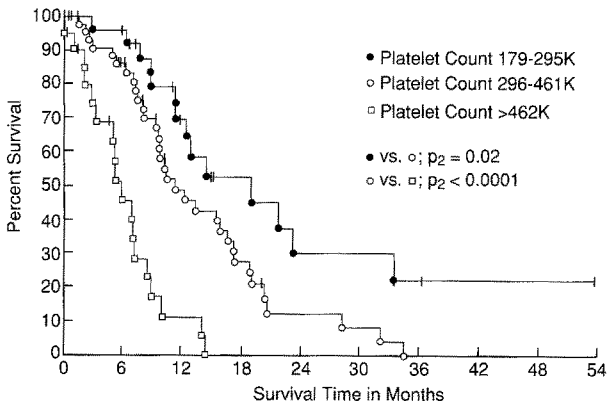

FIG. 6. Time to recurrence or progression in patients with MPM debulked to 5 mm stratified by preoperative platelet counts. Higher platelet counts were associated with shorter times to recurrence or progression.

and elevated platelet count were associated with decreased survival ($p < 0.05$) by Cox model.

DISCUSSION

The series of operations for mesothelioma described in this report differs from other series in a number of ways. The purpose of the operation in all instances was a debulking or cytoreductive approach, in which the tumor was removed to a maximum thickness of 5 mm. In the majority of cases, this included a sparing of a portion or all of the diaphragm by dissection within its fibers. This is not the standard approach in the literature, certainly, but if one believes that surgery can never render a patient with mesothelioma completely disease free, then any surgical procedure for the disease is a maximal cytoreduction, except in those rare instances of T1aNoMo disease as described in the new staging system as stage I (1). Patient selection also was different in this series compared with others. Because all of these patients were registered under phase I or II protocols, where adjuvant therapy was delivered either intraoperatively or postoperatively, we did not limit patient selection for cytoreduction to only those patients thought to have clinical stage I MPM. In fact, if one were to retrospectively classify the 66 patients who had nodal sampling in this series according to the recently published New International Staging System for MPM, three patients (all pleurectomy) would be stage I, seven (two pleurectomy and five EPP) would be stage II, 55 (19 pleurectomy and 36 EPP) would be stage III, and one would be stage IV.

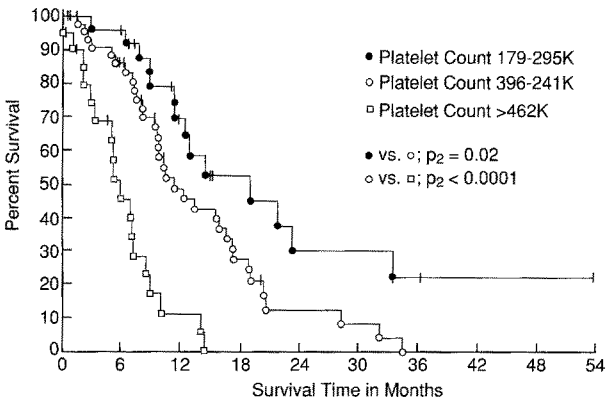

FIG. 5. Survival of patients with MPM debulked to 5 mm stratified by preoperative platelet counts. Higher platelet counts were associated with shorter survival from resection.

The series is similar to others with respect to the patient demographics. Most had a history of exposure to asbestos, the majority of the patients were in their fifth decade of life, and most were men. Over the past 15 years, the morbidity and mortality rates of these operations have decreased when performed routinely by selected surgical groups, and the complication rates in this series are compatible with those published in the literature (10). The operative mortality rate for the entire series (2%) and for EPP specifically (5%) compares favorably with that of Rusch et al. (3.8% and 6%, respectively) (9,11) and with Sugarbaker's EPP operative mortality rate of 4.8% (12).

Obvious differences are appreciated between the EPP and pleurectomy groups with regard to tumor volume measured preoperatively and preoperative platelet count. The decision as to whether a pleuropneumonectomy or a pleurectomy was performed

was not made based on these parameters or protocol restrictions, but rather on the intraoperative findings. If, preoperatively, a patient with a large tumor burden was found by ventilation perfusion scan to have minimal (i.e., <20%) function of the involved lung and by pulmonary function testing to have minimal predicted respiratory morbidity after pneumonectomy, the surgeon most likely would have recommended that an EPP be performed. Intraoperatively, however, the decision to perform an EPP was determined not only by the preoperative ventilation/perfusion scan and pulmonary function tests but also whether an expansible lung with <5 mm residual tumor on the visceral pleura could be achieved at the end of the cytoreduction. This selective approach was used instead of one that always called for an EPP to be performed or one that only admitted patients on protocol with minimal disease (who could uniformly have pleurectomy). The ability to perform EPP or pleurectomy decortication in the Lung Cancer Study Group series was 46 of 86 (53%) (9), whereas the most recent series from Memorial Sloan-Kettering (MSK) shows a 77% resection rate, and 54% of the total patients explored had a complete resection (11). We were able to achieve our debulking criteria in 78 of 95 patients explored (82%).

In comparing this approach with the more recently described series of surgical resection for mesothelioma, the 9.4-month survival of EPP patients compares favorably with the 9.9-month survival reported by Rusch and Venkatraman (11) and the 10-month survival achieved in the LCSG study (9). The 14.5-month median survival for pleurectomy patients is similar to the 18.3-month data recorded recently by Rusch (11), which was higher than that seen in the LCSG study. In the most recent series reported from Dana Farber Cancer Institute, median survival for the total series of 104 patients undergoing EPP and postoperative multimodal therapy was 21 months (Sugarbaker, personal communication). Why are these series results so different from those of the previously described studies? Sugarbaker's series is a product of excellent selection of lower risk patients, in that the number of node-positive patients was 38 of 104 (37%), whereas the number of node-positive EPP patients in our series was 79% and 57% in the most recent study from MSK (11). In Sugarbaker's series, the presence of positive nodes was a poor prognostic indicator, with node-negative patients having a median survival of 25.3 months, compared with the node-positive patients, who had a median survival of 16.6 months. We were unable to show an influence of nodal status in this series of patients, and this is probably a result of the failure to have complete nodal evaluation in all patients. Only 65 patients were evaluated completely for lymph node disease, and only two of the pleurectomies were sampled. This, in retrospect, makes our data uninterpretable with regard to the influence of lymph nodes, and we suspect that many of the patients with minimal volume disease who had longer survivals did not have lymph node involvement. In our present phase III studies, all patients are subjected to formal mediastinal lymph node sampling, but even this effort may not completely answer the question of nodal influence, for the first site of drainage for MPM may be the mediastinal lymph nodes and not the N1 nodes. It could be possible that early involvement of the visceral pleura, and subsequent N1 nodal involvement, could portend a poorer prognosis than N2 involvement.

Certain preoperative prognostic factors, some of which have never achieved acceptance in the oncologic community predictive of outcome despite positive studies, continued to surface in our study. As with the majority of other studies, both surgical and nonsurgical, nonepithelial histology was predictive of shortened survival. Platelet count was also predictive of both progression-free survival and overall survival, with the worst outcomes occurring in patients with significantly elevated platelet counts. The majority of our patients were men, and we do not know why women with mesothelioma seemed to live longer than men. However, what is unique to this series was the attempt to quantitate burden of disease preoperatively and relate this to outcome. Not only was tumor volume significant in predicting overall survival, but it also correlated with progression-free interval. These predictions were not influenced by differences in immediate postoperative residual tumor burden between patients because volume measurements performed within 6 weeks after maximal cytoreduction were equivalent (data not shown). Therefore, patients with more bulky disease who required pleuropneumonectomy for 5 mm residual debulking in this series (22 of 26 EPP patients, >100 cm^3) had decreased survival compared with those patients who underwent pleurectomy (16 of 32, > 100 cm^3) which would partially explain the differences in survival between the EPP and pleurectomy groups. However, patients who had a tumor volume exceeding 100 cm^3 who had a pleurectomy had a median survival similar to that of patients who underwent EPP (9 months),

indicating that there seems to be threshold volume above which either procedure is equally ineffective.

These data also verify that recurrence rates after EPP and pleurectomy are temporally similar, but the pattern of first recurrences is distinctly different (9). EPP seems to offer better local control than pleurectomy, but patients die from complications of distant sites. Therefore, local adjuvant therapies will most certainly need to be supplemented by an effective systemic regimen.

Improvements in the staging system for MPM, as described by the Mesothelioma Staging Working Group (1) and by Sugarbaker (12) certainly will help to define groups of patients with similar intraoperative parameters. Probably a result of such a staging system will be the recommendation for mediastinal nodal sampling before thoracotomy, at least in epithelial mesothelioma, to identify that parameter without major operation. However, the problem is that there are other parameters that cannot be accurately defined nonoperatively in 1996 even with the most sophisticated imaging devices. This is also exemplified by the need to perform laparoscopy in patients who have questionable transdiaphragmatic involvement seen on computerized tomography or magnetic resonance imaging. What may be most important is to define the most important prognostic factors on patient presentation that guide the clinician to avoid EPP or pleurectomy and move directly to experimental therapies. We feel that platelet count should be given strong consideration as a predictor of outcome, and patients with high platelet counts and bulky disease of nonepithelial histology should be considered for experimental therapies that (a) involve only minimal surgery (i.e., tissue biopsy for generation of experimental reagent) and (b) can be assessed accurately for response rates. The importance of tumor volume in MPM (which for the first time has been quantitatively expressed) should be assessed by prospective evaluation of this parameter at all institutions dealing with a large mesothelioma population to verify our results that there is a correlation between surgical T stage and preoperative volume. Not only will volume measurements be of use in attempting to verify our results in the surgical population, but they also may help to quantify response rates in a more objective manner.

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