A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma

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Background: Surgical resection of malignant pleural mesothelioma is reported to have up to an 80% rate of local recurrence. We performed a phase II trial of high-dose hemithoracic radiation after complete resection to determine feasibility and to estimate rates of local recurrence and survival.

Methods: Patients were eligible if they had a resectable tumor, as determined by computed tomographic scanning, and adequate cardiopulmonary function for extrapleural pneumonectomy or pleurectomy/decortication. After complete resection, patients received hemithoracic radiation (54 Gy) and then were followed up with serial computed tomographic scanning.

Results: From 1995 to 1998, 88 patients (73 men and 15 women; median age, 62.5 years) were entered into the study. The operations performed included 62 extrapleural pneumonectomies (70%) and 5 pleurectomies/decortications; procedures for exploration only were performed in 21 patients. Seven (7.9%) patients died postoperatively. Adjuvant radiation administered to 57 patients (54 undergoing extrapleural pneumonectomy and 3 undergoing pleurectomy/decortication) at a median dose of 54 Gy was well tolerated (grade 0-2 fatigue, esophagitis), except for one late esophageal fistula. The median survival was 33.8 months for stage I and II tumors but only 10 months for stage III and IV tumors ($P = .04$). For the patients undergoing extrapleural pneumonectomy, the sites of recurrence were locoregional in 2, locoregional and distant in 5, and distant only in 30.

Conclusion: Hemithoracic radiation after complete surgical resection at a dose not previously reported is feasible. This approach dramatically reduces local recurrence and is associated with prolonged survival for early-stage tumors. Stage III disease has a high risk of early distant relapse and should be considered for trials of systemic therapy added to this regimen of resection and radiation.

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Malignant pleural mesothelioma (MPM) is an uncommon cancer for which treatment options are limited. In its early stages, MPM remains localized to a single hemithorax, and therapeutic efforts have therefore focused on local treatment modalities, including surgical resection, radiation, intrapleural chemotherapy, and photodynamic therapy. Although extrapleural pneumonectomy (EPP) is associated with a lower risk of local recurrence than pleurectomy/decortication (P/D), surgical resection alone does not offer

long-term local control in most patients.[1,2] Previous experience with either adjuvant low-dose radiation or postoperative intrapleural chemotherapy showed that these approaches failed to prevent local recurrence.[3-5] We sought to test the use of high-dose hemithoracic radiation after complete surgical resection of all gross tumors in an effort to achieve local control in early-stage MPM. We now report the results of this phase II trial performed at Memorial Sloan-Kettering Cancer Center (MSKCC).

Methods

Objectives

The objectives of this phase II trial for resectable MPM were as follows: (1) to determine the feasibility of EPP combined with high-dose, postoperative external-beam hemithoracic radiation; (2) to determine the feasibility of combining P/D with intraoperative radiation and postoperative external-beam radiation; (3) to determine the patterns of local and distant recurrence after this combined modality treatment; and (4) to estimate overall survival after this combined modality treatment.

Eligibility Criteria

Patients were eligible for this prospective phase II study if they had potentially resectable, biopsy-proven MPM. The trial was approved by the MSKCC Institutional Review Board, and informed consent was obtained from all patients entered into the study.

The histologic diagnosis of MPM was confirmed in all cases by means of immunohistochemistry, electron microscopy, or both. All patients were evaluated with history and physical examination, computed tomographic (CT) scanning of the chest and upper part of the abdomen, laboratory data, pulmonary function testing, quantitative ventilation-perfusion scanning, echocardiography, and, if clinically indicated, radionuclide stress testing. Additional scans to determine whether distant metastases were present were performed as clinically indicated. Patients were considered ineligible for the study if they had another malignancy within the previous 5 years, had cardiopulmonary or renal insufficiency that made the planned surgical resection prohibitively hazardous, or had a tumor clearly involving the chest wall, abdomen, or distant organs, as determined by means of examination or imaging studies.

Surgical Treatment Plan

All patients were to undergo an EPP unless contraindicated by their preoperative pulmonary function or by the presence of concurrent medical problems that made the risk of pneumonectomy prohibitive, in which case a P/D was performed.

The surgical technique used for both EPP and P/D has been described previously.[6] EPP was defined as an en bloc resection of the entire pleura, lung, and diaphragm, with or without resection of the pericardium. For left-sided resections, the diaphragm was reconstructed with 2-mm thickness polytetrafluoroethylene,* and for right-sided resections, reconstruction was with Dexon mesh (Davis & Geck, Danbury, Conn). If resected, the pericardium was also reconstructed with Dexon mesh. P/D included resection of the parietal and mediastinal pleura and removal of involved areas of the visceral pleura, without resection of the lung. Involved areas of the pericardium and diaphragm were also resected and reconstructed as necessary. At thoracotomy, a complete mediastinal lymph node dissection was also to be performed.

Patients found to have an incompletely resectable or unresectable tumor at thoracotomy because of unsuspected diffuse involvement of the chest wall, transdiaphragmatic tumor extension (T4 disease), or metastatic (M1) disease were removed from the study and did not receive the planned adjuvant radiation. Final pathologic staging was performed according to the International Mesothelioma Interest Group staging system.[7]

Radiation Treatment Plan

For patients undergoing EPP, adjuvant external-beam radiation started 3 to 5 weeks postoperatively. The target volume included the entire hemithorax, the thoracotomy incision, and chest tube incisions. A total of 54 Gy was delivered through anterior and posterior fields in 30 daily fractions of 1.8 Gy by using 6-MV or higher photons. The spinal cord was protected after 41.4 Gy. Cerrobend blocks were used to limit the dose to the liver, heart, and stomach when these organs were in the treatment field. Electrons were used in the blocked regions to prevent underdosing to the pleura and diaphragm.

Patients undergoing P/D received intraoperative radiation with a previously described high-dose iridium applicator.[8,9] A dose of 15 Gy was to be delivered to the mediastinum and diaphragm, reducing this to 10 Gy over the heart and esophagus. For these patients, external-beam radiation was also started 3 to 5 weeks postoperatively. The dose administered was 45 to 54 Gy, and the target volume included the perimeter of remaining lung tissue with a 0.5- to 1.0-cm margin, the chest wall with a 1.0-cm margin, the diaphragm, and the mediastinum.

Post-treatment Follow-up Plan

A physical examination and CT scan of the chest and upper abdomen were performed 4 to 6 weeks after the end of external-beam radiation and then every 3 to 4 months thereafter. In accordance with previously reported criteria, local tumor progression was defined as an increasing radiographic abnormality on serial CT scans within or partially within the irradiated volume, provided such an abnormality was not considered to be solely caused by radiation pneumonitis.[10,11] Tumor progression identified by CT or other scans outside of the irradiated volume was considered to be metastatic disease. Cytologic or histologic documentation of disease progression was required whenever technically feasible. All patients were followed up until death or to the final date of analysis for this study. Postmortem examinations were not routinely performed because most patients who died of progressive disease received terminal care locally in their communities, often far away from MSKCC.

Statistical Methods

Survival probabilities were calculated by the product-limit method of Kaplan and Meier. The prognostic significance of factors were tested in a univariate model by the log-rank statistic for categoric

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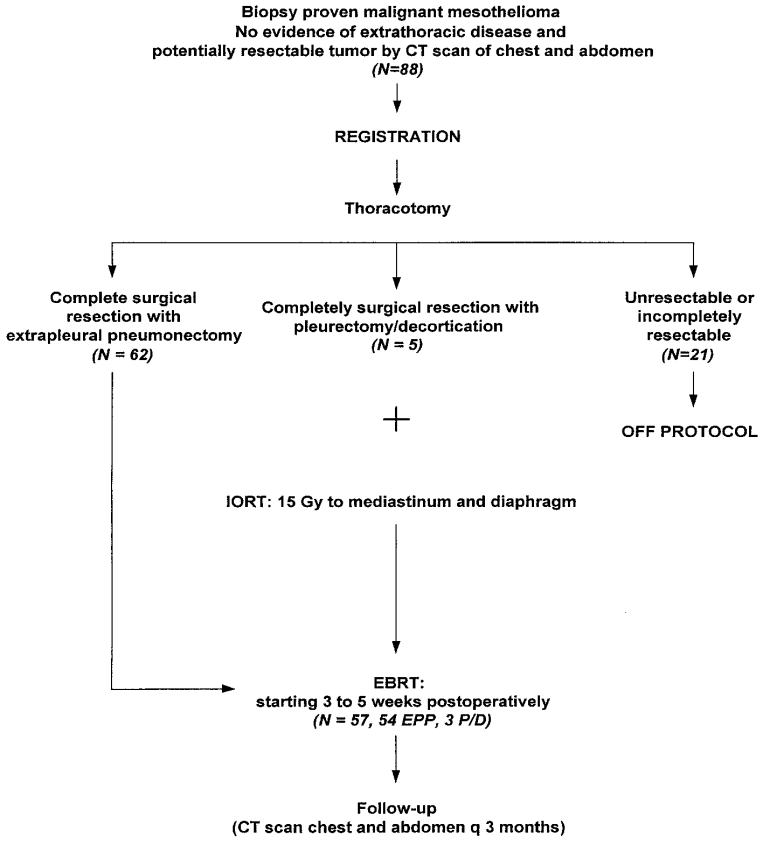

Figure 1. Study schema of MSKCC protocol #93-153A, with the numbers of patients noted at key study time points. *IORT*, Intraoperative radiation therapy; *EBRT*, external beam radiation therapy.

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TABLE 1. Demographic information for the 88 patients entered into MSKCC protocol #93-153A

Male/female ratio	73:15
Median (range) age, y	62.5 (24-78)
Right/left ratio	55:33
Tumor histologic type	
Epithelial	60
Mixed	20
Fibrosarcomatous	7
Desmoplastic	1

covariates and by proportional hazards regression for continuous covariates. Proportional hazards regression was used to test the prognostic significance of factors in a multivariate model.[12-14]

Results

From 1993 to 1998, 103 patients were entered into the study. As originally designed, the trial included intraoperative radiation after both EPP and P/D. However, after 15 patients were entered into the study (EPP, 7 patients; P/D, 4 patients; unresectable, 4 patients), it was noted that the intraoperative radiation unduly prolonged the length of the operation (median, 9.2 hours; range, 1.0-13.4 hours) and was associated with an unexpected frequency of infectious complications in the patients undergoing EPP, including empyemas. Therefore, with the approval of the institutional review board, the trial was closed for the revision of the protocol, eliminating the intraoperative radiation for patients undergoing EPP. The trial was then reopened for accrual. The intraoperative radiation was retained for patients undergoing P/D because of the limitations of external-beam radiation and the lower risk of infectious complications in these cases. This report focuses on the 88 patients entered into the revised protocol (MSKCC protocol #93-153A) between 1995 and 1998.

Patient Characteristics and Surgical Resection Data

The study schema and the numbers of patients in the study at important time points are shown in Figure 1. The demographic information for these 88 patients, shown in Table 1, reflects the usual sex, age, and tumor histology distribution

TABLE 2. Surgical and staging data for the 88 patients entered into MSKCC protocol #93-153A

Resection information	
Exploration only	21
EPP	62
P/D	5
Operative mortality and morbidity	
Mortality	7/88 (7.9%)
Morbidity (any type)	33/88 (37.5%)
T status	
T1	7
T2	36
T3	25
T4	20
N status	
N0	33
N1	4
N2	33
NX	18
M status	
M0	85
M1	3
Stage categories	
I	2
II	17
III	46
IV	23

of patients with MPM. Most patients were middle-aged or older men, and epithelial tumors were the most common histologic type.

Data related to surgical resection and tumor stage are shown in Table 2. Of the 88 patients entered into the study, 21 did not have a completely resectable tumor at thoracotomy and were removed from the study; 62 patients had EPP, and 5 underwent P/D. The median operative time was 4.1 hours (range, 1.0-10.3 hours), and the median blood loss was 1050 mL (range, 40-5700 mL). There were 7 postoperative deaths, all primarily related to pulmonary complications in patients who had undergone EPP. A total of 33 patients had at least one complication. The most common complications (some patients had multiple complications) were atrial arrhythmias (17 patients), respiratory failure (6 patients), pneumonia (5 patients), and empyema (5 patients).

Almost half of all patients had T1 or T2 tumors, and just over 40% of tumors were N0 or N1. The N status was not known for 18 patients who had unresectable or incompletely resectable tumors, most frequently because of diffuse chest wall invasion. However, because of either T3 or N2 status, 51% of all tumors were considered to be stage III, and only 22% were stage I or II.

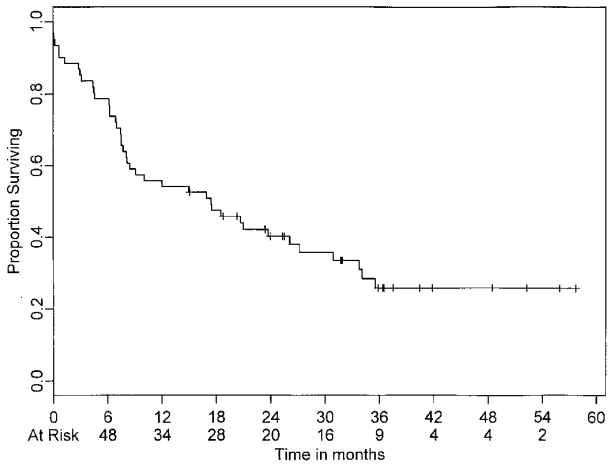

Figure 2. Overall survival of all extrapleural pneumonectomy patients (n = 61).

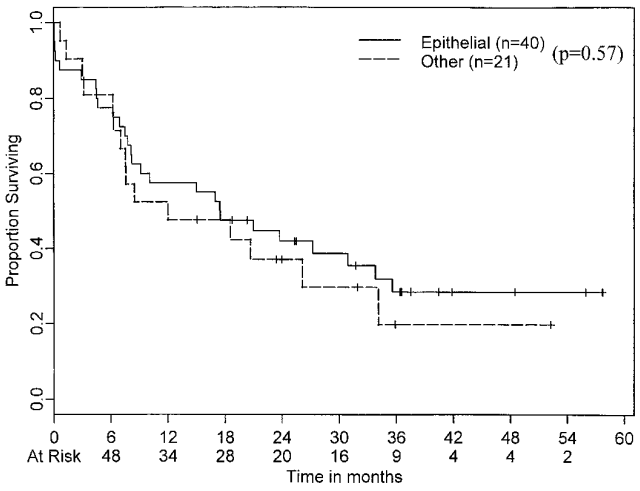

Figure 3. Overall survival of extrapleural pneumonectomy patients by histologic type.

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Adjuvant Radiation Data

Of the 60 patients who survived and had a complete surgical resection, 3 did not receive adjuvant radiation because of poor performance status. The remaining 57 patients (54 EPP and 3 P/D) received a median dose of 54 Gy of radiation (range, 20-64 Gy). Radiation-related complications are shown in Table 3. In general, radiation was well tolerated, with most toxicities being of grades 1 and 2. Grade 3 toxicities included fatigue, esophagitis, nausea, and vomiting. The most serious grade 4 toxicity was an esophagopleural fistula, which developed several months after the completion of radiation and required an Eloesser flap for drainage. Three years after EPP, the patient underwent substernal gas-

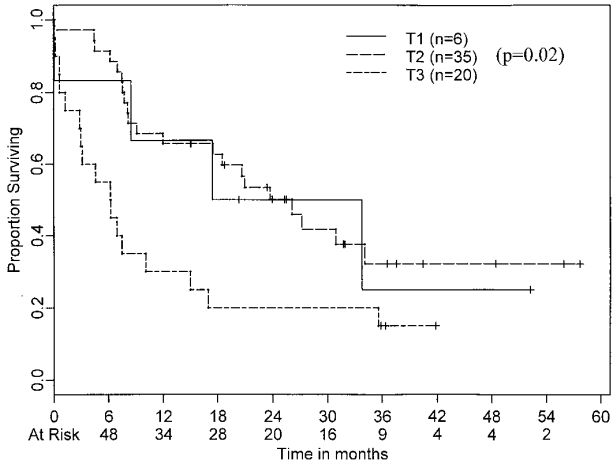

Figure 4. Overall survival of extrapleural pneumonectomy patients by T status.

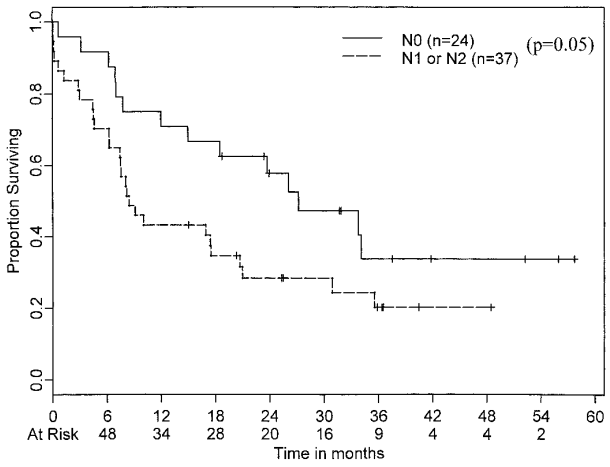

Figure 5. Overall survival of extrapleural pneumonectomy patients by N status.

TABLE 3. Complications of adjuvant hemithoracic radiation described by Radiation Therapy Oncology Group grade complications

	Grade					
Type	**0**	**1**	**2**	**3**	**4**	**LTF**
WBC	42	6	1	0	0	1
Hemoglobin	37	11	1	0	0	0
PLT	43	5	1	0	0	1
Fatigue	5	14	27	6	2	0
Nausea	15	20	16	3	1	0
Vomiting	25	17	10	3	0	0
Esophagus	11	20	21	2	1	0
Lung	30	17	5	1	0	0
Heart	51	2	0	0	0	0
Skin	5	31	16	2	1	0

LTF, Life-threatening or fatal; *WBC*, white blood cell count; *PLT*, platelet count.

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tric interposition to restore gastrointestinal continuity but died postoperatively of respiratory failure. At death, the patient remained clinically and pathologically free of disease. Review of the radiation doses and field did not reveal any protocol violations or specific causes for the development of the esophageal fistula.

Survival Estimates

Because just 5 patients underwent P/D, survival estimates were performed only for the patients who underwent EPP (Figures 2-6). One patient was lost to follow-up, and therefore 61 patients are included in these analyses. The median survival for this entire group of patients was 17 months, and the overall survival at 3 years was 27% (Figure 2). For stage I and II tumors, the median survival was 33.8 months, but survival was only 10 months for stage III and IV tumors. The relationship of several potential prognostic factors to overall survival was examined by univariable analysis, and those results are shown in Table 4. T and N status and stage all had a significant effect on survival, whereas tumor histologic type (epithelial vs all others) did not. None of these factors was significant in a multivariate analysis because histologic type is not significant univariately, and the other 3 factors are highly associated with each other. However, the analysis of prognostic factors in relation to survival should be interpreted cautiously because it was not an end point of the study design and because of the relatively small number of patients analyzed.

Sites of Relapse

The initial sites of relapse for the largest and most uniformly treated group of patients, namely the 54 patients who underwent both EPP and radiation, are shown in Table 5. A total

TABLE 4. Univariate analysis of potential prognostic factors on overall survival in patients who underwent EPP (n = 61)

	No. of patients	*P* value	Hazard ratio (95% CI)
Histology			
Epithelial	40	.57	1.20
Other	21		(0.63-2.29)
N status			
N0	24	.05	1.88
Other (N1 or N2)	37 (N1 = 4; N2 = 33)		(0.97-3.63)
T status			
T1	6	<.01	1.53
T2	35	(T1 + T2 vs T3)	(1.11-2.11)
T3	20		
T4	0		
Stage			
I	2	.02	1.54
II	17	(I + II vs III + IV)	(1.07-2.22)
III	41		
IV	1		

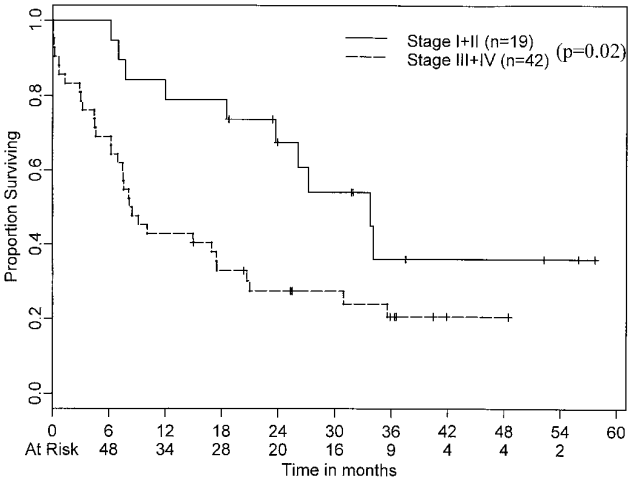

Figure 6. Overall survival of extrapleural pneumonectomy patients by stage.

of 7 (13%) patients had locoregional recurrence, but only 2 (3.7%) of these did not also have evidence of distant metastases. Three (5.5% of all patients receiving radiation) patients had locally recurrent disease in the region of the previously resected pleura at the margins of the radiation field. Distant metastases were the most common form of relapse, with the peritoneum, contralateral pleura, and contralateral lung being the most common sites.

TABLE 5. First sites of relapse in the 55 patients who underwent EPP with postoperative radiation

Locoregional only	2
Distant only	30
Locoregional and distant	5
Locoregional	
Pleural	3
Nodal	4
Distant	
Peritoneal	17
Intralateral visceral	5
Contralateral pleural	13
Contralateral lung	8
Bone	7
Central nervous system	0
Other	5

Some patients had more than one site of recurrent disease at relapse.

Discussion

MPM is an uncommon malignancy, which was long considered uniformly fatal and untreatable. However, recent series show that overall survival is much longer than previously thought when MPM is diagnosed at an early stage.[2,15-17] These series, which include larger numbers of patients than were entered into this prospective clinical trial, all suggest that tumor histologic type, T and N status, and stage significantly influence survival. Surgical resection and adjuvant therapy, either radiation, chemotherapy, or both, seem to have a beneficial effect on survival in selected patients.[16,18]

Despite some progress in treating MPM, including better surgical selection and management, local control remains a significant problem.[18-20] Baldini and colleagues[5] reported that low-dose hemithoracic radiation (median, 31 Gy) failed to provide local control after EPP, even when boost radiation was given to sites of diseased surgical margins. Adjuvant intrapleural chemotherapy and photodynamic therapy have also failed to prevent local recurrence in most patients after either P/D or EPP, even though they can be administered with acceptable toxicity.[2,4,21-23]

At MSKCC, we had a large historical experience with P/D and adjuvant radiation using an external beam with or without intraoperative brachytherapy.[24-27] A retrospective review of that treatment strategy in 105 patients showed that local recurrence was the predominant form of relapse and that survival was poor, except in patients who had very early-stage disease amenable to complete surgical resection by means of P/D. Radiation pneumonitis and pericarditis were also frequent complications.[3] This experience led us to explore other therapeutic approaches. Promising results with intracavitary chemotherapy in ovarian cancer and in patients with malignant pleural effusions led us to study adjuvant intrapleural cisplatin-based chemotherapy in patients who had MPM resected by means of P/D.[28] That

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phase II trial showed a marked pharmacologic advantage for the intrapleural administration of chemotherapy and a favorable median survival, but local recurrence was clearly the most common form of relapse.[4,29] The results of that study led us to develop the trial reported here, with the underlying hypothesis that complete surgical resection, preferably by EPP, coupled with high-dose hemithoracic radiation was feasible and might achieve local tumor control.

Our results show that adjuvant radiation, administered to the entire hemithorax at a higher total dose than has been reported previously, after EPP is feasible with acceptable toxicity. This treatment strategy is associated with a very low risk of local recurrence. These results differ strikingly from those of our previous experience and those reported by other centers.[5,30-32] The few local recurrences in this study appear to have been failures at the margins of the radiation field, emphasizing the importance of treating the entire hemithorax, including the diaphragm, costophrenic sulcus, and ipsilateral half of the mediastinum. Careful and complex radiation-treatment planning is required to avoid excessive radiation to the stomach for left-sided tumors and to the liver for right-sided tumors. It is also notable that the radiation used in this study essentially eliminates the risk of tumor recurrence in the chest wall that is commonly seen in patients with MPM who have had thoracic incisions. In this regard, our results are consistent with those of Boutin and colleagues,[33] who reported a randomized trial showing that adjuvant radiation after thoracoscopy could prevent tumor recurrence in the chest wall.

On the basis of the results of the study, we have adopted EPP and high-dose hemithoracic radiation as our standard approach to local tumor control in early-stage MPM. The number of patients in this study treated with P/D, intraoperative radiation, and postoperative external-beam radiation is too small to estimate the toxicity and effectiveness of that approach.

Our results clearly indicate that the greatest challenge now is to prevent the development of metastatic disease, especially in patients who have stage III tumors. The poor survival of this group of patients, who represent the largest subset in this study and in clinical practice generally, remains the greatest concern. With recent improvements in systemic therapy, it may be possible to add chemotherapy to the treatment of patients with T3 or N2 disease.[34] However, previous experience with postoperative chemotherapy after EPP does not suggest a marked survival benefit compared with what we observed in this study for patients with stage III tumors.[15] Extrapolating from the experience with induction chemotherapy in stage III lung cancer, we hypothesize that chemotherapy can be delivered more consistently and effectively in the preoperative setting.[35] Therefore, we have begun to test such an approach in patients identified as having T3 or N2 disease at diagnosis.

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