Radical pleurectomy/decortication and intraoperative radiotherapy followed by conformal radiation with or without chemotherapy for malignant pleural mesothelioma

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Objectives: We performed a retrospective review of the efficacy and morbidity of radical pleurectomy/decortication and intraoperative radiotherapy followed by external beam radiation therapy with or without chemotherapy for diffuse malignant pleural mesothelioma.

Methods: A total of 32 patients with diffuse malignant pleural mesothelioma were initially evaluated between January 1995 and September 2000. Three patients were excluded from analysis because of unresectable disease. Two patients died postoperatively, and one patient had recurrent disease previously treated at an outside institution. Of the remaining 26 patients included in the analysis, 24 received intraoperative radiotherapy. External beam radiation therapy was generally started 1 to 2 months after resection and delivered by means of 3-dimensional conformal radiation therapy or with inverse treatment planning intensity-modulated radiation therapy. When given, chemotherapy consisted of 2 to 3 cycles of cyclophosphamide, doxorubicin (Adriamycin), and cisplatin initiated 1 to 2 months after completion of radiation.

Results: At the time of data analysis, 5 of 26 patients were alive. The median follow-up was 9.7 months (range, 2-67.6 months). The median overall survival and progression-free interval from the time of the operation were 18.1 and 12.2 months, respectively. The Kaplan-Meier estimates of overall survival and freedom from progression at 1 year were 64% and 50%, respectively. The site of failure was mostly locoregional. However, there were 4 abdominal failures and 1 contralateral lung failure.

Conclusions: Radical pleurectomy/decortication with aggressive radiotherapy with or without chemotherapy might offer an alternative treatment option to those who cannot tolerate extrapleural pneumonectomy.

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Diffuse malignant pleural mesothelioma (DMPM) is an invasive, locally aggressive tumor that is almost always fatal. Tumor progression in the chest is typically manifested by increasing mass size and pleural effusion, causing physical compression of the ipsilateral lung and respiratory compromise. Although distant metastasis occurs with advanced disease, inadequate local control has been the main cause of death.

Approximately 2500 new cases of DMPM are diagnosed each year, and the incidence has been slowly rising.[1,2] The best-defined and most common risk factor is asbestos exposure. The main reason for the increase in incidence is due to the long latency period (40 years) and the prevalence of occupational exposure to asbestos in the mid-20th century.

Surgical intervention has been the most common treatment approach for this disease. One surgical approach is extrapleural pneumonectomy (EPP), which has been advocated by some as a way of achieving maximal cytoreduction. This procedure involves en bloc removal of the pleura (parietal and visceral), the entire ipsilateral lung, and portions of the pericardium, diaphragm, or both. Historically, this approach has met with a high operative and in-hospital mortality (on the order of 15%-20%). However, in highly specialized centers the perioperative mortality rates have been reported to be less than 5%.[3-5] Another surgical approach is radical pleurectomy/decortication (P/D), which allows debulking of the tumor while preserving the ipsilateral lung. In this procedure the parietal pleura is dissected from the endothoracic fascia, and an incision is made to allow exposure and decortication of the visceral pleura. Portions of the diaphragm and pericardium are also resected with reconstruction as needed. Although this approach is technically difficult, it is generally less morbid and better tolerated than EPP, with perioperative mortality rates of less than 5%.[6-8] As a single modality, the results of aggressive surgical resections have been disappointing, with median survivals of less than 1 year in most series.[3,4,6,7]

Radiation therapy has also been used for the treatment of DMPM. However, the results of radiation therapy alone have been disappointing and generally used for palliation.[9,10] Because of the amount of tumor that is often present at diagnosis, it is difficult to deliver a tumoricidal dose of radiation to the volume at risk (entire ipsilateral pleural surface) without damaging a significant volume of the underlying lung.

Chemotherapy has been tried with limited success. Currently available chemotherapy agents, such as platinum-containing regimens, doxorubicin-containing regimens, or both, have poor response rates on the order of 20% to 30%.[11,12] Newer agents, such as multitargeted antifolate, in combination with cisplatin in early clinical trials produced partial response rates of 40%.[13] Gemcitabine alone has been disappointing. A phase II trial by the Cancer and Leukemia Group B demonstrated no antitumor activity.[14] However, a combination therapy with gemcitabine and cisplatin might be more effective and has been shown to have a response rate of 47%.[15]

Multimodality therapy has been tried to improve survival over single-modality treatment. Different combinations of therapies, including surgical intervention (EPP or radical P/D) with intraoperative brachytherapy, intrapleural chemotherapy, postoperative radiation therapy, systemic chemotherapy, and/or intraoperative photodynamic therapy, have been used.[5,8,16-22] Sugarbaker and colleagues,[5] at the Dana-Farber Cancer Institute, have the largest series of patients with pleural mesothelioma treated with combined modality. Their approach involves the use of EPP, followed by postoperative chemoradiation. The most recent update reports a median survival of 19 months, with even better outcomes in certain subgroups of patients. In particular, node-negative patients with epithelial histologic characteristics who had complete resection have achieved median survivals of 51 months. However, because their series only included patients capable of tolerating EPP, a built-in selection bias might be present.

At the University of California, San Francisco (UCSF), radical P/D with adjuvant radiation therapy has been used to allow patients with a less favorable cardiopulmonary status to undergo resection. However, preservation of the lung might lead to an increased incidence of radiation pneumonitis if treated with even moderate doses of radiation. Intraoperative radiation therapy (IORT) at the time of resection can be used as a radiation boost to partially circumvent this problem. By delivering a single large fraction of radiation at the time of the operation, a modest dose of postoperative external beam radiation might be adequate to obtain local control while sparing lung parenchyma relative to full-dose postoperative radiation. Adjuvant chemotherapy was often given to suitable patients after the completion of external beam radiation. This series represents a retrospective review of patients treated at UCSF by using this approach.

Methods

A total of 32 patients were evaluated for multimodality treatment at UCSF between January 1995 and September 2000. After institutional review board approval had been obtained, data regarding patient outcome were obtained from hospital charts, the Social Security death index, and the patients' outside physicians. Informed consent was obtained for all patients for the surgical and radiotherapeutic components of this treatment. Patients were fully counseled on the risks of intraoperative and postoperative radiation therapy.

Before acceptance for treatment, histologic confirmation of malignant mesothelioma was made at UCSF. Preoperative requirements were normal liver function test results and creatinine levels,

as well as an estimated Karnofsky performance status of 70% or greater. Parameters on pulmonary function tests included a forced expiratory volume in 1 second of greater than 1.5 L and a diffusing capacity for carbon monoxide in the lungs of greater than 50%. Echocardiography with or without sestamibi scans were used to evaluate cardiac function before the operation. Finally, chest and upper abdominal computed tomographic (CT) scans and other radiologic studies, as clinically indicated, were used to evaluate resectability of the primary tumor and to rule out extrathoracic disease.

At the time of the operation, 3 of 32 patients were found to have unresectable disease. The remaining 29 patients underwent attempted definitive resections. One patient was excluded from the analysis because she had recurrent disease. There were 2 (7%) postoperative deaths. One patient died of a pulmonary embolus 1 day after the operation. One patient died of acute respiratory arrest with hypotension and subsequent multiorgan failure 10 days after the operation. The 26 patients who underwent radical P/D form the basis of this review.

Patients underwent resection through a posterolateral thoracotomy with an excision of the sixth rib and a second intercostal incision at the ninth intercostal space, as necessary. Isolated lung ventilation was used. For postoperative pain, thoracic epidural analgesia was used. A complete extrapleural dissection was performed on all patients. Occasionally, patients with locally extensive disease through the endothoracic fascia received limited en bloc chest wall resection. Thirty-one percent (8/26) of patients also underwent resections of the diaphragm with bovine pericardium or prosthetic reconstruction when indicated to achieve at least R1 resection. All efforts were made to avoid entry into the peritoneum. Patients underwent complete visceral pleurectomy, including clean dissection of the pulmonary artery and hilar structures. Twenty-three percent (6/26) of patients underwent prior talc pleurodesis, which did not preclude complete visceral pleurectomy. Sixty-two percent (16/26) of patients underwent mediastinal and hilar nodal sampling. Typical nodes sampled included levels 4, 6, and 7 and 9, 10, and 11. As a routine, radical mediastinal and hilar node dissection was not performed. All patients had disease-free mediastinal nodes (<1 cm), as determined with preoperative CT and positron emission tomography, and thus did not undergo preoperative mediastinoscopy. Patients were monitored postoperatively in an intensive care unit setting.

Of these 26 patients, 24 received IORT at the time of resection. One patient did not receive IORT because of logistic difficulties and the other because of hemodynamic instability during the operation. Before December 1997, IORT was delivered through a Clinac 2300 device (Varian, Palo Alto, Calif) in the Department of Radiation Oncology at UCSF. This required transportation of the patient from the operating room to the department. All subsequent IORTs were performed on the Mobetron (Intraop Medical, Santa Clara, Calif), a mobile intraoperative electron therapy unit in the operating room. All areas difficult to encompass by means of conformal radiation treatment planning were treated with IORT. These areas included the major fissure, the pericardium, and the diaphragm. The average number of sites treated with IORT was 3.3, with a range of 2 to 6 sites. The median dose was 15 Gy (range, 5-15 Gy) by using 4-, 6-, or 9-MeV electrons with a typical bolus of 5 to 10 mm.

TABLE 1. Treatment parameters

Treatment factors	
No. of IORT sites, n = 17	
Median (mean)	3 (3.3)
Range	2-6
IORT doses used per site (cGy)	
Median (mean)	1500 (1270)
Range	500-1500
Patients who completed post operative EBRT	
Yes	24
No	2
Method of post operative EBRT	
3D-CRT	14
IMRT	10
Post operative EBRT prescribed doses, n = 24 (cGy)	
Median (mean)	4135 (4029)
Range	3008-4880
Post operative EBRT maximum doses for 3D-CRT, n = 14 (cGy)	
Median (mean)	4950 (5017)
Range	3893-6475
Post operative EBRT maximum doses for IMRT, n = 10 (cGy)	
Median (mean)	5829 (5571)
Range	3008-7500
Patients who received chemotherapy	
Yes	12
No	14

EBRT, External beam radiation therapy.

Postoperative radiation therapy was given to 24 patients (one patient died before receiving external beam radiation therapy, and the other was medically unstable) starting approximately 1 to 2 months after the operation. Before November 1997, external beam radiation therapy was delivered by means of 3-dimensional conformal radiation therapy (3D-CRT; 14 patients). Since then, intensity-modulated radiation therapy (IMRT) with inverse treatment planned on the Corvus system (Nomos Corp, Sewickley, Pa) was used (10 patients). The goal of external beam radiation therapy was to treat the ipsilateral pleural surface and all surgical scars while sparing the underlying lung parenchyma. The radiation oncologist determined the external beam radiation dose on the basis of the coverage of the target volume, as well as the ability to spare the underlying lung parenchyma. The median prescription dose of external beam radiation therapy was 41.4 Gy (range, 30.1-48.8 Gy). Chemotherapy, when given, consisted of cyclophosphamide, doxorubicin, and cisplatin for 2 to 3 cycles, beginning 1 to 2 months after radiotherapy. Adjuvant treatment parameters are summarized in Table 1.

After completion of radiation therapy, patients were seen in follow-up every 3 months. New baseline CT scans and chest radiographs were obtained 1 to 2 months after completion of postoperative radiation. Serial chest radiographs were used to monitor patients every 3 to 4 months with CT investigation of evolving abnormalities. Patients also underwent annual CT evaluations.

TABLE 2. Patient and tumor characteristics

Characteristics	
Evaluable patients	26
Patients who received IORT	24
Sex (male/female)	21/5
Age (y)	
Median (mean)	69 (68)
Range	45-84
Karnofsky performance status	
Median (mean)	90 (85)
Range	60-90
History of asbestos exposure	
Yes	17
No	9
History of tobacco use	
Yes	17
No	9
History of prior talc pleurodesis	
Yes	6
No	20
Side of lung	
Left	10
Right	16
Histology	
Epithelial	19
Sarcomatous	1
Mixed	5
Not specified	1
AJCC TNM stage	
I	18
II	0
III	8
AJCC T Stage	
1	1
2	18
3	7
Node involved	
Yes	3
No	23

IORT, Intraoperative radiation therapy.

All statistical analyses were performed with a statistical software package (STATA; Computing Resource Center, Santa Monica, Calif). Overall survival time and progression-free interval were calculated from the time of the initial operation by using the Kaplan-Meier method. Failures were scored at the time of radiographic evidence of tumor progression. Univariate analyses of prognostic factors were performed with either a Cox proportional hazards model or a log-rank test.

Results

Patient Characteristics and Treatment Parameters

The overall patient and tumor characteristics are summarized in Table 2. A majority (16/26) of tumors were right sided. Eleven of 26 patients had a history of both smoking and asbestos exposure. As expected, the predominant histologic type was epithelial (n = 19). One patient had purely sarcomatous histologic characteristics, and 5 patients had mixed histologic features. On the basis of the 1997 American Joint Committee on Cancer TNM staging, 18 of 26 patients had stage I disease, and the remaining 8 patients had stage III disease. Three patients had pathologic evidence of nodal involvement. One patient had a level 8 node, and the other 2 had intrapulmonary nodes involved with tumor.

At the time of thoracotomy, 65% (17/26) of patients had complete removal of gross tumor (R0), whereas 31% (8/26) had microscopic disease (R1). One patient (4%) underwent incomplete resection (R2). This patient received treatment with IORT.

Survival, Local Control, and Prognostic Factors

Of the 26 patients, 5 were alive at the time of analysis. The median follow-up was 9.7 months from the time of radical P/D (range, 2-67.6 months). The median overall survival from the time of the operation was 18.1 months (Figure 1). The percentage of patients still alive at 1 and 2 years was 64% and 32%, respectively. A majority of deaths were due to tumor progression. Other causes of death included a pulmonary embolism in one patient after an unrelated surgical procedure (transurethral resection of prostate) approximately 2 months after radical P/D, and one patient committed suicide at 5 months without any evidence of disease.

The median progression-free interval from the time of the operation was 12.2 months (Figure 2). Progression-free survival at 1 and 2 years was 50% and 22%, respectively. The site of failure was mostly locoregional along the previous site of surgically resected pleural disease. In one patient the failure occurred at a chest tube site that was not included in the postoperative radiation therapy treatment volume. This patient was taken to the operating room for resection, and the area was further treated with electron beam therapy. He then died of local progression 9 months after completion of radiation therapy. There were 4 abdominal failures. Twenty-five percent (2/8) of patients with diaphragm reconstruction had abdominal failure versus 11% (2/18) of patients without reconstruction. One patient had failure in the contralateral lung with hematogenous metastasis.

A number of potential prognostic factors, including R0 versus R1, stage, histologic type, nodal involvement, Karnofsky performance status, radiation dose, and number of IORT sites, were tested by means of univariate analysis. Only a lower number of IORT sites was found to be predictive of overall survival, with a hazard ratio of 2.15 (95% confidence interval, 1.05-4.40). The same potential prognostic factors were then analyzed by means of univariate analyses for progression-free interval as the end point. There were no variables that predicted progression-free interval. Multivariate analysis was not performed because of the absence of multiple significant univariate prognostic factors.

Morbidity and Mortality From Therapy

Mean estimated blood loss from the operation was 1400 mL (range, 500-3500 mL). The median hospitalization was 9

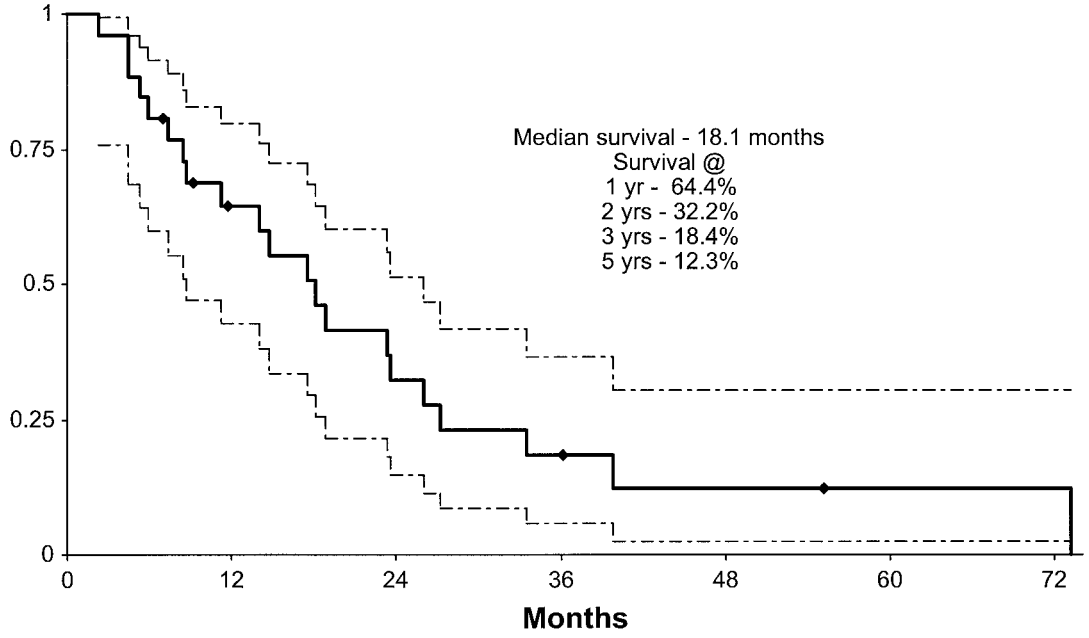

Figure 1. Kaplan-Meier curves for overall survival.

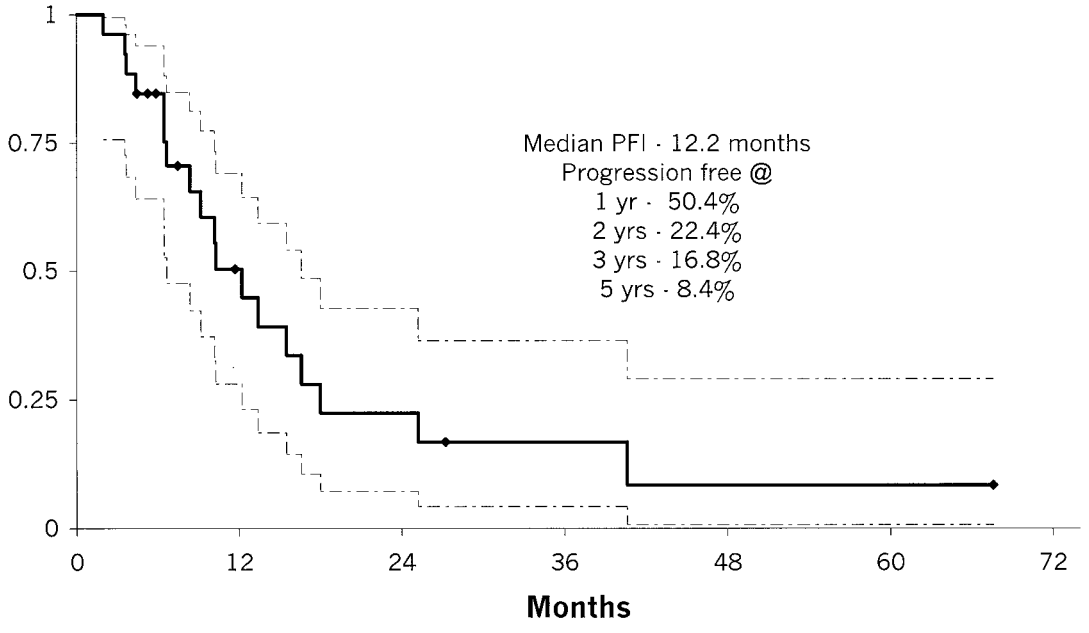

Figure 2. Kaplan-Meier curves for progression-free interval.

days, with a range of 7 to 18 days. Chest tubes were removed on the fourth to fifth postoperative day (range, day 2-12). Major postoperative complications included atrial fibrillation in 11% (3/26) of patients and persistent air leak, defined as greater than 7 days, in 4% (1/26) of patients.

The primary morbidity of postoperative external beam radiation therapy was radiation-induced pneumonitis. Symptoms of pneumonitis (eg, fever and persistent cough) were noted in 17% (4/24) of patients at 3 to 7 months after the completion of radiation therapy. One patient had symptoms consistent with pericarditis at 6 months' follow-up. In all 5 of these cases, symptoms were self-limiting and subsequently resolved with conservative management. Finally, 1 patient had an esophageal stricture that ultimately required

balloon dilatation. However, this case was complicated by the fact that a previous course of radiation therapy was given at an outside institution before radical P/D. The patient was subsequently treated with postoperative external beam radiation therapy at UCSF. This resulted in a high dose of radiation to the esophagus, which most likely is the reason for the complication.

Discussion

Local control appears to be the main problem in treating malignant pleural mesothelioma. Surgical intervention alone (either EPP or radical P/D) is clearly not enough to eradicate all local disease. This has led to an increased interest in adjuvant therapy. Although pilot studies on the use of intraoperative photodynamic therapy as adjuvant therapy were promising,[8,18] a phase III trial showed no apparent benefit on either progression-free or overall survival.[20] Rusch[21] reported on the use of postoperative intrapleural chemotherapy after radical P/D with moderate improvements in local control and survival. This approach might also be problematic in some settings. Intrapleural chemotherapy is limited by its diffusion capacity, preventing efficient treatment of disease that is more than a few millimeters deep. Intrapleural instillation of chemotherapy has an additional problem postoperatively; the pleural space often becomes adherent and leads to poor distribution of the drug.

The current treatment method at UCSF has involved IORT to the areas at highest risk for residual disease at the time of resection. IORT allows delivery of a single high dose of electron therapy to the target while limiting the dose to normal tissue. The underlying lung parenchyma can be spared because of the rapid dose fall off of the electron beam. Postoperatively, the pleural surface is given an additional dose by means of external beam radiation therapy to spare the underlying lung parenchyma.

The median prescribed dose of external beam radiation was 41.4 Gy (range, 30.1-48.8 Gy). The dose was selected on the basis of the coverage of the target volume and on the tolerance dose to the lung. Kutcher and colleagues[23] have previously published a technique for the treatment of pleural mesothelioma using a combination of photons and electrons to spare a significant portion of the lung. A similar technique was used at UCSF before November 1997 with 3D-CRT. However, with IMRT with inverse planning, it might be possible to improve the coverage of the pleural surface and decrease toxicity. An additional advantage of IMRT is the inherent heterogeneous dose distribution. This often results in a higher dose within the center of the target volume. Therefore, although the prescription dose (ie, minimum dose to target volume) might be similar between the 3D-CRT and IMRT, the maximum dose within the target volume is significantly higher in the IMRT plan. The median and mean maximum doses in the IMRT plans were 58.3 and 55.7 Gy, respectively. The median and mean maximum doses in the 3D-CRT plans were 49.5 and 50.2 Gy, respectively. The number of patients treated in this series was too small to conclude any difference in survival between 3D-CRT and IMRT.

Progression of disease in the chest remains a major problem with this approach. Better local control through dose escalation would be extremely difficult without increasing complication rates with currently available technology. Proton therapy or helical tomotherapy might potentially increase dose to the tumor without exceeding lung tolerance.

The complication rates were acceptable. The perioperative mortality rate was 7%, and there were few postoperative morbidities. Four percent (1/24) of patients had radiation pneumonitis in the IMRT group, whereas 13% (3/24) of patients in the 3D-CRT group experienced radiation pneumonitis. Four percent (1/24) of patients in the latter group experienced pericarditis, and 4% had esophageal stricture. It is our clinical impression that IMRT might be better at sparing normal tissue toxicity, but a more rigorous comparison should be performed.

The multimodality treatment at UCSF differs in some very important ways from the extensive experience at Dana Farber Cancer Institute, as reported by Sugarbaker and colleagues.[5,19] Unlike the EPP used by Sugarbaker, a radical P/D was used at UCSF. The decision to perform a lung-preserving procedure in this group of patients was not based solely on their ability to tolerate pneumonectomy but rather based on a bias that P/D is better tolerated in patients with an essentially incurable disease. The median age in our series was 69 years compared with 57 years in the Sugarbaker series, possibly contributing to an increased mortality rate. Although the number of patients to date is small, the overall results appear to be comparable with those reported by Sugarbaker and colleagues, with a median overall survival of 18.1 compared with 19 months.

Sugarbaker and colleagues[5] showed, through subset analysis, prolonged median survival of 26 months with epithelial histology. The results from our series did not show a significant difference in overall survival or progression-free interval between epithelial histology and sarcomatous-mixed histology. The small number of patients most likely contributed to the inability to detect a correlation. The higher number of IORT fields treated significantly inversely correlated with overall survival. An increased number of IORT fields reflects a greater extent of residual disease, which might account for the difference in survival.

Rusch and coworkers[22] reported their results of 61 patients treated with EPP and postoperative external beam radiation (median dose of 54 Gy). The median survival was 17 months, and the 3-year overall survival was 27%. For the 19 patients who had stage I or II disease, the median

survival was 33.8 months. For the 42 patients with stage III or IV disease, it was 10 months. The locoregional recurrence rate was only 13%, suggesting a benefit of a combined modality approach with higher doses of radiation, but distant metastases occurred in 57% of patients. Although patients with mesothelioma are commonly believed to die of local recurrences, this study illustrates the need for systemic therapy. In our series 19% of patients had distant recurrence, also demonstrating the potential of mesothelioma for distant metastasis.

The preliminary results of this experience are disappointing when analyzed for long-term survival and recurrence. The small size of the series, older median age, mixed histologic types, and proportion of R1 resections could account for part of the discrepancy between this experience and those reported in the literature. In addition, although a majority of patients had nodal sampling, pathologic staging not based on node dissection might not be precise. Inadvertent understaging might account for survival differences.

In summary, traditional single-modality treatment for DMPM has been disappointing. P/D can offer complete resections (R0) in a majority of cases, even in the setting of bulky disease. Combined with adjuvant chemoradiation, this therapeutic scheme might offer an alternative to those who cannot tolerate EPP as part of a combined modality approach. In addition, we intend to use our experience with P/D as a platform for developing adjuvant combined modality therapies with novel biologic agents. We hope that effective cytoreduction can be achieved with lung preservation, acceptable morbidities, and a high percentage of complete resection, while allowing targeted therapies to control microscopic residual disease and systemic micrometastasis. The use of P/D in a multimodality setting with improvements in biologics, cytotoxics, and radiation techniques might ultimately enhance long-term survival.

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