Extrapleural pneumonectomy for malignant pleural mesothelioma: Outcomes of treatment and prognostic factors

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Objective: This study aimed to evaluate the perioperative and long-term outcomes associated with extrapleural pneumonectomy for patients with malignant pleural mesothelioma.

Methods: From October 1994 to April 2008, 70 patients were selected for extrapleural pneumonectomy. Univariate analysis was performed using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis with entering and removing limits of *P* less than .10 and *P* greater than .05, respectively, was used. The prognostic factors included age, gender, side of disease, asbestos exposure, histology, positron emission tomography, date of surgery, neoadjuvant chemotherapy, completeness of cytoreduction, lymph node involvement, perioperative morbidity, adjuvant radiotherapy, and pemetrexed-based chemotherapy.

Results: The mean age of patients was 55 years (standard deviation = 10). Fifty-eight patients had epithelial tumors. Six patients received neoadjuvant chemotherapy, 28 patients received adjuvant radiotherapy, and 16 patients received postoperative pemetrexed-based chemotherapy. Forty-four patients had no lymph node involvement. The perioperative morbidity and mortality were 37% and 5.7%, respectively. Complications included hemothorax (n = 7), atrial fibrillation (n = 6), empyema (n = 4), bronchopulmonary fistula (n = 3), right-sided heart failure (n = 2), pneumonia (n = 1), constrictive pericarditis (n = 1), acute pulmonary edema (n = 1), small bowel herniation (n = 1), and disseminated intravascular coagulopathy (n = 1). The median survival was 20 months, with a 3-year survival of 30%. Asbestos exposure, negative lymph node involvement, and receipt of adjuvant radiation or postoperative pemetrexed-based chemotherapy were associated with improved survival on both univariate and multivariate analyses.

Conclusion: The present study supports the use of extrapleural pneumonectomy-based multimodal therapy in carefully selected patients with malignant pleural mesothelioma.

Extrapleural pneumonectomy (EPP) is en bloc resection of the disease involving the pleurae, lung, ipsilateral hemidiaphragm, and pericardium.[1-6] It has been used as a treatment option for selected patients with malignant pleural mesothelioma (MPM).[1,3,5,6] Recent evidence has suggested that EPP in conjunction with chemotherapy and radiotherapy may improve local disease control and survival, when compared with historical data.[6-9] However, the majority of patients with MPM present with extensive disease and poor performance status, precluding the possibility of undergoing an EPP.

The goal of primary surgery in treating mesothelioma is macroscopic tumor eradication to prolong survival. In contrast with pleurectomy with or without decortication, EPP provides radical cytoreduction.[10] However, the procedure has been associated with relatively higher morbidity and mortality, stressing the need for careful patient selection.[11-13] In the current literature, there is still a paucity of data on EPP for patients with MPM. On the basis of data prospectively collected in a computerized database, we performed an observational study on a cohort of 70 patients with MPM to evaluate the perioperative and long-term outcomes associated with EPP.

PATIENTS AND METHODS

Patient Selection

Between October 1994 and April 2008, 424 patients with a tissue diagnosis of MPM were treated by a thoracic surgical team led by the same surgeon (B.C.M.). Preoperative assessment included a review of all prior clinical information, physical examination, serum chemistry and hematology, chest x-ray, computed tomography of the chest, and upper abdomen and pulmonary function testing. Since the year 2000, positron emission tomography (PET) became available at our institution, The Royal Prince Alfred Hospital, Sydney, Australia. Patients with extrathoracic spread based on PET scan were considered inappropriate for EPP. The criteria for EPP were as follows: extent of disease limited to the ipsilateral hemithorax

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Abbreviations and Acronyms
EPP = extrapleural pneumonectomy
MPM = malignant pleural mesothelioma
PET = positron emission tomography

with no transdiaphragmatic, transpericardial, or extensive chest wall involvement; good performance status (World Health Organization Performance Status $\leq$ 2); normal renal and liver function test results; and adequate cardiac (ejection fraction > 50%, based on preoperative echocardiogram) and pulmonary function (forced expiratory volume in 1 second > 70% and vital capacity > 3 L) assessment. Informed consent was obtained from all patients before surgery. On the basis of the assessment described below, 70 patients (16%) were selected for EPP and are included in this study's analysis. Six patients (9%) received preoperative pemetrexed combined with cisplatin or carboplatin before EPP.

Pleurectomy/decortication was reserved for patients with insufficient cardiopulmonary reserve, advanced age, anatomic constraints, or only limited disease. In patients who were not candidates for EPP or pleurectomy/decortication, palliative pleurodesis was performed via a thoracotomy or thoracoscopic technique, and talc was instilled to cause sterile pleural inflammation and subsequent obliteration of the pleural space. Of these 424 patients, 70 patients (16%) underwent EPP, 177 (42%) underwent pleurectomy or decortication and the remaining 177 (42%) had pleurodesis or biopsy.

Operative Techniques

EPP was performed with en bloc resection of the lung, pleurae, ipsilateral hemidiaphragm, and pericardium. EPP was approached from an extended posterolateral thoracotomy incision at the entire costal surface of the lung and extending over the apex of the pleura, mobilizing mediastinal pleura down to the hilum. The main pulmonary vessels were ligated and divided separately, and the bronchus was stapled. On control of these structures, the dissection was carried anteriorly by entering the pericardium, and the resection of the pericardium and hemidiaphragm was performed en bloc with the lung and parietal pleura. Systematic mediastinal lymph node dissection was routinely performed, and the specimens were submitted for histologic examination. The pericardial and diaphragmatic defects were repaired with 2-mm polytetrafluoroethylene (Gore-Tex; WL Gore & Associates, Inc, Flagstaff, Ariz) dual mesh.

Adjuvant Therapy

Adjuvant radiotherapy after EPP was introduced in 2002 in an attempt to improve locoregional disease control.[8,9] Patients were referred to a radiation oncologist for assessment within 6 weeks of surgery. Selection criteria for radiotherapy include good performance status, adequate residual cardiopulmonary function, and satisfactory recovery from surgery. Radiotherapy would commence within 12 weeks of surgery after mediastinal shift settled and patients had recovered from surgery. In most of the patients, a 4-beam mixed photon and electron technique was used, delivering a total dose of 45 Gy in 25 daily fractions with 9 Gy boost to the entire hemithorax, ipsilateral mediastinum bed, and ipsilateral chest wall. Chemotherapy was not routinely used as an adjuvant therapy. However, in recent years some evidence suggested that pemetrexed plus cisplatin or carboplatin resulted in superior survival time.[14-16] In the present study cohort, a proportion of patients received postoperative pemetrexed combined with cisplatin or carboplatin.

Data Analysis

The chairperson of the ethics committee approved the current study and waived the need for patient consent because individual patients were not identified. Patient characteristics and clinical data were recorded in a prospective electronic database. All tissue specimens were submitted for histopathologic examination. The current International Union Against Cancer staging identifies metastases in the ipsilateral bronchopulmonary or hilar lymph nodes as N_1 and metastases in the subcarinal or ipsilateral mediastinal lymph nodes, including the ipsilateral internal thoracic artery nodes, as N_2, whereas diaphragmatic nodes are not specifically considered.[17] Patients were followed postoperatively with clinical examination and chest computed tomography scan every 3 months for the first year and every 6 months thereafter until the last time of contact or death.

In this study, overall survival was used as the primary end point, which was determined from the time of surgery. The statistical analyses of 13 potential prognostic factors were performed. These prognostic factors included age, gender,[11,18] left side versus right of disease,[11] prior asbestos exposure,[11,19] histopathologic subtype,[20] whether preoperative PET was performed, date of surgery, neoadjuvant chemotherapy, complete versus incomplete macroscopic cytoreduction,[20] presence versus absence of lymph nodes,[18,20,21] presence versus absence of perioperative morbidity, and whether postoperative radiotherapy[8] or pemetrexed-based chemotherapy regimens[14] were given. The reasons for including these variables in the data analysis are because they have been found to have significant prognostic values in other studies (as referenced above) or they may have potential clinical implications for future patient management (eg, PET, neoadjuvant chemotherapy,[22,23] perioperative morbidity, and adjuvant therapies[8]). Survival analysis included perioperative deaths. Secondary end points were perioperative morbidity and mortality. Hospital mortality was defined as any death that occurred during the same hospital admission or within 30 days after surgery. Survival analysis was performed using the Kaplan–Meier method and compared using the log-rank test. For multivariate analysis, a Cox regression (Cox proportional hazards model) was used with a forward stepwise selection of covariates and with entering and removing limits of P less than .10 and P greater than .05, respectively. Statistical analyses were performed by the intention-to-treat principle, using the Statistical Package for the Social Sciences for Windows (Version 14.5; SPSS GmbH, Munich, Germany).

Patient Characteristics

Between October 1994 and April 2008, 70 patients with MPM were judged preoperatively to be candidates for EPP. The follow-up of these 70 patients was complete, with a median follow-up of 13 months (range 0–104 months). By each 3-year interval, 3, 11, 9, 21, and 26 patients were treated during the study period. The mean age at the time of EPP was 55 years (standard deviation = 10). Fifty-five patients (79%) were male. Forty-eight patients (69%) reported to have prior asbestos exposure. Fifty-eight patients (83%) had epithelial tumors, and 12 patients (17%) had biphasic or sarcomatoid tumors. Thirty-two patients (46%) had left-sided EPP, and 38 patients (54%) had right-sided EPP. Forty-five patients (64%) had preoperative PET. Sixty-three patients (90%) had complete macroscopic cytoreduction, and the remaining 7 patients (10%) had residual macroscopic disease at the end of surgery. The incomplete resection sites included the chest wall (n = 3), superior mediastinum (n = 1), aortic arch (n = 1), pericardium (n = 1), and esophagus (n = 1). Six patients (9%) underwent neoadjuvant chemotherapy (pemetrexed combined with cisplatin or carboplatin). Postoperatively, 28 patients (40%) received adjuvant ipsilateral radiotherapy and 16 patients (23%) received pemetrexed combined with cisplatin or carboplatin. Eleven patients (16%) received more than 1 adjuvant therapy, including 1 patient who received neoadjuvant chemotherapy, adjuvant radiotherapy, and pemetrexed combination chemotherapy; 6 patients received adjuvant radiotherapy and pemetrexed combination chemotherapy; 2 patients received neoadjuvant chemotherapy and adjuvant radiotherapy; and the remaining 2 patients received neoadjuvant chemotherapy and pemetrexed combination adjuvant chemotherapy.

Forty-four patients (63%) had no lymph node involvement (N_0). Nineteen patients (27%) had 1 lymph node station involved. This included 9 patients with N_1 (6 ipsilateral bronchopulmonary and 3 hilar) and 10

patients with skip lymph node metastases, in whom N_2 nodes were positive (7 subcarinal, 2 superior mediastinal, and 1 diaphragmatic) but N_1 nodes were negative. The remaining 7 patients (10%) had more than 1 lymph node station involved (both N_1 and N_2 involved: 5 ipsilateral bronchopulmonary, 4 hilar, 7 subcarinal, 3 superior mediastinal, and 3 inferior mediastinal).

RESULTS

Morbidity and Mortality Data

Twenty-six patients (37%) experienced 1 or more perioperative complications. These adverse events included hemothorax (n = 7), atrial fibrillation (n = 6), empyema (n = 4), bronchopleural fistula (n = 3), right-sided heart failure (n = 2), aspiration pneumonia (n = 1), constrictive pericarditis (n = 1), acute post-pneumonectomy pulmonary edema (n = 1), small bowel herniation through chest wall (n = 1), and disseminated intravascular coagulopathy (n = 1). Four patients (5.7%) died perioperatively. One patient died of intrathoracic hemorrhage secondary to disseminated intravascular coagulopathy; 1 patient died of acute coronary embolus causing ventricular fibrillation; 1 patient died of post-pneumonectomy acute pulmonary edema; and 1 patient had a sudden death, the cause of which was undetermined even at postmortem.

Survival Data

The median survival was 20 months (range 0–104 months), with 1-, 2-, 3-, and 5-year survivals of 62%, 41%, 30%, and 15%, respectively (Figure 1). Twenty-six patients (37%) remained alive at the last follow-up.

Four clinicopathologic factors were found to be associated with an improved overall survival on univariate analysis: prior asbestos exposure ($P = .002$), absence of lymph node involvement ($P = .020$), adjuvant radiotherapy ($P = .001$), and postoperative pemetrexed combined with cisplatin or carboplatin ($P = .010$) (Table 1). The same 4 factors were also independently associated with an improved survival on the multivariate analysis: prior asbestos exposure ($P = .021$), absence of lymph node involvement ($P = .033$), adjuvant radiotherapy ($P = .047$), and postoperative pemetrexed and cisplatin or carboplatin ($P = .019$) (Table 2).

Age at the time of surgery ($P = .431$), gender ($P = .266$), side of disease ($P = .449$), histopathologic subtype ($P = .069$), PET scan ($P = .062$), date of surgery ($P = .234$), neoadjuvant chemotherapy ($P = .481$), macroscopic complete cytoreduction ($P = .920$), and perioperative morbidity ($P = .479$) were not significant prognostic indicators for overall survival in the present series (Table 1).

Subgroup analyses demonstrated that skip lymph nodal metastases (7 ipsilateral subcarinal, 2 superior mediastinal, and 1 diaphragmatic) were associated with a better survival when compared with other N_2 categories (median survival: 21 vs 7 months, $P = .015$), and that survival for these patients was not significantly different from that of patients with N_1 disease ($P = .468$).

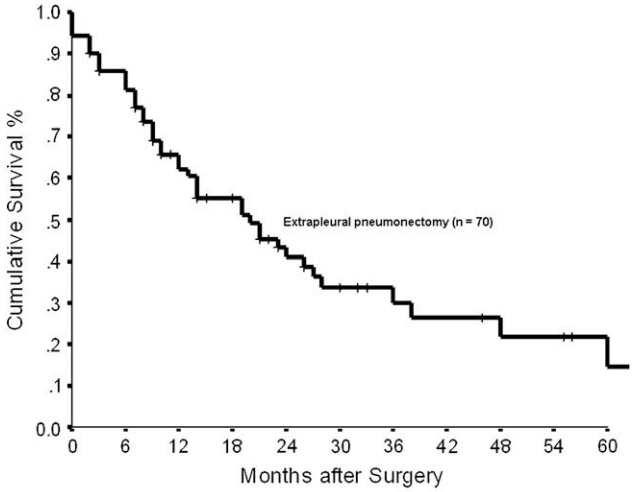

FIGURE 1. Overall survival after extrapleural pneumonectomy for MPM at the Royal Prince Alfred Hospital in Sydney, Australia (n = 70).

DISCUSSION

Despite recent advances in surgical techniques and perioperative management, EPP remains a major challenge for general thoracic surgeons. It is technically more complex than pleurectomy and decortication, with a higher risk of perioperative complications and death.[24] Although it is generally accepted that palliative pleurodesis, pleurectomy, and decortication are justified for the control of pleural effusion and relief of respiratory symptoms in patients with MPM, EPP is seldom performed in general thoracic centers. Recent series have suggested that EPP may offer some promise to patients with this debilitating disease. However, the benefits of this radical surgical approach must be evaluated in terms of the risk it presents. In the current literature, the overall mortality associated with EPP alone or in conjunction with chemotherapy or radiotherapy varies from 4% to 13%, and morbidity ranges from 20% to 60%.[2,3,11-13,24]

Early series reported relatively high morbidity and mortality results. In 1976, Butchart and colleagues[1] reported perioperative morbidity and mortality of 45% and 31%, respectively, in 29 patients who underwent EPP. In 1989, Ruffie and collaborators[3] conducted a multi-institutional registry study of 332 patients with MPM over a 20-year period. Although the study lacks the technologic advances available today, it provided a historic control against which many modern studies can be compared. Of the 23 patients who underwent EPP, the operative mortality was 13% and major perioperative morbidity was 26%.[3] Branscheid and coworkers[2] reported a perioperative mortality of 12% in 76 patients with MPM who underwent EPP. Several tertiary referral centers with a high volume of experience in EPP have reported improved perioperative outcomes through accumulated experience in recent years. Flores and colleagues[11] demonstrated a perioperative mortality of 5.3% for EPP (n = 11/208). Sugarbaker and

TABLE 1. Univariate analysis of clinicopathologic factors affecting survival

Variable	Patients n	Median survival (mo)	Survival %		*P*
			1 y	3 y	
Total	70	20	62	30	—
Age at the time of surgery	—	—	—	—	.431
≤55 y	31	21	69	67	—
>55 y	39	14	58	37	—
Gender	—	—	—	—	.266
Male	55	20	62	27	—
Female	15	27	61	41	—
Side of disease	—	—	—	—	.449
Left	32	23	59	39	—
Right	38	19	66	19	—
Prior asbestos exposure	—	—	—	—	.002
Yes	48	28	68	43	—
No	32	12	50	10	—
Histopathologic subtype	—	—	—	—	.069
Epithelial	58	23	63	36	—
Sarcomatoid/biphasic	12	14	58	0	—
PET	—	—	—	—	.062
Performed	45	26	65	43	—
Not performed	25	14	56	17	—
Time of operation	—	—	—	—	.234
Before October 2003	35	19	63	22	—
After October 2003	35	NR	62	50	—
Neoadjuvant chemotherapy	—	—	—	—	.481
Yes	6	21	100	33	—
No	64	19	59	30	—
Macroscopic complete cytoreduction	—	—	—	—	.920
Complete cytoreduction	63	21	62	30	—
Incomplete cytoreduction	7	19	53	27	—
Lymph node involvement	—	—	—	—	.020
No lymph node involvement	44	24	70	36	—
1 lymph node station involvement	19	19	58	20	—
>1 lymph node station involvement	7	7	0	0	—
Perioperative morbidity	—	—	—	—	.479
Yes	44	21	66	32	—
No	26	19	56	27	—
Adjuvant radiotherapy	—	—	—	—	.001
Performed	28	90	76	62	—
Not performed	42	14	53	17	—
Pemetrexed + cisplatin or carboplatin	—	—	—	—	.010
Performed	16	60	92	68	—
Not performed	54	14	54	16	—

PET, Positron emission tomography.

colleagues[12] reported that 11 of 328 patients died perioperatively, for an overall mortality of 3.4%. The overall minor and major morbidity rate was 60.4%.[12]

In our current study, the causes of perioperative death were different in all 4 cases. One patient died of ipsilateral intrathoracic bleeding and disseminated intravascular coagulopathy on postoperative day 7. Acute respiratory failure developed in 1 patient on postoperative day 1; the patient required endotracheal intubation and died on postoperative day 2 of acute coronary embolus causing fatal ventricular fibrillatory arrest. Acute pulmonary edema developed in 1 patient on postoperative day 2; despite urgent reintubation, reopening thoracotomy, further patching of pericardium, and establishment of extracorporeal membrane oxygenation, the patient died. The cause of death for the fourth patient was probably sepsis, but postmortem autopsy examination was inconclusive. A perioperative mortality rate of 5.7% and an overall morbidity rate of 37% seem to be within the acceptable range.

The survival of patients with MPM with best supportive care or nonsurgical therapy is variable. A recent multicenter randomized trial demonstrated a median survival of 7.6

TABLE 2. Multivariate analysis of prognostic factors for overall survival after extrapleural pneumonectomy for malignant pleural mesothelioma

	Multivariate analysis		
Prognostic factor	**HR**	**95% CI**	***P***
Prior asbestos exposure	5.330	0.204–0.878	.021
Lymph node involvement	–	–	.033
No vs 1 lymph node station	0.598	0.645–2.750	.439
No vs > 1 lymph node stations	7.985	1.634–15.088	.005
Adjuvant radiotherapy	3.954	0.204–0.989	.047
Pemetrexed chemotherapy	5.497	0.153–0.846	.019

HR, Hazard ratio; *CI,* confidence interval.

months in the active symptom control without chemotherapy group compared with 8.5 months in the group with chemotherapy.[25] To evaluate the role of EPP, it is necessary to investigate long-term survival in addition to perioperative safety. In this study, the median survival was 20 months, with a 3-year survival of 30%. These results support the benefit of EPP in selected patients with MPM. Four clinicopathologic factors were found to be significant for overall survival in multivariate analysis: prior asbestos exposure, absence of lymph node involvement, adjuvant radiotherapy, and postoperative pemetrexed combined with cisplatin or carboplatin.

The lymphatic drainage from the visceral pleura generally follows the ipsilateral bronchopulmonary or hilar nodes to the subcarinal or mediastinal lymph nodes.[17,21] The drainage pattern of the parietal pleura may not flow to the bronchopulmonary or hilar nodes but may pass through those along the internal thoracic artery or diaphragm to the subcarinal or mediastinal lymph node stations.[17,21] Skip metastases, where N_2 nodes are involved but N_1 nodes are spared, have not been characterized in MPM as they have in non–small cell lung cancer, in which they might correlate with a better prognosis than other N_2 categories.[26] The current International Union Against Cancer staging identifies the subcarinal or ipsilateral mediastinal lymph nodes, including internal thoracic artery nodes, as N_2.[17] It has been hypothesized that some N_2 nodes are involved earlier or more frequently in MPM, because the tumor arises in the parietal pleura and their involvement may not confer a poorer outcome.[17] However, because of the limited numbers of patients with N_1 disease alone or skip lymph nodal metastases in published studies, a statistical difference between the 2 groups has not been demonstrated.[21,27] In the present study, the subgroup analyses demonstrated that skip metastases were associated with better survival compared with other N_2 categories and that the survival for patients with skip metastases was similar to that of patients with N_1 disease. Although this finding is significant, its interpretation is limited by the small number of cases and subjectivity in lymph node evaluation by different pathologists. It is possible that some of the patients classified as having skip node metastases were inaccurately staged, that is, there were positive N_1 nodes that were missed or the diagnosis of N_2 pathology represented a false positive. The latter would falsely elevate the reported survival of patients with reported N_2 skip metastases. Nevertheless, all patients in the present study were surgically managed in a uniform manner and had systematic lymph node dissection, which provides meaningful information about the patterns of lymph node spread. These observations on the differential influence of skip metastases suggest that the potential implications of N_1 versus N_2 metastases in MPM should be carefully examined in future confirmatory multicenter studies.

Clear resection margins are difficult to obtain in EPP, and this may contribute to the locoregional treatment failure.[5] Recognizing that surgery alone may not provide adequate local disease control has led to the development of multimodality approaches involving surgery followed by chemotherapy or radiotherapy.[7-9] A direct comparison of the multimodality therapy with other treatment approaches has not yet been published in the literature. Rusch and colleagues[8] demonstrated that adjuvant radiation, administered to the entire ipsilateral hemithorax at a high total dose after EPP, is feasible with acceptable toxicity and that this treatment regimen is associated with a low risk of local recurrence. The overall median survival for their entire group of 61 patients was 17 months with a 3-year survival of 27%.[8] On the basis of the encouraging results from this study, adjuvant radiotherapy after EPP was introduced in 2002 at our institution, The Royal Prince Alfred Hospital, Sydney, Australia. Patients who had a good performance status, an adequate residual cardiopulmonary function, and a satisfactory recovery from surgery were considered for adjuvant radiotherapy. The present study demonstrated that adjuvant radiotherapy was independently associated with an improved survival. However, given that postoperative adjuvant therapy was only used after 2002, the superior survival outcome may also be associated with improved surgical technique or better case selection over the years.

Until recently, chemotherapy has not been commonly accepted as standard treatment for MPM. Vogelzang and colleagues[14] reported the largest trial in patients with unresectable MPM and demonstrated that combination chemotherapy (pemetrexed plus cisplatin) achieved an improved survival, time to progression, and response rates compared with cisplatin alone (median survival time 12.1 vs 9.3 months; log-rank $P = .020$; hazard ratio 0.77). Carboplatin, a platinum analog that is better tolerated and easier to administer, produced similar response rates in a few phase II studies.[15] In recent years, our patients with MPM also received pemetrexed plus cisplatin or carboplatin after EPP. The combination chemotherapy was also independently associated with an improved survival on the multivariate analysis.

Many studies have demonstrated that patients with epithelial histologic subtype have an improved survival compared

with patients with non-epithelial tumors. This survival difference was not demonstrated in our current report. This may be partly due to the small numbers of patients with sarcomatoid and biphasic tumors in our series. The histologic subtype alone was not a patient selection criterion. However, because patients with non-epithelial tumors are generally more likely to have extensive disease, they are more likely not to be candidates for EPP.

The main limitation of the present study is that the data were nonrandomized; thus, unknown confounders may exist that influenced the outcome. In addition, the inherent presence of selection bias and the timing factor may account for the apparent improved survival in patients who received adjuvant radiotherapy and combination chemotherapy. It is possible that the improved survival in the present study compared with historic controls reflects a ''lead-time bias,'' where patients underwent surgery earlier in their natural course of disease as a result of early diagnosis and prompt referral. This might be related to modern diagnostic technologies and increased awareness of surgical treatment options for MPM in the recent years. Nevertheless, these results should encourage early diagnosis and treatment for MPM. Although multivariate analysis has helped to identify 4 prognostic factors, the true significance of each factor is difficult to assess when interrelated factors are entered into the analysis, and one must bear in mind the limitation of this methodology when interpreting the results. Over the years there has been an evolution of treatment strategies, which included addition of adjuvant radiotherapy, pemetrexed combination chemotherapy, familiarity with surgical procedures, and better imaging modalities. All of these factors may have contributed to the improvement in survival in this study compared with historic controls. Prospective studies are needed to evaluate the role of adjuvant therapy in the treatment of MPM.

CONCLUSIONS

The present study demonstrated a perioperative mortality of 5.7% and an overall morbidity of 37% in 70 patients with MPM who underwent EPP at a high-volume center. The median survival time was 20 months, with a 3-year survival of 30%. These results support the use of EPP in carefully selected patients with MPM. Negative lymph node involvement and adjuvant radiotherapy or combination chemotherapy were associated with an improved survival. Although this preliminary information is encouraging, the potential benefit of various types of adjuvant therapy should be systematically explored in prospective clinical trials. The main value of this experience is to provide a benchmark against which the results of clinical trials can be judged.

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