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Extrapleural Pneumonectomy in the Treatment of Epithelioid Malignant Pleural Mesothelioma:

Novel Prognostic Implications of Combined N1 and N2 Nodal Involvement Based on Experience in 529 Patients

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Abstract

Objective—We review our 24-year experience with extrapleural pneumonectomy (EPP) in the treatment of epithelioid malignant pleural mesothelioma (MPM).

Background—Recent publications, particularly the MARS (Mesothelioma and Radical Surgery) feasibility study by Treasure et al, have questioned the safety and efficacy of EPP for MPM.

Methods—An institutional review board–approved, prospective, single-center database was retrospectively reviewed. Descriptive statistics and Kaplan-Meier analysis of overall survival are reported.

Results—From 1988 to 2011, a total of 529 patients with epithelioid MPM underwent complete resection by EPP as part of a multimodality strategy. Among these, 131 (25%) were women, and the median age was 59 (range, 17–79) years. Median postoperative hospital stay was 10 (range, 1–101) days. Twenty-six patients (5%) experienced 30-day or in-hospital mortality. Median overall survival was 18 months, with 1-, 3-, 5-, and 10-year survival rates of 67%, 28%, 14%, and 4%, respectively. Outcome by pathologic lymph node status (N, median overall survival) was N0: 224, 26 months; N1: 118, 17 months; N2: 181, 13 months; N3: 5, 7 months; Nx: 1, not evaluable.

Conclusions—EPP has evolved as an effective method for macroscopic complete resection. This study confirms that lymph node status is significantly correlated with overall survival in patients with epithelioid MPM undergoing EPP and suggests that those with simultaneous involvement of N1 and N2 stations are at increased risk. This observation underscores the need for thorough staging of both N1 and N2 stations and has implications for revision of MPM staging criteria.

Keywords

epithelioid mesothelioma; extrapleural pneumonectomy; macroscopic complete resection; malignant pleural mesothelioma; multimodality therapy

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Malignant pleural mesothelioma (MPM) is a rare, usually fatal, malignancy of the pleura associated in most cases with identifiable prior exposure to asbestos. The tumor most commonly arises within the parietal pleura. Early in its course it spreads locally to the ipsilateral visceral pleura, lung, chest wall, diaphragm, pericardium, and mediastinum. Most patients are not candidates for surgical resection as a result of having clinically advanced disease at presentation, advanced age, or comorbidity. Management options for such patients are palliative in nature, with median survival of approximately 7 to 12 months.^{1,2}

For selected patients with disease confined to the ipsilateral hemithorax, however, surgical resection, combined with systemic or intracavitary chemotherapy, radiation therapy, and/or other local modalities, has been offered with reports of more optimistic outcomes. The operative procedures most commonly used in multimodal approaches include the following: extrapleural pneumonectomy (EPP), involving en bloc resection of the lung, pericardium, diaphragm, visceral, and parietal pleura; pleurectomy/decortication (P/D), involving resection of the visceral and parietal pleurae leaving the lung, pericardium, and diaphragm intact; and extended P/D, involving pleurectomy with preservation of the lung and resection of pericardium and/or diaphragm.³ Three main histologic subtypes are distinguished—epithelioid, biphasic, and sarcomatoid.⁴ These subtypes differ significantly in terms of clinical behavior, response to therapy, and overall survival,⁵ prompting the authors to advocate for separate or annotated staging and outcome reporting⁶ and to focus this study on the epithelioid subtype.

Although retrospective reports of case series and early-phase prospective trials suggest benefit from surgery for selected patients treated at experienced centers, the relatively small number of patients presenting with resectable MPM, combined with patient and surgeon preference, has thus far precluded an adequately powered randomized trial. A randomized study would be particularly informative in the case of EPP, which involves the largest degree of resection and is usually applied to the most locally advanced among resectable tumors. The MARS (Mesothelioma and Radical Surgery) feasibility trial, however, indicated a low likelihood of randomizing an adequate number of patients to power such a trial.⁷ The authors argued that the small number of patients randomized in the feasibility study provided evidence that EPP is associated with excessive morbidity and mortality, lacks efficacy, and should be abandoned. This report provoked a counterpoint response,⁸ a published statement by International Mesothelioma Interest Group surgeons,⁹ and ongoing debate within the international MPM treatment community. It remains unlikely that an adequately powered randomized trial will be conducted. Therefore, we report our experience with EPP-based multimodality therapy in 529 patients with pathologically proved epithelioid MPM over a 24-year period, with emphasis on long-term outcome.

METHODS

The Division of Thoracic Surgery at Brigham and Women's Hospital has provided surgery-based multimodality therapy for MPM patients since 1988. Early in this experience, EPP was performed for most patients whereas P/D was considered for those who could not tolerate pneumonectomy. As the preoperative use of computed tomography became routine and a standard chemotherapy regimen was established, the use of P/D and extended P/D for

curative intent increased. Currently, P/D is preferred for tumors apparently confined to the pleura, as in this circumstance, a macroscopic complete resection (MCR) usually can be obtained. Specific indications for EPP thus have included clinical evidence of tumor invasion of lung parenchyma, interlobar fissures, diaphragm, and pericardium, all of which complicate MCR via pleurectomy.

Preoperative surgical staging has also evolved during the study period. The prognostic significance of nodal metastasis was described in 1993.¹⁰ Cervical mediastinoscopy began to be performed routinely in 2004, after cisplatin-pemetrexed was accepted as a standard chemotherapy regimen for MPM.² Since that time, patients found to have mediastinal metastases on mediastinoscopy have undergone neoadjuvant chemotherapy before reevaluation for surgery.

With institutional review board approval, a patient data registry was established in 2005. Data in this registry have been abstracted retrospectively for patients treated before 2005 and prospectively for patients treated since then. Data derived from source documents in the medical record are entered into a custom client-server relational database using on-screen forms for all patients who undergo resection. Follow-up data are obtained via outpatient clinic records and/or contact with treating physicians. Patient death is documented in the registry on the basis of notifications appearing in the electronic medical record or via the Social Security Death Index or obituaries. This data registry was examined for the current study to identify all patients who underwent EPP through December 31, 2011, with epithelioid subtype tumors identified by final pathologic analysis.

Patient data extracted from the registry included sex, age, vital status, follow-up interval, and length of hospitalization after EPP. Tumor parameters included laterality and pathologic involvement with lung parenchyma, interlobar fissures, diaphragm, and regional lymph nodes. Staging parameters included cervical mediastinoscopy and tissue biopsy. Length of hospital stay was calculated as the interval from the date of surgery to the date of discharge. Overall survival (OS) was calculated as the interval from the date of surgery to the date of death or most recent contact.

Descriptive statistics, Kaplan-Meier survival functions, log-rank comparisons, and Cox proportional hazards modeling were applied to characterize the patient and tumor characteristics in relation to the OS for this cohort. For analysis of lymph node status, indicator variables were created using N0 as reference (hazard ratio = 1.0). Statview software (version 4.5; Abacus Concepts, Piscataway, NJ) was used for all calculations and plots. Two-sided *P* values less than 0.05 were considered significant.

RESULTS

Between 1988 and 2011, a total of 1258 patients recorded in the registry underwent surgery for MPM, of which 832 were EPP and the remainder were P/D, extended P/D, or partial pleurectomy. Among patients undergoing EPP, 529 were found upon final pathologic examination to have epithelioid subtype tumors, and these constitute the current cohort. Two hundred eighty-one patients (53%) underwent right-sided EPP. One hundred thirty-one

patients (25%) were women. The median age was 59 (range, 17–79) years. Among these patients, 469 (89%) are known to have died, 22 (4%) were lost to follow-up, and 38 (7%) are alive in active follow-up. The median length of hospital stay was 10 days, with a range of 1 to 101 days. Length of hospital stay above or below the median was not associated with OS duration ($P = 0.1263$). Twenty-six patients (5%) died within 30 days of the procedure or during their postoperative hospitalization. The 90-day mortality rate was 8% (44/529 patients).

Five hundred two patients (95%) had a pleural biopsy before EPP that was diagnostic of MPM. Of these, 485 (97%) were concordant with the final diagnosis of epithelioid MPM and 17 (3%) were called biphasic. The remaining 27 patients had MPM diagnosed on cytology without determination of subtype and/or had a nondiagnostic tissue biopsy. Cervical mediastinoscopy was performed for 196 patients (37%), with nodal metastasis detected in 27 patients (14%). Seventy-one patients (13%) underwent induction chemotherapy before resection, and 218 patients (55%) underwent hyperthermic intraoperative intracavitary chemotherapy.

Upon pathological examination, tumor invasion of lung parenchyma was documented in 311 cases (59%), of interlobar fissures in 426 cases (81%), of pericardium in 314 cases (59%), and/or of diaphragm in 334 cases (63%). American Joint Commission on Cancer (AJCC) staging information is provided in Table 1. Lymph node status was N0 for 43% of patients, N1 for 22% of patients, N2 for 34% of patients, N3 for 1% of patients, and Nx for 1 patient. In addition to maximal efforts to stage N2 disease, N1 nodes were removed and analyzed in 525 patients (99%) as part of a standardized pathologic protocol for EPP specimens. One hundred thirty-six patients (26%) with N2 involvement also had N1 nodal involvement, and 45 (9%) had N2-only involvement. Stage distribution was as follows: stage I, 3%; stage II, 10%; stage III, 65%; and stage IV, 22%. Two patients could not be staged as a result of no tumor being found (pT0) and unknown lymph node status (Nx), respectively.

Median OS for the entire cohort was 18 months (Fig. 1). Table 2 depicts the univariate relationship of OS to patient factors. Age and sex were significantly prognostic, whereas tumor laterality and hospital length of stay were not.

Patient OS was correlated with pathologic AJCC tumor stage (Fig. 2). Lymph node status was prognostic, with increasing N classification level associated with decreasing median OS and increasing hazard for all-cause death (Fig. 2A). When N2 cases were separated into 2 subgroups, representing those with simultaneous N1 metastases and those without, it was further revealed that patients with N2-only or N1-only metastasis had similar, more favorable survival functions than patients with simultaneous N2 and N1 metastases (Fig. 2B).

DISCUSSION

This retrospective study describes the long-term outcome of a large cohort of patients with epithelioid MPM who underwent EPP. The procedure was generally well-tolerated, with most patients requiring 1 to 2 weeks in the hospital postoperatively. Most perioperative

complications were manageable or self-limiting such that length of stay extending beyond the median 10 days was not associated with reduced overall survival duration. Operative mortality was 5%, which is reasonable in this elderly, often comorbid, cohort comprising 87% stage III and IV disease. These findings support EPP as a safe and effective component of an evolving multimodality paradigm for MPM confined to one hemithorax.

The decision as to the appropriate procedure for an individual patient with apparently resectable MPM at our institution is made with consideration of disease distribution and patient fitness. MCR, whether by EPP or P/D, is part of a 2-step therapeutic strategy based on surgical removal of macroscopic tumor, followed by adjuvant local and systemic treatment modalities to control micrometastatic disease. Generally, P/D is preferred for tumors apparently confined to the pleura, as it affords an MCR while sparing the lung.¹¹ Our specific indications for EPP thus have included clinical evidence of tumor invasion of lung parenchyma, interlobar fissures, diaphragm, and pericardium, which complicate MCR via pleurectomy. Extended P/D or partial pleurectomy (which leaves macroscopic tumor unresected) is sometimes applied in patients who would otherwise require EPP for MCR but lack fitness to tolerate pneumonectomy.

This study reemphasizes the well-established prognostic role of lymph node status in epithelioid MPM.^{6,10,12} There is evidence that its prognostic impact is relatively less pronounced for patients with biphasic subtype tumors¹³ and that lymph node metastasis is only rarely associated with sarcomatoid subtype tumors (unpublished observations). Unlike non-small cell lung cancer, N2 metastasis in MPM may develop independently of N1 involvement in approximately 40% of cases.^{14–16} Nodal classification for non-small cell lung cancer staging is based on the pattern of pulmonary lymphatic drainage, whereas for MPM, direct metastasis to N2 stations, bypassing N1 nodes, is possible via drainage from the diaphragmatic pleura directly to the mediastinal lymphatic chain.¹⁷ It is unlikely that the observation of N2 without associated N1 resulted from incomplete sampling of N1, because meticulous dissection with N1 along with sampling and microscopic examination of nodes was accomplished in 99% of cases.

The current edition of the staging system does not distinguish between N1 and N2 metastasis in determining stage. The observations in the current study, namely, that increasing N classification level is associated with a progressively worse prognosis and simultaneous involvement of N1 and N2 lymph node stations portends worse prognosis than either N1 or N2 involvement alone, should be of interest as the AJCC staging system is revised.

These findings also reinforce the point that preoperative assessment of lymph node status should be helpful in selecting patients for appropriate therapy. Cervical mediastinoscopy began to be performed routinely in our program in 2004, with the advent of an available standard neoadjuvant chemotherapy regimen. Patients with mediastinal metastases undergo neoadjuvant chemotherapy before reevaluation for surgery. The sensitivity of this procedure, alone, for determining nodal status is low. However, given the inaccessibility of relevant nodal stations, it is reasonable to consider whether endoscopic ultrasonography,

endobronchial ultrasonography, thoracoscopy, or other procedures should be routinely performed as part of a surgical staging strategy.^{18,19}

The limitations of this study include those biases common to all retrospective, single-institution reviews. Furthermore, the patients have been treated in a multimodal fashion using strategies and regimens that have evolved over a 24-year time span. In addition, patients completed their treatment regimens to varying degrees. These short-comings are balanced somewhat by the completeness of the data set, the prospective nature of much of the data, and the size of the cohort in this rare disease. The exclusive focus on the epithelioid subtype also mitigates some of the interpretive issues that plague many studies of outcome in MPM.

CONCLUSIONS

This study supports the safety and feasibility of a 2-step approach to treatment: EPP with MCR, followed by eradication of micrometastatic disease by adjunctive local and systemic therapy. Also highlighted is the importance of thorough staging of both the N1 and N2 stations. Combined involvement of N1 and N2 has a worse prognosis than involvement of N2 or N1 stations separately. This novel finding has implications for the revision of the MPM staging criteria. The goal of future work should be better patient selection and more effective agents for controlling micrometastatic disease.

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FIGURE 1.

Kaplan-Meier estimate of overall survival function for the entire cohort of 529 patients with epithelioid MPM treated with EPP.

FIGURE 2.

A, Kaplan-Meier plot depicting estimated survival functions according to AJCC nodal status. B, Analysis as in (A) but with N2 cases divided into 2 subgroups according to whether simultaneous metastasis to N1 lymph nodes was detected. CI indicates confidence interval; HR, hazard ratio; LNS, lymph node status.

TABLE 1

AJCC Stage Distribution of Cohort Patients

Classification	n	%
T0	2	<1
T1	21	4
T2	105	20
T3	290	55
T4	111	21
N0	226	43
N1	116	22
N2	181	34
N3	5	1
Nx	1	<1
Stage I	14	3
Stage II	55	10
Stage III	343	65
Stage IV	115	22

TABLE 2

Univariate Analysis of Association of OS to Patient Factors

Factor	n	Median OS	<i>P</i>
Sex			
Female	131	28 mo	0.0005
Male	398	17 mo	
Laterality			
Left	248	19 mo	0.5027
Right	281	17 mo	
Age			
≤59 yr	276	20 mo	0.0009
>59 yr	253	16 mo	
Length of stay			
≤10 d	293	18 mo	0.1263
>10 d	236	17 mo	