Updated patterns of failure after multimodality therapy for malignant pleural mesothelioma

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ABSTRACT

Objective: We have previously described patterns of failure after extrapleural pneumonectomy and multimodality therapy for malignant pleural mesothelioma and sought to update our results with a larger cohort of recent patients.

Methods: A total of 169 patients underwent extrapleural pneumonectomy without preoperative chemotherapy between 2001 and 2010. Data for treatment, recurrence, and survival were determined from medical records. A thoracic radiologist reviewed postoperative computed tomography or positron emission tomography computed tomography scans to determine sites of recurrence. Time to recurrence was estimated by the Kaplan–Meier method. Rates were compared using the Fisher exact test.

Results: The median age of patients was 62 years. Histology on final pathology was epithelial for 104 patients (62%) and nonepithelial for 65 patients (38%). A total of 132 patients (78%) received heated intraoperative chemotherapy; 77 patients (45%) received adjuvant chemotherapy, and 71 patients (42%) received adjuvant radiation therapy. Most chemotherapy regimens included platinum or pemetrexed. Median radiation therapy dose was 54 Gy. Among 158 evaluable patients, a recurrence developed in 118 (75%). Median follow-up was 83 months, median time to recurrence was 13.1 months, and median survival was 15 months. Sites of first recurrence were in the ipsilateral hemithorax or mediastinum for 54% of patients, in the abdomen for 39% of patients, in the contralateral hemithorax for 28% of patients, and in other distant sites for 5% of patients. Some patients had simultaneous recurrences in multiple sites.

Conclusions: The most common site of recurrence after extrapleural pneumonectomy and planned multimodality therapy remains the ipsilateral hemithorax (including mediastinum), and true distant failure (other than the abdomen or contralateral hemithorax) remains unusual. The distribution of recurrences is strikingly similar to our prior report. (J Thorac Cardiovasc Surg 2015;149:1374-81)

Site of Failure	N	% of all Patients (n=158)	% of all Failures (n=118)	% of all Failures from 1997 report (n=49)[10]
Ipsilateral Hemithorax +/or Mediastinum (Local Failure)	85	54%	72%	67%
Abdomen	62	39%	53%	50%
Contralateral Hemithorax	45	28%	38%	33%
Distant	8	5%	7%	8%

Sites of first failure for 158 patients in current cohort compared with previous cohort.

Central Message

Most common site of failure after EPP, heated intra-operative CT, systemic CT, and RT remains the ipsilateral hemithorax.

Perspective

The most common site of recurrence after EPP and planned multimodality therapy remains the ipsilateral hemithorax and true distant failure (other than abdomen or contralateral hemithorax) remains unusual. The distribution of recurrences is strikingly similar to our previous report and highlights the need for aggressive adjunctive therapies that would be best tested on prospective multicenter trials.

See Editorial Commentary page 1382.

Malignant pleural mesothelioma (MPM) is a rare but aggressive disease with poor prognosis. Median survival ranges from 7 months with supportive care to 12 months with chemotherapy, and perhaps longer with multimodality therapy including various combinations of surgery, radiation, and chemotherapy.[1-6] There are numerous potential local and systemic treatment strategies for MPM, including extrapleural pneumonectomy (EPP), pleurectomy/decortication, hemithoracic radiation therapy (RT), intracavitary and intravenous chemotherapy, photodynamic therapy, and novel targeted therapies. The optimal treatment approaches for various clinical scenarios of

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Abbreviations and Acronyms

CHT = contralateral hemithorax
CI = confidence interval
CT = computed tomography
EPP = extrapleural pneumonectomy
EPT = electron-photon technique
HIOC = heated intraoperative chemotherapy
IHT = ipsilateral hemithorax
IMRT = intensity-modulated radiation therapy
MCR = macroscopic complete resection
MPM = malignant pleural mesothelioma
PET = positron emission tomography
RT = radiation therapy

MPM have not been determined and are the subjects of active debate.[7-9] However, it is clear that local control for disease confined to the ipsilateral hemithorax (IHT) is a major challenge, and for this reason, at Brigham and Women's Hospital and Dana-Farber Cancer Institute, we have pursued multimodality therapies including EPP for patients with localized node-negative MPM, nonsarcomatoid histology, and good performance status.

Understanding the specific patterns of failure after treatment strategies helps inform decisions regarding where to direct subsequent treatment efforts. In 1997, we reported patterns of failure for 49 patients after EPP, adjuvant chemotherapy (cyclophosphamide, doxorubicin, and cisplatin), and 2-dimensional RT.[10] We found the most common site of failure was in the IHT, followed by failures in the abdomen, contralateral hemithorax (CHT), and, less frequently, in other distant sites. Since 1999, we have added heated intraoperative chemotherapy (HIOC) to our regimen in an attempt to augment local and abdominal control.[11-13] In addition, the introduction of pemetrexed has established for the first time a standard-of-care regimen for intravenous chemotherapy.[2] Another change is the routine availability of computed tomography (CT) scans for preoperative staging and post-treatment surveillance, which has improved both patient selection for surgery and detection of recurrent disease. Our practice also has incorporated specialist radiographic review. In the current analysis, we evaluate a separate and larger cohort of patients treated with intended multimodality therapy in the HIOC and pemetrexed era (between 2001 and 2010) to determine to what degree the patterns of failure have been affected by the evolution of MPM management since our prior analysis. Our group has recently described perioperative morbidity and mortality and overall survival for patients with epithelial MPM treated with EPP since 1988.[14] Although some of the patients in the current cohort were included in the former report, the current report describes different outcomes, namely, patterns of failure for patients treated in the modern era, and is the first from Brigham and Women's Hospital and Dana-Farber Cancer Institute to describe recurrence patterns since 1997.

MATERIALS AND METHODS

A total of 447 patients who underwent EPP for MPM between 2001 and 2010 were identified from the Brigham and Women's Hospital International Mesothelioma Program Patient Data Registry. Unlike many institutions that use treatment strategies offering all patients neoadjuvant chemotherapy before resection, our strategy has been to treat eligible patients with initial surgery except in cases of mediastinoscopy-proven nodal involvement. For this reason, we have excluded patients treated with initial chemotherapy from the current analysis because they comprise a distinct cohort with poorer prognosis because of advanced stage at presentation. With institutional review board approval, records were reviewed to identify eligible patients who underwent macroscopic complete resection (MCR) by EPP at Brigham and Women's Hospital, who did not receive preoperative chemotherapy, and for whom a preoperative chest CT scan was available. A total of 169 patients met these criteria and constitute the study cohort.

After our prior experience with trimodality therapy, the intention-to-treat strategy during this study era was EPP with HIOC and subsequent evaluation for adjuvant chemotherapy and RT. Adjuvant chemotherapy or RT was recommended at the discretion of the treating oncologists and based on factors such as patient performance status, relative concerns of potential cumulative toxicity, and patient choice. EPP involved MCR achieved by en bloc resection of the lung, parietal pleura, ipsilateral pericardium, and ipsilateral diaphragm. Limited resection was also performed for previous biopsy, chest tube sites, or areas of localized gross tumor. Further details of the EPP technique have been reported.[15] HIOC entailed intraoperative instillation into the ipsilateral chest and abdomen of heated cisplatin with or without gemcitabine. HIOC was delivered on 1 of 2 treatment protocols active during the study time period or off protocol using protocol-established safe and effective dose and administration parameters. These parameters included MCR followed by cisplatin 175 to 225 mg/m^2 for a 1-hour lavage at 42°C with sodium thiosulfate rescue and with or without amifostine protection.[12,13] Reasons that some patients did not receive HIOC included ineligibility related to renal function, complete blood count or other factors, lack of an available spot on protocol because of a waiting period, and patient refusal. Adjuvant therapy was initiated 6 to 12 weeks postoperatively. Systemic chemotherapy agents typically included cisplatin, pemetrexed, or both given every 3 weeks. Adjuvant RT to the hemithorax was delivered using previously described techniques, including a matched electron-photon technique (EPT) during the earlier years of the study period and intensity-modulated RT (IMRT) during the later years.[16,17] Some patients treated at outside institutions received other 3-dimensional conformal RT techniques. Follow-up was typically a physical examination and chest CT or positron emission tomography (PET)/CT scan every 3 to 4 months for the first 3 years and every 6 months, thereafter.

Central review of all preoperative CT scans and all available postoperative studies (mostly CT scans and PET/CT scans) was performed by a dedicated thoracic radiologist (R.R.G.) to determine sites of recurrence. All sites of first recurrence were recorded and categorized as involving the IHT or mediastinum (local), CHT, abdomen, or other distant sites. Recurrence was scored as present if detected on imaging or physical examination. Biopsy or cytology confirmation was performed for many cases, but was not required in an effort to avoid under-reporting recurrences.

Recurrence-free interval was calculated as the time from surgery to first radiographic recurrence or biopsy determination of recurrence, with censoring on the date of the most recent study if recurrence was not demonstrated or the patient was subsequently lost to follow-up, or on the date of death if death from another cause (other than mesothelioma) was documented. Local recurrence-free survival was calculated as the time from surgery to the time of local recurrence, with censoring at the time