Trimodality Treatment of Malignant Pleural Mesothelioma

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Introduction: Multimodality treatment has achieved significant success in local control and treatment of early-stage malignant pleural mesothelioma patients. However, its favorable effect on survival is questionable.

Methods: We have instituted a trimodality treatment protocol consisting of extrapleural pneumonectomy, adjuvant high-dose (54 Gy) hemithoracic irradiation, and platin-based chemotherapy in a multi-institutional setting. Preoperative pulmonary function tests, echocardiogram, chest computed tomography, and magnetic resonance imaging scans were performed in all patients. Twenty patients have been treated with this protocol during 2003–2007. Seventeen had a history of environmental asbestos/erionite exposure. Clinical stages were T1-3N0-2.

Results: Median age was 56 (41–70, 8 female). There was one postoperative mortality (% 5) due to ARDS. Morbidity occurred in 11 patients (% 55). Histology was epithelial in 17, mixed in 2, and sarcomatoid in 1. Sixteen patients underwent extrapleural pneumonectomy. Microscopic margin positivity was present in 14 patients with macroscopic complete resection. Twelve patients completed all three treatments. Median follow-up was 16 months (1–43). Overall median survival was 17 months (24% at 2 years). Eight patients had extrapleural lymph node involvement (internal mammary [$n = 3$], subcarinal [$n = 2$], pulmonary ligament [$n = 1$], diaphragmatic [$n = 1$], subaortic [$n = 1$]). There was better survival in patients without lymph node metastasis (24 versus 13 months median survival, $p = 0.052$). Currently, 7 patients are alive, 6 without recurrence, and 2 patients at 40 and 45 months.

Conclusions: Trimodality treatment in malignant pleural mesothelioma seems to prolong survival in patients without lymph node metastasis. Novel techniques are needed for preoperative assessment of extrapleural lymph nodes.

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/08/0305-0499

Key Words: Malignant pleural mesothelioma, Extrapleural pneumonectomy, High-dose hemithoracic irradiation, Adjuvant chemotherapy.

(*J Thorac Oncol.* 2008;3: 499–504)

Optimal treatment for malignant pleural mesothelioma (MPM) is still under investigation. Several treatment strategies have been used with very limited success. Recent studies have shown that some patients benefit from multimodality treatment including aggressive surgery, radiation, and chemotherapy.[1–3] The multimodality treatment protocols have achieved a median survival of 19 to 46 months depending on the stage, histology, and completeness of the surgical resection.[1–5] In a certain subgroup of patients with epithelial histology, no lymph node involvement and complete surgical resection the results were even more favorable with occasional long-term survival.[1]

During the evolution of the treatment of MPM, successful local control of the disease with acceptable morbidity and mortality has been achieved through extrapleural pneumonectomy (EPP) and adjuvant high-dose hemithoracic irradiation.[2,3,6] The feasibility of high-dose hemithoracic irradiation following EPP was investigated in a phase II trial from Memorial Sloan Kettering Cancer center with local control rates over 90%.[2,6] In a similar study from MD Anderson Cancer center, despite successful local control, distant recurrence, especially in the abdomen, was a major problem in long term.[7]

We designed a protocol to test the feasibility of EPP, followed by adjuvant high-dose irradiation and cisplatin-based chemotherapy. This protocol was designed to achieve a low local and distant recurrence rate and thus prolong survival.

MATERIALS AND METHODS

Study Design

The study was performed during 2003–2007. All patients with a histologically proven MPM were enrolled. The protocol was approved by the faculty ethical council. The protocol schema is depicted in Figure 1.

Pretreatment Assessment

The patients underwent radiologic evaluation including chest and upper abdominal computed tomography scans, thoracic magnetic resonance imaging, and positron emission tomography scan after 2004. Brain or bone scanning was not routinely performed. Cardiac evaluation included electrocar-

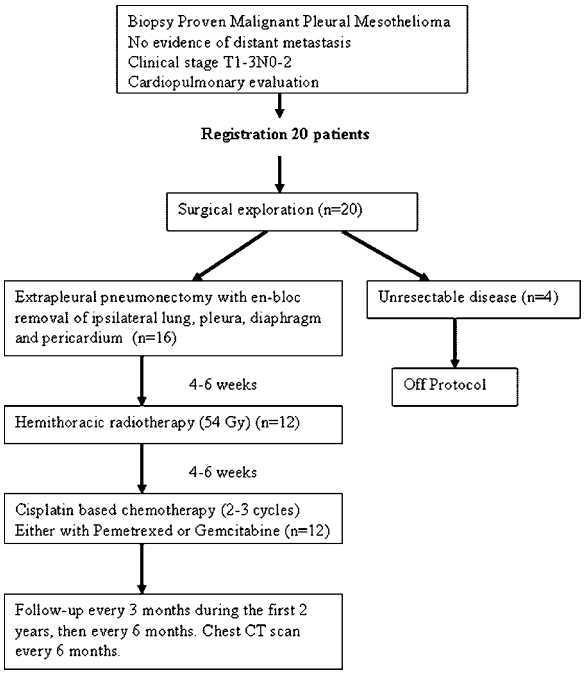

FIGURE 1. The study protocol.

diogram and echocardiography. Patients with ejection fractions less than 45% were excluded. Pulmonary evaluation included spirometry and ventilation-perfusion scintigraphy in patients with FEV_1 <60%.

Surgery

All patients underwent general anesthesia and double lumen intubation with an intention to perform EPP. A posterolateral thoracotomy was performed with removal of the 6th rib. Resectability was assessed with extrapleural dissection. EPP was performed with en-bloc removal of the pleura, ipsilateral lung, diaphragm, and pericardium in all patients without gross chest wall or intrathoracic other organ invasion. After removal of the specimen, the pleural cavity was scrubbed three times with povidone-iodine sponges and irrigated with sterile water and saline. Diaphragm was reconstructed using 2 mm PTFE or polyprolene mesh. Pericardium was reconstructed with vicryl or vicryl-polyprolene composite mesh. The chest wound was closed accordingly with a single 28 Fr chest drain. Patients were extubated in the operating room and kept in ICU typically for 2 days. The chest drain was removed 48 to 72 hours postoperatively.

Pathology Protocol

All EPP specimens were sampled at 20 different sites including costodiaphragmatic sulci, pericardium, lateral thoracic wall, apical, and mediastinal pleural margin. If all samples did not show any tumor invasion beyond surgical margins, the outcome was defined as a microscopic complete resection. Otherwise, it was accepted as a macroscopic complete resection with positive microscopic margins.

Hemithoracic Irradiation Protocol[8]

Adjuvant radiotherapy was delivered using photons by a dual energy (6 and 18-mV) linear accelerator. A minimum total dose of photons fields of 54 Gy (1.8Gy/fraction, 1 fraction/d, 5 d/wk) was delivered to the hemithorax, the thoracotomy incision, and sites of chest drains. A boost dose of 9 Gy was considered for patients who had residual disease marked by surgical clips with photon fields. The radiotherapy planning ensures the coverage of the entire ipsilateral thoracic cavity from the apex to the diaphragm, ipsilateral mediastinum, and surgical incisions and all scars. The treatment technique consisted of two opposed fields with custom blocks for each field, AP-PA, to the whole hemithorax, shielding organs at risk. The organs at risk were defined as spinal cord, kidneys, and liver (for right-sided tumors). All of the treatment plans were done with computed tomography based planning system with adequate dose volume distribution for the target volumes and organs at risk.

Adjuvant Chemotherapy

Adjuvant chemotherapy was given as cisplatin and gemcitabine in 2003–2005. The regimen was changed to cisplatin and pemetrexed since 2005. In the first regimen, cisplatin was given 75 mg/m^2/d iv on day 1, gemcitabine 1250 mg/m^2 iv on days 1 and 8. In the second regimen, cisplatin was given 75 mg/m^2 on day 1 iv, pemeterexed 500 mg/m^2 iv on day 1. Chemotherapy cycles were repeated every 21 days. The patients typically received three cycles of chemotherapy. Cisplatin was administered in 500 mL of normal saline over 2 hours (with precisplatin and postcisplatin hydration and antiemetics). To prevent nephrotoxicity, precisplatin and postcisplatin hydration and diuresis were carried out by administering 1 L of normal dextrose over 2 hours, furosemide with each liter of dextrose and 10% mannitol. Emesis was prevented with ondansetron or a combination of metoclopramide and dexamethasone. Gemcitabine was administered over 10 minutes in 100 mL dextrose/saline. In patients who were scheduled to receive pemetrexed, vitamin D and dexamethasone was administered 10 days before the cycle.

Before each cycle, the patients underwent a complete physical examination, chest radiograph, ECG, respiratory function tests, complete blood count, serum biochemistry, and urine analysis. In addition, patients were screened for side effects on 7th and 14th days of the drug administrations. The side effects were graded according to the WHO toxicity scale.[9]

Statistical Analysis

The study was designed to enroll 20 patients. Overall survival was calculated using Kaplan-Meier method. Survival differences were analyzed with log-rank test. Postoperative/in-hospital deaths were included in the survival analysis.

RESULTS

Demographics

From 2003 to 2007, 37 patients were evaluated in our clinic for multimodality treatment of mesothelioma. Twenty patients were enrolled to the protocol. Median age was 56 (41–70) Patient characteristics are depicted in Table 1. Eleven patients had a history of smoking.

TABLE 1. Patient Characteristics

Gender	
Male	12 (60)
Female	8 (40)
Exposure	
Environmental[a]	16 (80)
Other	4 (20)
Diseased side	
Right	11 (55)
Left	9 (45)
Histology	
Epithelial	17 (85)
Mixed	2 (10)
Sarcomatoid	1 (5)

All values inside parentheses indicate percentages.
[a] Three patients had erionite exposure. Others had asbestos exposure.

Surgical Results

EPP could not be performed in 4 patients. In 2 patients (one with epithelial and other with sarcomatoid MPM) tumor was found to be unresectable because of diffuse chest wall invasion. One patient was noticed to have diffuse millimetric nodular implants within the intercostal muscles. Other patient did not tolerate single lung ventilation. Both patients underwent partial pleurectomy to achieve pleurodesis. Sixteen patients underwent EPP (8 right and 8 left). There was 1 (5%) in-hospital mortality. The patient had a ruptured diaphragmatic mesh, was re-explored and subsequently developed ARDS and sepsis. Eleven (55%) patients developed complications, all in patients who underwent EPP. Six patients developed supraventricular tachycardia. Five patients were reexplored, 3 because of postoperative bleeding, 1 because of diaphragmatic rupture, and 1 because of unexplained supraventricular tachycardia. Recurrent laryngeal nerve injury ($n = 1$), bronchopleural fistula ($n = 1$), and hypoxic brain damage ($n = 1$) were among other major complications.

Pathology

The histologic subtype was epithelial in 17, sarcomatoid in 2, and mixed in 1 patient. Only 2 patients who underwent EPP were found to have microscopic complete resection. Microscopic tumor positivity was present in 14 patients at apical pleura ($n = 8$), lateral chest wall ($n = 7$), mediastinal pleura ($n = 3$), costodiaphragmatic sulci ($n = 3$), and pericardium ($n = 2$).

Radiotherapy

Out of 16 patients who received EPP, 12 patients underwent postoperative high-dose RT. Adjuvant radiation was not administered to three patients who had postoperative complications and one patient who had abdominal relapse before the initiation of radiotherapy. The median total dose given was 54 Gy (52–63 Gy). Overall treatment was well tolerated, with mild dysphagia, fatigue, loss of appetite, nausea, and vomiting without any treatment interruptions.

Chemotherapy Adverse Events

All 12 patients who completed multimodality therapy were assessable for toxicity. The toxicity of these drug combinations was mild and well-tolerated. There were no chemotherapy-related deaths. Myelosupression, which was the most frequent adverse event (12% of all cycles), was mostly mild-to-moderate, occurring mostly after the third cycle. In the beginning, most patients suffered from prolonged and delayed nausea and vomiting (74% of the patients), which affected their daily life quality. However, almost all patients with these symptoms responded well to orally administered ondansetron and the rate of nausea/vomiting decreased in the following days by the use of ondansetron intravenously or orally.

Survival and Recurrence

The overall median survival in the whole cohort ($n = 20$) was 17.2 months (Figure 2). It was 19.6 and 23.9 months in patients who underwent EPP ($n = 16$) and who completed the trimodality treatment ($n = 12$), respectively. There was no statistically significant difference ($p = 0.52$).

In eight patients, extrapleural lymph node metastasis was detected. The patients had metastasis at internal mammary ($n = 3$), subcarinal ($n = 2$), pulmonary ligament ($n = 1$), diaphragmatic and paraesophageal ($n = 1$), and subaortic ($n = 1$) lymph nodes. The median survival was 13.3 months in patients with extrapleural lymph node metastasis and 23.9 months in patients without lymph node metastasis (Figure 3). This survival difference was very close to significance ($p = 0.052$). Two patients who had mixed histology and no lymph node involvement died at 24 and 15 months because of chest wall and intrathoracic recurrence. When these two patients were excluded from the survival analysis, the median survival was not reached in patients with epithelial histology and without lymph node metastasis. Three-year survival rate was 56% ($n = 6$).

Nine patients who underwent EPP recurred. Median time to recurrence was 10 months (2–26). Five recurrences occurred

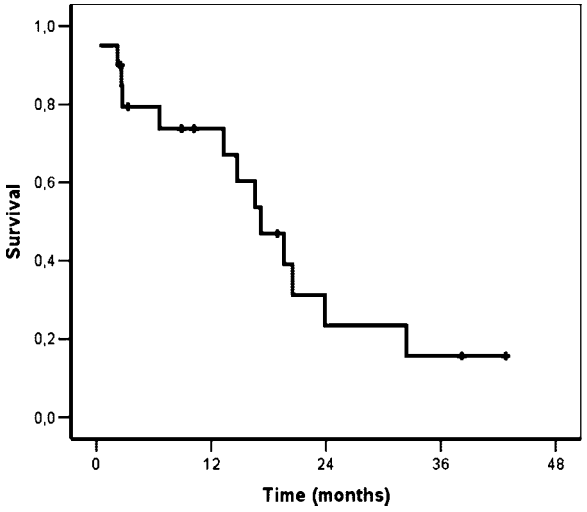

FIGURE 2. Overall survival of the 20 patients who have been included in the study. Median survival was 17.2 months.

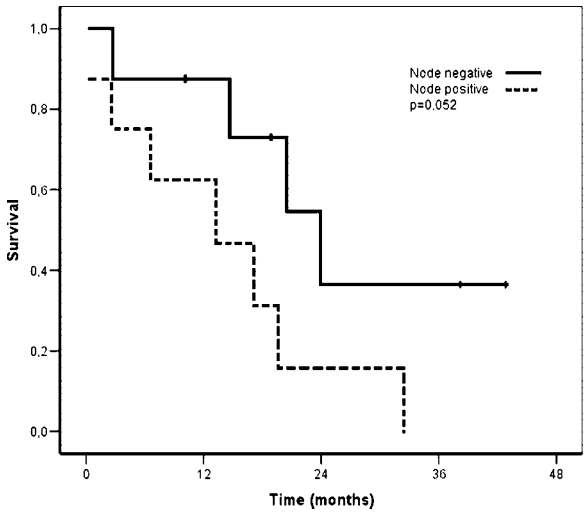

FIGURE 3. Survival curves of patients with and without extrapleural lymph node metastasis. The median survival of patients with lymph node metastasis was 13.3 months. Patients without lymph node metastasis had a median survival of 23.9 months ($p = 0.052$).

in patients with extrapleural lymph node involvement. The sites were only peritoneum ($n = 2$), peritoneum and local ($n = 1$), liver ($n = 1$), and contralateral lung ($n = 1$). Four patients recurred in patients with no lymph node involvement and 2 of these patients had mixed histology. The other two patients had local and peritoneal ($n = 1$) and solitary chest wall recurrence ($n = 1$). Chest wall recurrence occurred at the previous needle puncture site, despite high-dose hemithoracic irradiation. The lesion was excised and additional radiation was administered. He is currently alive without recurrence at 21 months.

DISCUSSION

Several modifications of multimodal treatment modalities have been investigated in the management of MPM. Reasonable success was achieved with several versions of multimodality treatment that included EPP, radiotherapy and/or chemotherapy (Table 2).[1–3,5,10–12] However, almost all of the patients with MPM eventually recur in the chest, abdomen, or elsewhere. Prophylactic radiation is recommended to puncture or incision sites in all of the MPM patients.[13]

Aggressive surgery and radiation combination has proved to be successful in local control of MPM.[2,3,6,8,14] Especially after removal of the lung with EPP, higher doses of radiation can be administered to the hemithorax without any remaining lung tissue. In a study from Memorial Sloan Kettering Cancer center, local recurrence rate following EPP and high-dose hemithoracic irradiation was less than 10% with most of the patients dying of distant metastatic disease.[2] In the same study, median survival of 34 months was achieved in early stage patients with EPP and high-dose hemithoracic irradiation. IMRT also resulted in superb early local control (100%) of the disease at clinical target volumes of 45 to 50 Gy with boosts taken to 60 Gy.[7] In our study, 5 (31%, 5 of 16) local recurrences occurred following EPP. However, our follow up was longer (16 months, 1–44), compared with the study that instituted intensity modulated radiation treatment (9 months, 5–27). Additionally, two of the local recurrences occurred in patients with mixed histology. Our radiation protocol was identical with the Memorial Sloan Kettering Cancer center protocol.[8]

Intensification of radiation plays critical role in the multimodality treatment of malignant mesothelioma for increasing local control after EPP.[8] Delivering high doses to the hemithorax after surgery is challenging as the target volume, which is the entire hemithorax including the mediastinum and all pleural surfaces, are very close to critical organs such as liver, kidney, heart, spinal cord, and remaining lung and they could easily be affected from high-dose radiation. The use of combined photon and electron fields to deliver a total dose of 54 Gy is a convenient technique with adequate doses to these normal organs. There have been some studies looking for the benefits of more homogeneous dose distribution with IMRT after EPP to the hemithorax.[15] Although they have good local controls, the rate of pneumonitis was more than conventional or so what we call the MSKCC technique.[8] In this study, we have applied this technique with comparable local controls and toxicities.

Involvement of extrapleural lymph nodes was also shown to be a poor prognostic factor in several studies.[1,16,17] Some

TABLE 2. Survival of Patients Who Underwent Extrapleural Pneumonectomy (EPP) and Multimodality Treatment for MPM

Author	No. of Patients	Multimodality Treatment	Overall Median Survival (mo)	Median Survival in Patients without LN Metastasis (mo)
Sugarbaker et al.[1]	183	EPP + RT + CH	19	21
Rusch et al.[2]	62	EPP + HDRT	NS	34
Flores et al.[5]	208	EPP + RT + CH	20	NS
Stewart et al.[9]	132	EPP + RT + CH	17	NS
Weder et al.[10]	45	CH + EPP + RT	23	NS
Rea et al.[3]	17	CH + EPP + HDRT	26	NS
de Perrot et al.[11]	50	EPP + RT	11	29
Batirel et al.[a]	16	EPP + HDRT + CH	20	24

MPM, malignant pleural mesothelioma; LN, lymph node; CH, chemotherapy; RT, radiotherapy; NS, not stated; HDRT, high-dose radiotherapy.
[a] Current study.

centers advocate routine cervical mediastinoscopy in the preoperative evaluation of MPM.[18] However, in our patients, metastatic lymph nodes were at inaccessible stations in more than half of the patients (5 of 8). Our finding was observed by other researchers, as 49% of mediastinal lymph nodes were inaccessible with cervical mediastinoscopy in a study from Leicester[17] and similar results were found in the Toronto study.[12] Two of our 3 patients with internal mammary lymph node metastasis recurred in the peritoneum and abdominal wall, which may suggest a common lymphatic drainage and spread to the anterior abdominal wall and peritoneum other than direct peritoneal seeding during surgery. All of our patients with internal mammary lymph node metastasis were from the famous Karain village in Central Anatolia and MPM were due to erionite exposure. Overall, five of our patients recurred in the abdomen and it is an important issue in the long-term survival of these patients.[18]

Our study was a phase II protocol to test the applicability of this treatment protocol. Our relatively long follow-up also allows us to make conclusions regarding the impact of the protocol to overall survival. Our survival figure of 23.9 months in patients who completed trimodality treatment is concordant with the literature data. The outcome in patients (56% 3-year survival) without lymph node metastasis is highly supportive of a multimodality approach as the standard treatment in this subgroup of patients. Additionally, the benefit of adjuvant chemotherapy seems to be in patients with extrapleural lymph node metastasis. Our survival rate of 13.3 months (1–32) in this patient group seems to be longer than that is reported in the literature (9 months).[1,19]

Currently, we perform PET scans to all of our patients to assess extrapleural lymph node metastasis. Unfortunately, there is not enough data regarding the accuracy of PET for this task and it failed to correctly identify extrapleural lymph node metastasis in the initial studies.[20,21] All of the invasive mediastinal staging procedures should be performed, if there is any suspicion of lymph node involvement. Neoadjuvant chemotherapy can be considered as a treatment option if there are any positive extrapleural lymph nodes.[6,11,22] The median survivals are promising in Weder (23 months) and Flores (34 months) studies following EPP after neoadjuvant chemotherapy.[6,11]

There are several obstacles in performing our protocol, which is typical of such protocols. First, the treatment is very difficult for the patient and it usually takes about 4 to 6 months to complete the trimodality regimen if the postoperative course is uneventful. In our series, 75% (12 of 16) of patients who underwent EPP could complete the trimodality protocol. Of the 4 patients who could not complete the protocol, 3 patients had postoperative complications and 1 patient with multiple metastatic lymph nodes and aggressive histology (diffuse intratumoral vascular and lymphatic invasion) recurring at 3 months in the abdomen. Second, the chemotherapy regimens are not standard. The typical regimens were three cycles of pemetrexed-cisplatin or gemcitabine-cisplatin. Most of the patients received their treatments at their home towns.

In conclusion, our study shows that trimodality treatment consisting of aggressive surgery and adjuvant high-dose irradiation and chemotherapy can achieve significantly long survival times in patients without extrapleural lymph node involvement. Although the number of patients treated with this protocol is limited, this is a prospective patient series that includes patients treated with relatively newer chemotherapeutic agents. Our survival results are similar to other versions of multimodality treatment options. It is well tolerated by the patients (75% completion in patients who underwent EPP) and local and distant recurrence rates are low. However, the benefit of this treatment in patients with extrapleural lymph node involvement is questionable. Better extrapleural lymph node staging methods are needed to stratify patients who will benefit most from trimodality approach.

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