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Multimodal treatment for resectable epithelial type malignant pleural mesothelioma

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Abstract

Background: Malignant pleural mesothelioma is a rare malignancy. The outcome remains poor despite complete surgical resection.

Patients and methods: Eleven patients with histologicaly proven epithelial type malignant pleural mesothelioma undergoing extrapleural pneumonectomy with systemic chemotherapy and/or radiotherapy before and after surgical resection were retrospectively reviewed.

Results: Ten out of 11 patients underwent complete surgical resection, of these 7 patients had stage I disease. Of these 7 patients, 5 are alive without any recurrence, a 2-year survival rate of 80% was observed in this group. There was no operative mortality or morbidity.

Conclusion: Extrapleural pneumonectomy with perioperative adjuvant treatment is safe and effective procedure for epithelial type malignant pleural mesothelioma.

Introduction

Malignant pleural mesothelioma (MPM) is a relatively rare entity among intrathoracic malignancies, as compared with lung cancer, although its prevalence has shown an increase in recent years [1]. Extrapleural pneumonectomy (EPP) is the surgical treatment of choice for MPM that do not extend in to the mediastinum or on to the chest wall, although its survival benefit is still not clear [2]. In a retrospective study of 189 Japanese cases [3], there were no significant differences in survival at 2-years between palliative surgery, such as decortication, and EPP (26% and 30%, respectively). EPP with adjuvant chemotherapy and/or radiotherapy has been reported to be effective against the MPM in its early stages [4,5]. Jaklitsch *et al.*, [6] advocated that EPP plus postoperative chemotherapy using paclitaxel and carboplatin with radiotherapy is effective for MPM if it's of epithelial histology, negative surgical margin, and if extrapleural lymph nodes are negative for metastasis. This study reports on resectable

Table 1: Clinical summary

Case	IMIG stage	BWH stage	Resection	Adjuvant therapy	Recurrence	Survival status/months
1 49 F	III(T3N2M0)	III	Complete	Pre CDDP/Hemithorax RTx	Pericardium	Died 22
2 63 M	III(T3N2M0)	III	Complete	Pre CDDP/Hemithorax RTx	Ipsilateral thorax	Died 30
3 61 M	III(T3N2M0)	III	Incomplete	Pre CDDP/Hemithorax RTx	Ipsilateral thorax	Died 1
4 59 F	III(T1N2M0)	III	Complete	Post CDDP/GEM/UFT	Lung	Dead 28
5 58 M	II(T2N0M0)	I	Complete	Pre CDDP/Hemithorax RTx	None	Alive 28
6 50 M	II(T2N0M0)	I	Complete	Pre CDDP/GEM/VNR	Ipsilateral thorax	Alive 35
7 55 M	II(T2N0M0)	I	Complete	Pre CDDP/GEM/VNR	Pericardium	Died 6
8 66 M	III(T3N0M0)	I	Complete	Pre CDDP/GEM/VNR	None	Alive 15
9 48 M	III(T3N0M0)	I	Complete	Post CDDP/GEM/UFT	None	Alive 32
10 57 M	I(T1N0M0)	I	Complete	Post CDDP/GEM/UFT	None	Alive 39
12 58 M	I(T1N0M0)	I	Complete	Pre CDDP/GEM/VNR	None	Alive 12

IMIG – International mesothelioma Interest group; BWH – Brigham and Women's Hospital; F – Female; M – male; Pre – Pre Operative; Post – Post operativ; CDDP – Cisplatin; RTx – Radiotherapy; GEM – gemcitabine; VNR – Vinorelbine; UFT – Uracil/tegafur

epithelial type MPM with perioperative treatment consisting of radiation and/or chemotherapy.

Patients and methods

Between 1995 and 2002, 10 patients with epithelial type MPM underwent EPP with postoperative or preoperative chemotherapy and/or radiotherapy. The clinical profiles of these patients are detailed in Table 1. The lesions were staged by computed tomographic (CT) scan using International Mesothelioma Interest Group (IMIG) classification. There were 6 stage III, 3 stage II and 1 stage I patient. A bone scan and Magnetic Resonance Imaging (MRI) of the brain were performed if metastasis was suspected. Using the Brigham and Womens Hospital (BWH) staging system of Sugarbaker *et al*. [4], after the surgical resection 6 patients were stage I, in terms of having completely resected primary tumors including chest wall invasion at the biopsy site.

A standard EPP was performed as described earlier [7]. Following a posterolateral incision, extrapleural space was entered from the 5^{th} or 6^{th} rib bed, and dissection was carried superiorly toward the apex, antero- and postero-laterally, and inferiorly toward the diaphragm. During the dissection, port site disease at the chest wall was resected *en block*. Following an antero-medial pericardiotomy, hilar vessels were resected using a mechanical stapler, followed by resection of the main bronchus. The diaphragm was divided from the peritoneum, and EPP was completed. The defects of pericardium and diaphragm were reconstructed with prosthetic patches. A complete mediastinal lymph node dissection was performed in all cases.

In a preoperative adjuvant setting, one course of concurrent chemoradiotherapy using cisplatin (CDDP) (80 mg/m^2, on days 1 and 29) with 40 Gy external beam radiotherapy to the hemithorax [5], was performed in 4 patients (Case 1, 2, 3 and 5) and 2 or 3 courses of chemotherapy using CDDP (40 mg/m^2 on days 1 and 8), gemcitabine (GEM) (800 mg/m^2, on days 1 and 8), and vinorelbine (VNR) (20 mg/m^2, on days 1 and 8) were given at intervals of 3 to 4 weeks in 4 patients (Case 6, 7, 8 and 11) (Table 1). Three patients received 2 courses of postoperative chemotherapy using CDDP (80 mg/m^2, on day 1 and 8), GEM (800 mg/m^2 on days 8 and 15) and UFT (tegafur/uracil) (400 mg/m^2 postoperative on days 1–15) with 3 to 4 weeks interval (Case 4, 9 and 10) (Table 1). One patient received 50 Gy postoperative radiation to the previous thoracic drainage site (Case 10).

Results

Postoperative course of the patients were uneventful, and no morbidity or mortality was experienced. Six patients experienced a relapse in the thorax. One patient underwent resection of the chest wall for recurrence at 12 months after EPP. Other 5 patients (Case 5, 6, 8, 9 and 11) are surviving without any disease. All the survivors had BWH stage I disease, which showed an 80%, 2-year survival. The survival in 4 patients with BWH stage II-III disease was 37% at 2-year. Postoperative chemotherapy was started 2 to 3 months after surgery, and grade 4 neutropenia was observed in all 3 cases, while grade 3 loss of appetite was observed in one. Of the 3 patients who underwent preoperative chemotherapy, a reduction in size of the tumors by 18 to 74% was seen following chemotherapy (Figure 1). Pathological examination of the resected specimens in all 3 cases showed extensive fibrosis with only a small focus of tumor cells (Figure 2). In Case 10, an exploratory thoracotomy was done for suspected recurrence, however, the intrathoracic lesion was found to be a herniated liver from the defect of the reconstructed diaphragm.

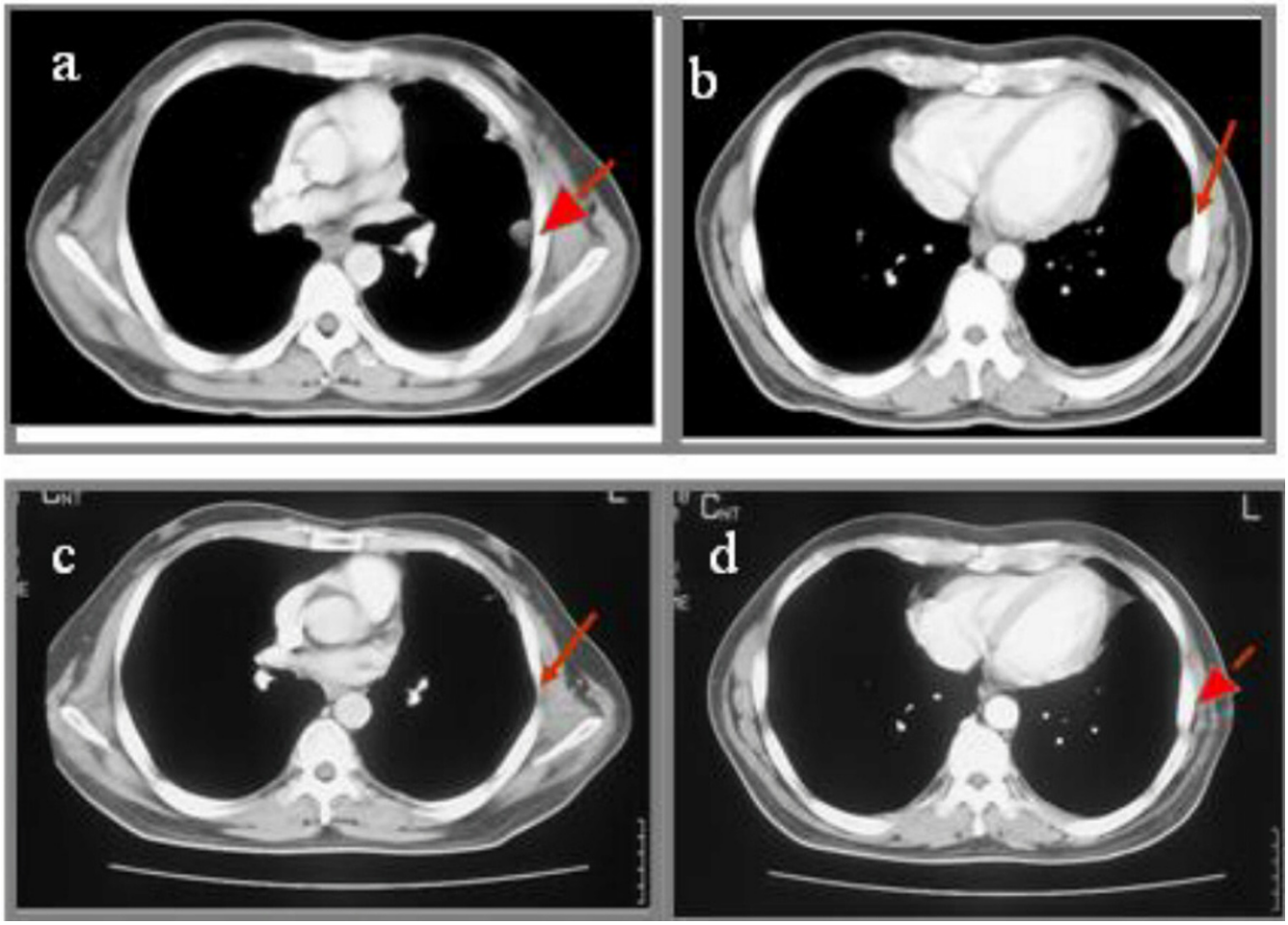

Figure 1
The effect of preoperative chemotherapy using CDDP/GEM/VNR in Case 5: Chest CT before (a, b) and after chemotherapy (c, d). The size of the primary tumors, measured two-dimensionally (arrows) decreased by 74% after chemotherapy.

Discussion

Early stage MPM, especially of the epithelial type, is a disease localized to the hemithorax. Therefore, EPP with or without perioperative adjuvant therapy should be effective, as is shown previously. Sugarbaker *et al.*, [4] reported that the treatment with EPP and adjuvant chemotherapy and hemithorax radiotherapy is effective for select patients with MPM. Nearly 50% of the cases who undergo complete resection of epithelial type MPM survive at 5 years. Rusch *et al.*, [5] showed favorable results with EPP followed by radiation. Survival rate at 5-years for patients with stage I/II IMIG classification was 40% [5].

The aim of the perioperative adjuvant therapy is to control tumor cells located at the front line and the lymphatic system and to sterilize the margin of EPP. However, a therapeutically active modality must be considered from the standpoint of patient benefit and safety. The mortality rates for EPP reported in literature are 3.8% by Sugarbaker *et al.*, [4] and 7.9% by Rusch *et al.*, [5]. In our series, all patients returned to active social life following their treatment, indicating that EPP with perioperative adjuvant therapy is well tolerated. Complete resection of capsulated MPM was achieved in 6 cases that had been designated as BWH stage I. Interestingly, as shown in table 1, BWH stage predicted the prognosis well however IMIG stage failed to do so. This indicated that local therapy for epithelial type MPM might be crucial for staging and prognosis as well.

Sugarbaker *et al.*, [4] started chemotherapy using carboplatin and paclitaxel within 4 weeks after EPP. In our series, chemotherapy was started 2 months after EPP in 4 patients who received CDDP/GEM/UFT. Of the 3 patients

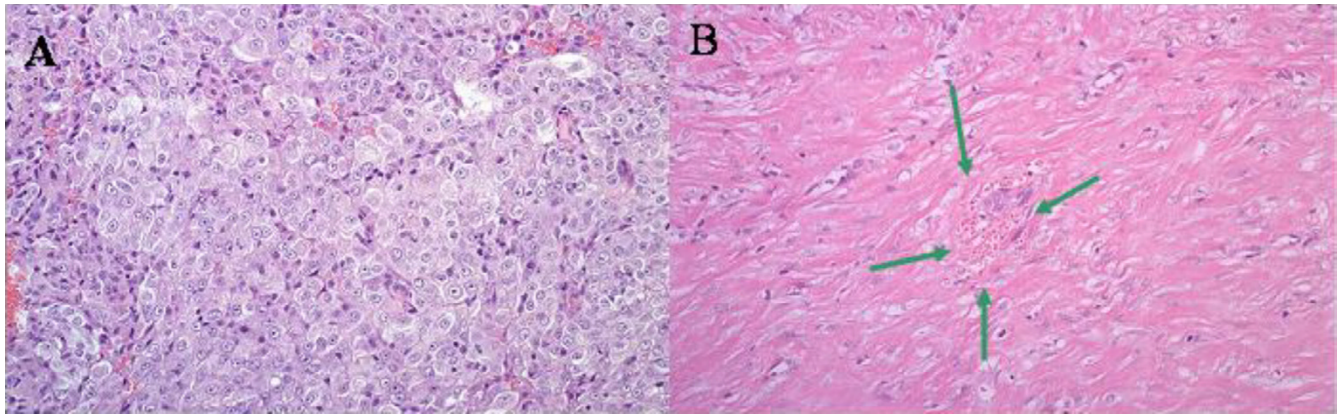

Figure 2
Photomicrograph of case number 5 showing the effect of preoperative chemotherapy. A). Histology of pretreatment biopsy and resected specimen in the above case (× 400, hematoxylin and eosin) B.) Only a small focus of epithelial type mesothelioma cells was found in the resected specimen.

receiving preoperative chemotherapy using CDDP/GEM/VNR, 2 patients received 2 courses and the other received 3 courses. EPP was performed within 5 weeks after cessation of chemotherapy. The clinical and pathological effects were remarkable. Among chemotherapeutic agents, GEM [8] and VNR [9] are reported to be active and the combination of them with CDDP was used in our study. Neutropenia was the main adverse effect of this regimen observed, which reversed with G-CSF. We therefore suggest that preoperative chemotherapy using such active agents followed by EPP is effective and safe procedure. However, this needs to be tested in a randomized controlled trial.

Competing interests
None delcared.

Authors' contributions
IY. Conceived of the study, participated in its design and coordination and drafted the manuscript.

MY. Carried out the literature search and helped in drafting the manuscript.

TO. Participated in the data retrieval and analysis also helped in literature search.

CU. Participated in the design of the study and helped in drafting the manuscript.

YI. Shape the idea for the study, coordinated the study and helped in editing the manuscript.

YM. Helped to shape the idea for the study, coordinated the study and edited the manuscript.

All authors read and approved the final manuscript.

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