Multimodal treatment for resectable epithelial type malignant pleural mesothelioma

Ichiro Yoshino*1, Masafumi Yamaguchi1, Tatsuro Yokamoto2, Chie Ushijima2, Yasuro Fukuyama2, Yukito Ichinose2 and Oshihiko Maehara1

Address: 1Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan and 2Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka 811-1395, Japan

Email: Ichiro Yoshino* - iyoshino@surg2.med.kyushu-u.ac.jp; Masafumi Yamaguchi - masafumi@surg2.med.kyushu-u.ac.jp; Tatsuro Yokamoto - tokamoto@nk-cc.go.jp; Chie Ushijima - koromo@pop21.odn.ne.jp; Yasuro Fukuyama - yfukuyama@nk-cc.go.jp; Yukito Ichinose - yichinos@nk-cc.go.jp; Oshihiko Maehara - maehara@surg2.med.kyushu-u.ac.jp

* Corresponding author

Abstract

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

Patients and Methods: Eleven patients with histologically 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
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 Women's 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 5th or 6th 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/m², 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/m² on days 1 and 8), gemcitabine (GEM) (800 mg/m², on days 1 and 8), and vinorelbine (VNR) (20 mg/m², 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/m², on day 1 and 8), GEM (800 mg/m² on days 8 and 15) and UFT (tegafur/uracil) (400 mg/m² 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 chemotheraphy 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.

| Case | IMIG stage | BWH stage | Resection | Adjuvant therapy | Recurrence | Survival status/months |
|------|------------|-----------|-----------|------------------|------------|------------------------|
| 1    | III(T3N2M0)| III       | Complete  | Pre CDDP/Hemithorax RTx | Pericardium | Died 22                |
| 2    | III(T3N2M0)| III       | Complete  | Pre CDDP/Hemithorax RTx | Ipsilateral thorax | Died 30               |
| 3    | III(T3N2M0)| III       | Incomplete| Pre CDDP/Hemithorax RTx | Ipsilateral thorax | Died 1              |
| 4    | III(T1N2M0)| III       | Complete  | Post CDDP/GEM/UFT | Lung | Dead 28            |
| 5    | II(T2N0M0) | I         | Complete  | Pre CDDP/Hemithorax RTx | None | Alive 28          |
| 6    | II(T2N0M0) | I         | Complete  | Pre CDDP/GEM/VNR | Ipsilateral thorax | Alive 35          |
| 7    | II(T2N0M0) | I         | Complete  | Pre CDDP/GEM/VNR | Pericardium | Died 6          |
| 8    | II(T3N0M0) | I         | Complete  | Pre CDDP/GEM/VNR | None | Alive 15          |
| 9    | III(T3N0M0)| I         | Complete  | Post CDDP/GEM/UFT | None | Alive 32          |
| 10   | III(T3N0M0)| I         | Complete  | Post CDDP/GEM/UFT | None | Alive 39          |
| 12   | II(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
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 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.
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 declared.

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.

References
1. Connelly RR, Spirtas R, Myers MH, Percy CL, Frameni JF Jr. Demographic patterns for mesothelioma in the United States. J Natl Cancer Inst 1987; 78:1053-1060.
2. Harvey JC, Fleischman EH, Kagan AR, Streeter OE. Malignant pleural mesothelioma: a survival study. J Surg Oncol 1990; 45:40-42.
3. Takagi K, Tsuchiya R, Watanabe Y. Surgical approach to pleural diffuse mesothelioma in Japan. Lung Cancer 2001; 31:57-65.
4. Sugarbaker DJ, Flores R, Jaklitsch MT, Richards WG, Srauss GM, Corson JM, DeCamp MM Jr, Swanson SJ, Bueno R, Lukanich JM, Baldini EH, Mentzer SJ. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: Results in 183 patients. J Thorac Cardiovasc Surg 1999; 117:54-65.
5. Rusch VW, Venkatraman E. The importance of surgical staging in the treatment of malignant pleural mesothelioma. J Thorac Cardiovasc Surg 1996; 111:815-826.
6. Jaklitsch MT, Grondin SC, Sugarbaker DJ. Treatment of malignant mesothelioma. World J Surg 2001; 25:210-217.
7. Garcia JP, Richards WG, Sugarbaker DJ. Surgical treatment of malignant mesothelioma. In Mastery of cardiothoracic surgery. Edited by: Kaiser LR, Kron IL, Spray TL. Lippincott-Raven, Philadelphia, New York; 1998:230-236.
8. Byrne MJ, Davidson JA, Musk AW, Dewar J, van Hazel G, Buck M, de Klerk NH, Robinson WS. Cisplatin and gemcitabine treatment for malignant mesothelioma: a phase II study. J Clin Oncol 1999; 17:25-30.
9. Steele JPC, Shamash J, Evans MT, Gower NH, Tischkowitz MD, Rudd RM. Phase II study of vinorelbine in patients with malignant pleural mesothelioma. J Clin Oncol 2000; 18:3912-3917.