

**Survival and Relapse Pattern after Trimodality Therapy
for Malignant Pleural Mesothelioma**

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Abstract

Objective: Multimodality therapy has been applied for resectable malignant pleural mesothelioma, however, tolerability of the treatment and relapse pattern in detail remain unknown. We reviewed our experience of trimodality therapy as a single institute study in Japan.

Methods: Sixteen patients with resectable malignant pleural mesothelioma were intended to treat with an extrapleural pneumonectomy followed by platinum-based chemotherapy and external beam radiation therapy. Histology was epithelioid in 10, sarcomatoid in 4, and biphasic in 2. International mesothelioma interest group staging was stage II in 1, stage III in 11, and stage IV in 4. Tolerability of the combined treatment, survival, and relapse pattern were examined.

Results: All patients underwent a macroscopic complete resection. Fourteen patients received chemotherapy and subsequently thirteen patients received radiotherapy, indicating tolerability was 81%. Overall median survival was 28.1 months, and 2-year and 5-year survival rates were 53.3% and 26.7%, respectively. In patients with stage III or lower median survival was 37.9 months. Recurrence was seen in 8 patients; first relapse site was local in 7 and distant in 2. The local recurrences occurred within 24 months, mostly around 12 months, after the extrapleural pneumonectomy, while the distant metastases occurred later.

Conclusion: Trimodality therapy showed survival benefit in stage III or lower malignant pleural mesothelioma. The majority of recurrence was local, therefore, better local control would be required to improve prognosis of the disease.

Introduction

Malignant pleural mesothelioma (MPM) is a dismal disease with median survival of 9-12 months after diagnosis [1-3]. The incidence of MPM in Japan is rising; annually from 500 patients in 1995 to 1050 patients in 2006, according to the Statistics of the Ministry of Health, Labour, and Welfare, Japan [4]. Asbestos exposure is thought to be a cause of the disease, and industry or environment related health damage has been a social problem.

Since Sugarbaker and colleagues reported a median survival of 19 months with multimodality therapy for MPM [5], a number of clinical trials with multimodality therapy have been reported from Western countries [6-8]. In Japan multimodality approach for MPM has rarely been reported, and tolerability and relapse pattern after the combined treatment in detail remain unknown. We reviewed our own experience of trimodality therapy for resectable MPM as a single institute study in Japan.

Patients and Methods

In 1998 we started a prospective trimodality therapy, which consists of surgery, chemotherapy and radiotherapy, for presumably resectable MPM. Indications for the treatment were histologically proven MPM, surgically resectable (T1-3N0-2), without distant metastasis, and tolerable for multimodality therapy. Sixteen patients were intended to treat with the combined therapy; 15 men and 1 woman with the mean age of 63.6 years (range 50-73 years). Nine patients had a right-side disease, while 7 patients had a left-side disease. Radiological findings at the time of diagnosis were pleural effusion in 13 patients including 2 patients with hydropneumothorax, and intrathoracic mass in 3 patients. Pretreatment assessment included thoracoabdominal CT scan, brain CT or MR, and PET scan if available. Pathological diagnosis was obtained through videothoracoscopic biopsy in 14 patients, and direct or open biopsy in 2 patients. We did not examine mediastinoscopic node biopsy for staging. In the same period we had 8 patients with MPM who were not treated with surgery: 3 patients had

unresectable disease (bilateral lesions or with pericardial effusion), 3 patients had a compromised status (pulmonary function or performance status), and 2 patients refused the aggressive treatment.

The details of the trimodality therapy have been modified (Figure 1). Throughout the period an extrapleural pneumonectomy (EPP), which consists of the removal of all parietal and visceral pleura including underlying lung and combined resection of adjacent pericardium and diaphragm along with complete mediastinal lymph node dissection, was followed by systemic platinum-based chemotherapy; 1) 1998-2003: cisplatin 70mg/m², doxorubicin 60mg/m², and cyclophosphamide 600mg/m², day1 (D1) each, 2) 2004-2006: cisplatin 80mg/m² D1 and gemcitabine 1000mg/m² D1&8, and 3) 2007-: cisplatin 75mg/m² and pemetrexed 500mg/m², D1 each. The chemotherapy was planned to administer 4 cycles, if possible. Following chemotherapy, the external beam radiation therapy was planned to deliver; 1) 1998-May 2006: conventional two-beams radiotherapy to entire hemithorax of 50-60Gy, a daily fraction of 2Gy with or without boost 10-12Gy, and 2) October 2006-: intensity modulated radiation therapy (IMRT) for extensive operative area after EPP of total 50-54Gy, a daily fraction of 1.8-2Gy were planned.

The subclassification of histology and the international mesothelioma interest group (IMIG) staging [9] were determined after EPP. Histology was epithelioid in 10, sarcomatoid in 4, and biphasic in 2. Ipsilateral hilar node metastasis was identified in 3, mediastinal node metastasis was identified in 5, other internal thoracic node was identified in 2, and no node metastasis was identified in 11. The IMIG staging was stage II in 1 (T2N0), stage III in 11 (T3N0; 7, T3N2; 4), and stage IV in 4 (T4N0: 3, T4N2: 1). The reasons of T4 classification were extension through to internal surface of the pericardium in 2, extension to SVC in 1 and extension to the chest wall with rib destruction in 1.

Tolerability of each treatment modality, overall survival, time to recurrence, and the site of tumor recurrence after the treatment were examined. The adverse events with the

treatment was defined and graded with Common Terminology Criteria for Adverse Events version 3.0 [10]. Overall survival was defined as the duration from the EPP to the last follow-up or the death with any reason. Time to recurrence was defined as the duration from the EPP to the time when a recurrence was found. The sites of the tumor recurrence were divided to local and distant. Recurrence in the organ adjacent to the pleura or surgically explored area, including chest wall, peritoneum and retroperitoneum, was defined as local. Recurrence in the non-contiguous organ to the pleura was defined as distant. Continuous data are presented as means, and categorical data are presented as exact numbers. Survival estimates were derived by Kaplan-Meier analysis. Stratified log-rank analysis was used to investigate prognostic and stratification factors. A two-sided probability value of less than 0.05 was considered statistically significant. Informed consent for the study was obtained in all patients. The study was performed in accordance with the Declaration of Helsinki. Kyoto University institutional review board approved this study.

Results

Surgery

All patients underwent an EPP with a macroscopic complete resection. Adjacent pericardium was removed and reconstructed with polytetrafluoroethylene (PTFE) patch in all patients. Hemidiaphragm was removed in all patients and reconstructed with reversed latissimus dorsi muscle flap in 7 patients and with polypropylene mesh in 9 patients. Opened peritoneum was reconstructed with PTFE patch in 2 patients. Additionally, SVC wedge resection was done in 1 patient, and chest wall (4-5th ribs) was resected and reconstructed with composite mesh of polypropylene and PTFE in 1 patient. There was no operative mortality, however, postoperative complication occurred in 9 patients; cardiac failure requiring high-dose ($>10\mu\text{g/kg/min}$) or long-term ($>7\text{days}$) catecholamine in 7, atrial fibrillation in 3, and pleuritis in 1. These were treated appropriately.

Chemotherapy

Fourteen patients received chemotherapy 5-11 weeks after EPP. Seven patients received a regimen of cisplatin, doxorubicin, and cyclophosphamide, 5 patients received a regimen of cisplatin and gemcitabine, and 2 patients received a regimen of cisplatin and pemetrexed. Cycles of administered chemotherapy were four in 7 patients, three in 2 patients, two in 3 patients, and one in 2 patients. The remaining two patients, one with constrictive malignant pericarditis two months after EPP for stage IV-disease and the other who lost a will for further treatments after EPP, were not able to receive chemotherapy. Adverse events with the chemotherapy were Grade 4 hematological toxicity in 11 patients (granulocytopenia 10, thrombocytopenia 4, anemia 2) and Grade 3 non-hematological toxicity in 2 patients (anorexia 1, confusion 1). All patients recovered from the adverse events, however, one patient with anorexia refused following radiotherapy.

Radiotherapy

Thirteen patients were planned to receive radiation therapy. Ten patients received conventional hemithorax radiation therapy and 3 patients received IMRT. Two patients with hemithorax radiation therapy received additional boost 10-12Gy to the field where surgical margin was thought to be close. Irradiation was ceased at the dose of 36Gy because of fatigue in one patient with hemithorax radiation therapy. Total twelve patients received 40Gy or more to the planned field.

Tolerability of trimodality therapy

Among 16 patients 14 patients received surgery and chemotherapy, and 13 patients received three combined modalities; surgery, chemotherapy and radiotherapy, indicating 81% tolerated trimodality therapy (Figure 2).

Survivals

Overall survival curve in all 16 patients is shown in Figure 3. Median survival was 28.1 months, and 2-year and 5-year survivals were 53.3% and 26.7%, respectively. Survival

curves of patients with stage III or lower and patients with stage IV are shown in Figure 4. Median survival in patients with stage III or lower (n=12) was 37.9 months, and 2-year and 5-year survivals were 64.8% and 32.4%, respectively. Median survival of patients with stage IV (n=4) was 15.1 months. No significant difference was seen between these groups. There were no significant differences in survivals among histology types or status of node involvement. Median survival in patients who received three combined modalities (n=13) was 37.9 months.

Relapse Pattern and Time to Recurrence

Recurrence of MPM was seen in 8 patients. First relapse site was local in 6 patients, distant in 1 patient, and both local and distant in 1 patient. The local relapse included intrathoracic mass in 3, chest wall at the lowest skin incision in 1, retroperitoneum adjacent to the mesh in 1, and malignant peritonitis (ascites) in 1. The distant relapse included contralateral lung in 1 and contralateral pleural effusion in 1. Time to recurrence is shown in Figure 5. All local relapse occurred within 2 years, mostly around 12 months, after EPP, while distant relapse occurred later.

Discussion

Nationwide survey from the results of a questionnaire by Japanese Association of Chest Surgery in 1997 reported a median survival of 12 months after 189 surgical treatments (108 EPPs) for MPM during 10 years [11]. The survival with EPP showed no difference from that with palliative pleurectomy, indicating no survival benefit in EPP. Following survey collecting 132 surgical cases (73 EPPs) in 1997-2002 through Japan Lung Cancer Society showed 1-year and 2-year survival rates of 54% and 33%, respectively [12]. The report concluded no improvement in the surgical treatment for MPM in about 20 years. Recent survey regarding the status of multimodality treatment for MPM showed that among 171 patients who underwent an EPP only 7% received trimodality therapy in 2002-2006 in Japan

[13]. Most therapeutic approach for MPM was surgery alone, and prospective multimodality treatment has rarely been reported in Japan.

Sugarbaker and colleagues reported multimodality therapy consisting of surgery, chemotherapy, and radiotherapy in 183 patients with MPM, resulting in median survival of 19 months [5]. Since then several trials of multimodality treatment for MPM have shown median survivals of 17-24 months [7,8,14-16]. Because most of multimodality trials were from the United States or Europe, the tolerability of the treatment and relapse patterns in detail remain unknown.

We started this prospective trimodality therapy for resectable MPM in 1998. Because of the rarity of the disease it took certain time to accrue patients with MPM in single institute. Combination chemotherapy using gemcitabine and cisplatin showed high response rates in phase II studies [17,18], and pemetrexed plus cisplatin showed survival benefit compared with cisplatin alone in a randomized control study [3]. Proven effective chemotherapy was chosen into our combined treatment. Although the details in protocol, chemotherapy regimen and irradiation methods, have been modified with the emerge of available treatment, all our patients were intended to treat with an EPP followed by platinum-based chemotherapy and external beam radiation therapy throughout the period.

In this study the tolerability of the trimodality therapy was 81%. Two patients were unable to receive chemotherapy after EPP because of rapid recurrence or mental discouragement; however, they might have had no indication for the aggressive treatment from a retrospective point of view. It is important to tolerate the combined therapy, because patients who received three modalities showed a favorable survival. Good performance status, reserved cardiopulmonary function, and a strong will for cure to accept long-term treatment are required to proceed with trimodality therapy.

Overall median survival of 28.1 months in all patients was comparable with literatures. In patients with stage III or lower median survival was 37.8 months. It is of note

that 4 of 16 patients were classified as stage IV postoperatively, although patients with stage IV were not initially indicated for trimodality therapy. IMIG staging was based on pathological findings [9]. It was not until exploration that tumor extension into the internal surface of the pericardium or mediastinal organ involvement was identified. The discrepancy of preoperative staging and final pathological staging occurred frequently, and would be diminished with more sophisticated staging system. Patients with epithelial histology, no lymph node involvement and complete surgical resection have shown more favorable results on survival in the literatures [5]. We did not find significant differences in survivals between patients with and without node metastasis or among histological subtypes, which might be explained by the small number of subgroup patients in this study.

Local disease progression is the main cause of symptoms and death in MPM. Disseminated disease is seen only in the late course of MPM [19,20]. In this study 8 out of 16 patients showed a recurrence of disease, and local recurrence was the most common site of first relapse, which is consistent with literatures [21]. Local recurrence occurred within 24 months, mostly around 1 year, and distant metastasis occurred later. Further investigation into 6 local recurrences after radiation therapy revealed that 4 recurrences were at the margin of hemithorax-radiation fields; two intrathoracic masses were at the medial margin and the retroperitoneum and the lower chest wall were at the inferior margin. These findings indicate that more effective local control is required to improve overall survival.

A novel method of radiation delivery, IMRT has been developed that allows for significant improvements in the dose delivery of radiation therapy and can allow for improved local control [22,23]. However, in the initial experience with this technique, a high rate of death from treatment was seen [24]. Although we did not experience a severe adverse event with IMRT in the limited number of patients, careful application with improved irradiation technique [25] is required, and risk and benefit should be examined in the future clinical use.

In summary, trimodality therapy showed survival benefit in patients with MPM of

stage III or lower. The trimodality therapy was tolerable in selected patients. The majority of the first relapse site was local and the local recurrence occurred within 24 months after the initial treatment. To improve the prognosis of MPM effective local control would be required.

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Figure Legends

Fig. 1 Time trend and details of the trimodality therapy.

CDDP: cisplatin, ADM: doxorubicin, CPM: cyclophosphamide, GEM: gemcitabine,
PEM: pemetrexed, IMRT: intensity modulated radiation therapy

Fig. 2 Tolerability of the trimodality therapy. Thirteen of 16 patients (81%) tolerated the trimodality therapy.

Fig. 3 Overall survival curve of all patients (n=16).

Fig. 4 Survival curves of patients with stage III or lower (n=12) and stage IV (n=4).

Fig. 5 Time to recurrence in all patients (n=16) and first relapse site.

Fig. 1

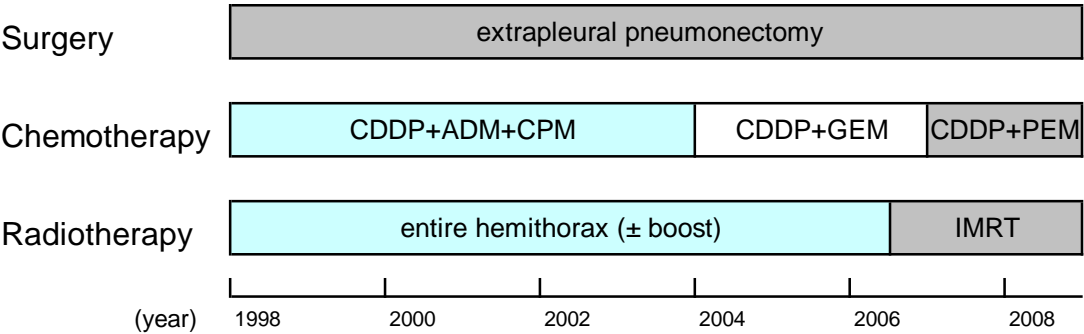


Fig. 2

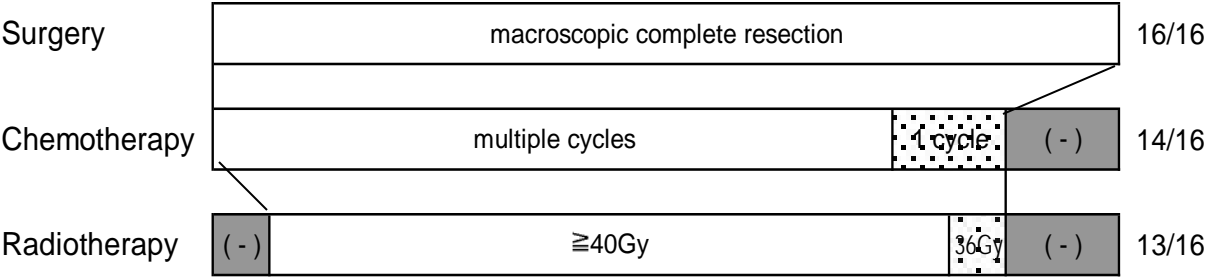


Fig. 3

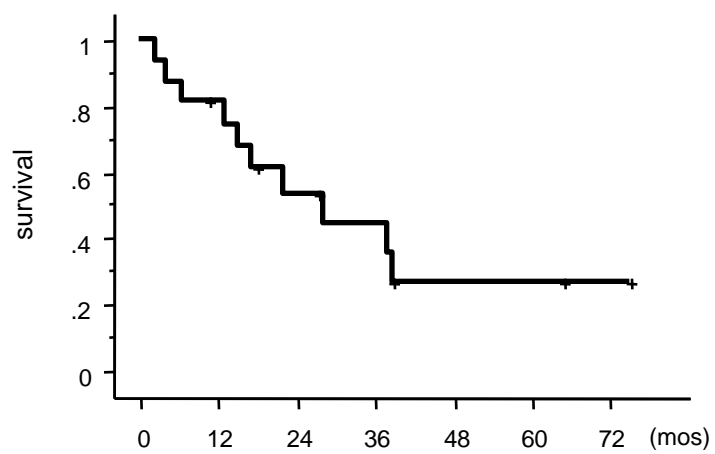


Fig. 4

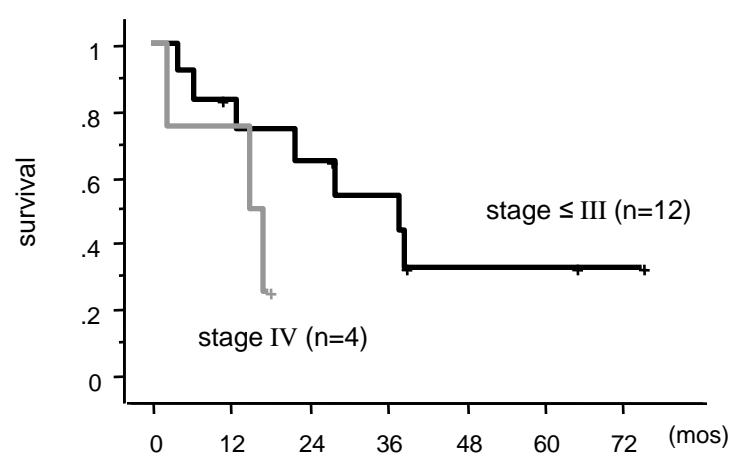


Fig. 5

