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The Current Status of the Diagnosis and Multimodality Therapy for Malignant Mesothelioma

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Abstruct：An extrapleural pneumonectomy was performed in 6 patients with malignant mesothelioma in our unit over the past 10 years. The patients ranged from 48–57 years of age. All of them were males and had experienced occupational asbestos exposure. The mean survival time after an extrapleural pneumonectomy was 888 days. Two of the 6 patients had malignant mesothelioma with an excellent reduction by induction therapy using CDDP＋Docetaxel, an extrapleural pneumonectomy. One of these patients is doing well with no recurrent of mesothelioma for 2 years after the operation. The other patient died due to a recurrence of mesothelioma at 5 years after operation. We herein discuss the usefulness of intrapleural perfusion hyperthermo–chemotherapy for malignant mesothelioma, and the effectiveness of Positron Emission Tomography (PET) for diagnosing and determining the clinical staging of malignant mesothlioma.

Key words：**Malignant mesothlioma, extrapleural pneumonectomy, induction chemoradiation therapy**

Introduction

The best treatment for malignant mesothelioma is still controversial, and there have been some attempts of the treatment with chemotherapy, radiation therapy and surgical option. An extrapleural pneumonectomy is a traditional standard therapy for malignant mesothelioma.[1)2)] However, an extrapleural pneumonectomy is a highly invasive surgical option, so thoughtful perioperative treatment are needed

Patients and methods

Twenty–three cases with malignant mesothelioma have visited to our institute over the past 10 years. In those patients, 6 cases underwent an extrapleural pneumonectomy at the request of the patients. The range in the age was from 48–57 year of age. All of them were male and had experienced occupational asbestos exposure (Table 1). The indications for induction therapy were for patients with clinical stage T1– T4, N0– N2, M0, while also taking the performance status, informed consent and the patients own requests into account.

The other 2 patients underwent intrapleural perfusion hyperthermo–chemotherapy. These 2 patients were 59–year–old and 73–year–old females, who selected the hyperthermo–chemotherapy without an extrapleural pneumonectomy (Table 2). We used a circuit with a heat exchanger and a bio–pump, and Cisplatin (CDDP) (100 mg/body) was administrated through the circuit. We carefully controlled the pump flow and the heat exchanger of our circuit to maintain a temperature of 430C at the pleural surface for 60 minutes. The data were retrospectively obtained from their charts.

We attempted to evaluate a malignant mesothelioma patient using FDG–PET. After a minimum

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Table 1 Cases undergoing an extrapleural-pneumonectomy

Age/gender	Diagnosis	Clinical stage	adjuvant therapy	Prognosis (day)
1) 57/M	Rt-mesothelioma	T3N2M0 Stage Ⅲ	Induction CDDP 100 mg	1935 died
2) 48/M	Lt-mesothelioma	T3N0M0 Stage Ⅲ	Chest wall resection for local recurrent	687 died
3) 50/M	Lt-mesothelioma	T3N2M0 Stage Ⅲ		715 died
4) 51/M	Rt-mesothelioma	T3N2M0 Stage Ⅲ	Chest wall resection for local recurrent	583 died
5) 55/M	Lt-mesothelioma	T3N0M0 Stage Ⅲ		352 died
6) 53/M	Rt-mesothelioma	T3N0M0 Stage Ⅲ	Induction CDDP 110 mg +Docetaxel 80 mg	720 alive

Table 2 The cases undergoing intra-pleural hypotonic perfusion hyperthermo-chemotherapy

Age/gender	Diagnosis	clinical stage of UICC	Anti-cancer agent	Prognosis (day)
1) 59/F	Rt-Malignant Mesothelioma	T1N0M0 Stage Ⅰ	CDDP 100 mg	2920 alive
2) 73/F	Rt-Malignant Mesothelioma	T1N0M0 Stage Ⅰ	CDDP 150 mg	2250 alive

Table 3 The regimens and outcomes of chemotherapy for malignant mesothelioma

Chemotherapy for malignant mesothelioma						
	regimen	No. of pts	No. of responders			Response rate (%)
			CR	PR	others	
Fizazi	CDDP+INF-α	26	0	10	16	40
Fizazi	CDDP+INF-α +mitomycin	24	0	5	19	21
Nowak	CDDP+gemcitabine	46	0	12	34	26
Fizazi	CDDP+paclitaxel	18	0	1	17	6
Calvert	Carboplatin +ALIMTA	20			10	50
Fizazi	Oxaliplatin +raltitrexed	30	0	9	21	30
Brodin	Methotrexate +INF-α	46	0	12	34	26

of 45 minutes post injection of at least 10 mCi of FDG, whole body emission scans were performed.

Results

Case No. 6

A 53-year-old male, who had experienced occupational asbestos exposure, visited our hospital with right pleural effusion and he was diagnosed to have malignant mesothlioma (Fig. 1). A chest CT scan showed a large soft tissue mass to fully occupy the right thoracic cavity while closing the esophagus and trachea (Fig. 2). He also had hyposensitisation and hyposystolia of the right upper extremity. As a result, we diagnosed malignant mesothelioma, c-T4N0M0 stage Ⅳ, based on the UICC classification and we decided to performed induction chemo-radiation therapy. He was systemically administrated CDDP 80 mg/m^2+ Docetaxel 60 mg/m^2, and 40 Gy radiation therapy to the mediastimun and the superior sulcus of the right thoracic cavity. He showed renal dysfunc-

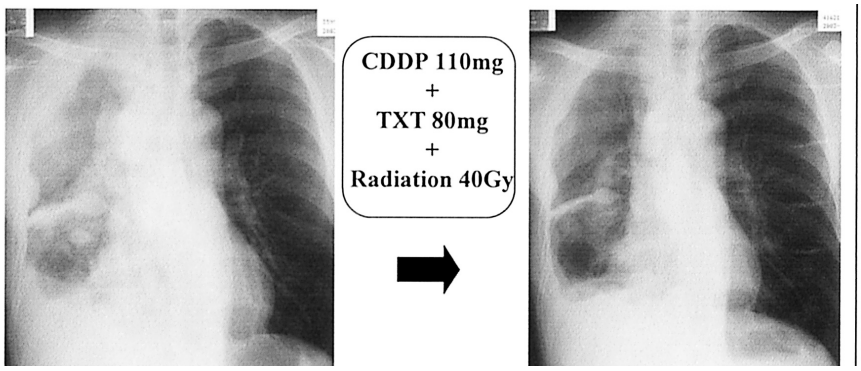

Figure 1. The findings of the chest X-ray of the case No. 6 before and after induction therapy.

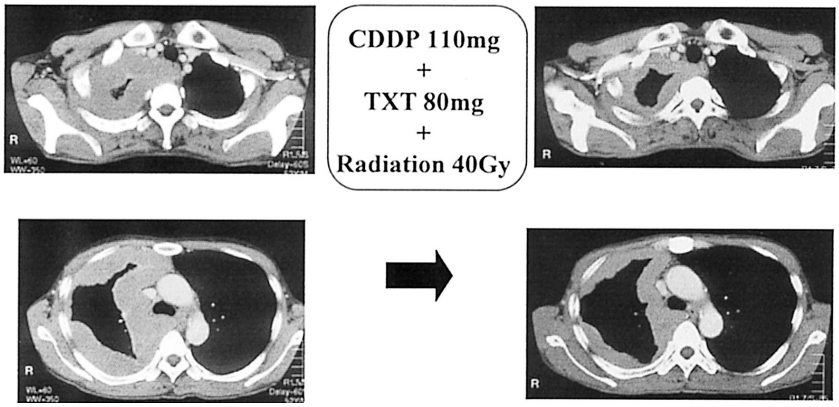

Figure 2. The findings of the chest CT scan of the case No. 6 before and after induction therapy.

tion as a side effect of the chemo-radiation therapy. As a result, we stopped the therapy at just one cycle, and the reduction rate of the tumor was about 40% (Fig. 1, 2). He therefore underwent an etrapleural pneumonectomy and the operation time was 4 hours and 55 minutes, with a bleeding volume of 2835 ml. He is presently doing well and there is no sign of any recurrent disease (Fig. 3).

All 6 cases who underwent an extrapleural pneumonectomy are shown in Table 1. The clinical stage of all patients was stage Ⅲ based on the UICC classification.

The mean survival time of all patients after an extrapleural pneumonectomy was 888 days. In those 6 cases, we experienced two cases of malignant mesothelioma with an excellent reduction by induction therapy with CDDP+Docetaxel, who continuously underwent an extrapleural pneumonectomy. One of them had induction chemotherapy of CDDP 110 mg+Docetaxel 80 mg and induction radiation therapy of 40 Gy to the superior sulcus of the chest. He has had no recurrence of the mesothelioma for 2 years after the operation (case No. 6). Another patient undrwent induction chemotherapy of CDDP 100 mg, but he died due to a recurrence of mesothelioma at 5 years after the operation (case No. 1).

The other 2 cases of intrapleural perfusion hyperthermo-chemotherapy are shown in Table 2. Both patients were also stage Ⅰ, and they were requested to have intrapleural perfusion therapy. Both patients are presently alive with primary disease at 2920 days and 2250 days after perfusion therapy.

We used positoron emission tomography (PET) to diagnose and evaluate the staging of patient No 5 (Fig. 4). PET showed a positive uptake of the malignant mesothelioma, and also demonstrated

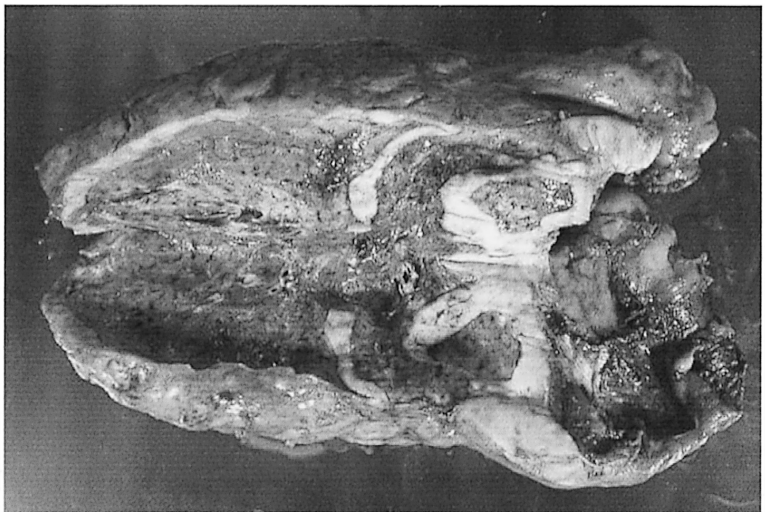

Figure 3. The macroscopic findings of the malignant mesothelioma of the case No. 6.

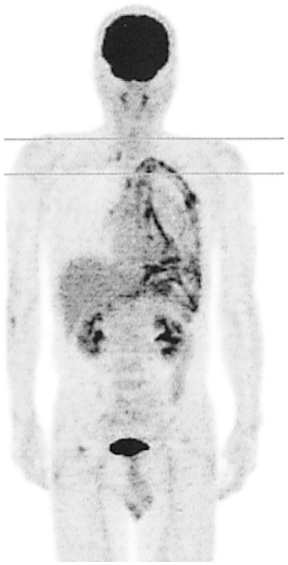

Figure 4. The findings of the PET scan of the case No. 5.

the T status of the tumor.

Discussion

Although an extrapleural pneumonectomy is a rather standard surgical option, the 2 year-survival rate of 33-48% is still unsatisfactory.[1] In this series, the mean survival rate of the extrapleural pneumonectomy was 888 days. We had one survival case of malignant mesothlioma who survived 1935 days after an extrapleural pneumonectomy. However, the surgical outcome of an extrapleural pneumonectomy for malignant mesothelioma still remains unsatisfactory.

The chemotherapy for malignant mesothlioma still remains controversial, Some regimens are shown Table 3.[3)-6)] However, the response rate for chemotherapy is 6%～50%. As a result the best regimen remains to be elucidated. The most popular chemotherapy in the literature is based on platinum drugs, for example, CDDP+interferon, CDDP +gemcitabine and CDDP+paclitaxel. In this study, we tried induction therapy with CDDP+Docetaxel for case No. 6, and the response rate was 40%.

Matsuzaki[7] showed the local effectiveness of the intrapleural perfusion hyperthermo-chemotherapy for malignant pleural dissemination and effusion. We performed intrapleural perfusion hyperthermo-chemotherapy for the 2 patients with stage I malignant mesothelioma. They are both still alive with the tumor over 7 years after intrapleural perfusion. The effectiveness of intrapleural perfusion hyperthermo-chemotherapy for the malignant mesothelioma still remains unclear, however, it is one of the therapeutic options for malignant mesothelioma patients who do not select an extrapleural pneumonectomy.

Recently, we are using the positoron emission tomography (PET) to diagnose and evaluate the staging of the malignant mesothlioma (Fig. 3). This is a highly interesting topic, which it needs further examination and study.[8]

Conclusions

1) The results of an extrapleural pneumonectomy for advanced malignant mesothelioma remain unsatisfactory.
2) Intrapleural hyperthermo-chemotherapy for high risk patients or early staging mesothelioma apperars to be a reasonable treatment.
3) Induction therapy for advanced mesothelioma using the CDDP+Docetaxel intra venous administration may be a potentially effective modality. We therefore would like to perform a prospective study in the future to evaluate the effect of induction therapy using this regimen.

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