

Lung-sparing Decortication Pleurectomy with Intraoperative Adjuvant Therapy for Malignant Mesothelioma: A Single Institute Experience in Taiwan

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Abstract

Background: In Taiwan, the incidence of Malignant Pleural Mesothelioma (MPM) has been increasing over the past three to four decades. This study aimed to analyze the outcomes and overall survival rates in patients undergoing cytoreductive lung-sparing decortication pleurectomy surgery and intraoperative adjuvant therapy (hyperthermic intrathoracic chemotherapy or photodynamic therapy) for malignant pleural mesothelioma at a single center in Taiwan.

Methods: This was a retrospective review of patients who underwent cytoreductive lung-sparing decortication pleurectomy surgery and intraoperative adjuvant therapy for malignant pleural mesothelioma from April 2013 to December 2021.

Results: A total of 17 patients with malignant pleural mesothelioma underwent surgery. There was one case of surgical mortality due to intraoperative uncontrolled bleeding. The subtypes according to histology were epithelioid mesothelioma (58.8%), pleomorphic subtype of epithelioid malignant mesothelioma (5.9%), biphasic mesothelioma (11.8%), and sarcomatoid mesothelioma (23.5%). The median survival was 14.0 months. However, for the epithelioid type, the median survival was 20.0 months.

Conclusion: To our knowledge, this is the first report from a single center in Taiwan devoted to lung-sparing decortication pleurectomy with intraoperative adjuvant therapy for malignant pleural mesothelioma. Although our hospital did the most operations for patients with malignant pleural mesothelioma in Taiwan, we were still far away from being a high-volume center in the world. The outcome is not satisfactory, but still slightly better than that of patients who received chemotherapy alone, especially those with the epithelial subtype disease. One of our patients survived for more than 6 years. We provide an option for the treatment of patients with malignant pleural mesothelioma in Taiwan.

Keywords: Malignant pleural mesothelioma • Lung-sparing decortication pleurectomy • Intraoperative adjuvant therapy • Overall survival

Introduction

Malignant mesothelioma is an aggressive type of malignancy associated with previous asbestos exposure [1] and in 2017, it accounted for about 29,900 deaths worldwide [2]. More than 90% of malignant mesotheliomas arise from the pleura [3]. The incidence of Malignant Pleural Mesothelioma (MPM) in Taiwan is approximately 1–2 per million person years, which is lower than that reported from western countries; however, the incidence has been increasing in the past three to four decades. The incidence of MPM in Taiwan is expected to peak by 2030 [4,5]. The incidence of MPM in Taiwan is slightly lower than that in other developing countries. The small number of MPM cases in Taiwan may be because most hospitals have limited experience in its diagnosis. Most of the pleural cancers in the Taiwan Cancer Registry System have no final pathological diagnosis, which makes the number of MPM cases low; therefore, it is likely underdiagnosed, and the incidence is underestimated [4,5]. Moreover, the mean survival of MPM in Taiwan is reported to be 9 months for all cases [4,5].

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Given that most hospitals have little experience in diagnosing and treating MPM, the disease is usually diagnosed at a late stage. Moreover, only a few thoracic surgeons are experienced in performing surgery for MPM; therefore, the majority of Taiwanese patients with MPM are treated with chemotherapy or palliative care, leading to a low Overall Survival (OS) rate. Only a few hospitals have reported treatment outcomes for MPM, including two of the top major medical centers in Taiwan. According to Dr. Lee, there were 93 patients with MPM treated at the National Taiwan University Hospital during the 40 years from 1977 to 2016, and these patients showed an average survival of 15 months [6]. According to Dr. Liu's statistics, from 1960 to 1996, there were only 17 patients with MPM treated at Taipei Veterans General Hospital, and the average survival was only 6 months [7].

Our institution started the first mesothelioma program in Taiwan in 2012, involving multimodality methods including pleurectomy/decortication surgery and intraoperative adjuvant therapy (Hyperthermic Intrathoracic Chemotherapy [HITHOC] or Photodynamic Therapy [PDT]), followed by adjuvant chemotherapy and radiotherapy for the chest wall and the suspected residual region. Herein, we report our treatment experience of this condition over the past 10 years.

This manuscript is written following the STROBE checklist.

Methods

Ethical statement

This study represents a retrospective review performed with the approval of the Taoyuan General Hospital Institutional Review Board under a protocol entitled, "Lung-sparing decortication pleurectomy with intraoperative adjuvant therapy for malignant mesothelioma: A single institute experience in Taiwan."

The requirement for informed consent was waived (TYGH111065). All patient data (including individual details, images or videos) were de-identified.

Patients

From 2013 to 2021, 17 patients (median age, 62.5 years; range, 53–71 years; male/female ratio, 11/2) underwent radical pleurectomy, intraoperative adjuvant therapy, adjuvant chemotherapy, and radiotherapy. One patient was diagnosed with mesothelioma and received definite chemotherapy with pemetrexate and cisplatin for 1 year at another hospital. This patient was referred to our hospital for surgery due to local disease progression. The other 16 patients underwent surgery without neoadjuvant chemotherapy.

Preoperatively, all patients were diagnosed with MPM by video-assisted thoroscopic surgery biopsy or transcutaneous pleural biopsy. The radiographic staging workup, which included a Positron-Emission Tomography (PET) scan, Computed Tomography (CT) scan of the chest/abdomen, and brain imaging, revealed no distant metastases outside the pleural cavity. Five patients received intraoperative PDT, and 12 received HITHOC for adjuvant intraoperative therapy. The choice of intraoperative adjuvant procedure was not randomized and was chosen by the patients themselves after discussion about the operative procedures, benefits, risks, and cost. Porfimer sodium (Photofrin) is an off-label treatment used for MPM in Taiwan, and approval from the IRB must be obtained for each individual patient. Additionally, neither PDT nor HITHOC are covered by national insurance; therefore, they are self-funded. The operative procedures followed those described in previous studies [8,9]. All patients received curative intent radical pleurectomy/decortication. The goal in all patients was to achieve maximal cytoreduction and a complete macroscopic resection of the tumor (R1 resection).

Surgery

Patients were positioned in the lateral decubitus position and the chest was typically entered through a posterolateral thoracotomy through the fifth intercostal space, with resection of the sixth rib. The first step of the surgery was to mobilize the cancer off the bony hemithorax, followed by the posterior and superior mediastinum, identical to the initial steps of an extrapleural pneumonectomy. The anterior mediastinum was approached by sweeping off all pericardial fat in an anteroposterior direction and then attempting to separate the cancer from the pericardium, such that there was no visible or palpable disease. If this was not possible, an attempt was made to resect the cancer with the fibrous pericardium, leaving the underlying serous pericardium. The dissection was continued to the anterior hilum, whilst attempting to preserve the phrenic nerve by skeletonizing it from the encasing tumor. The diaphragm dissection was started in the costophrenic recess, attempting to bluntly separate the pleura from the underlying bare musculature. Limited areas of full thickness invasion were resected, and the diaphragm was primarily reconstructed. Usually, the muscular part of the diaphragm can be preserved, and the central tendon part of the diaphragm may be resected with the tumor. In all our cases, the diaphragm was preserved, avoiding intraperitoneal seeding.

Photodynamic therapy

Intraoperative PDT was performed on five patients as follows: each patient received 2 mg/kg intravenous porfimer sodium 24 hours preoperatively; subsequently, 630 nm laser light was delivered to a measured dose of 60 J/cm², as registered on seven strategically placed isotropic light detectors using a custom-built dosimetry system. The chest was then filled with 0.01% dilute intralipid solution to facilitate light dispersion, and light delivery typically took approximately 2 hours to complete.

Hyperthermic intrathoracic chemotherapy

Intraoperative HITHOC was performed on 12 patients as follows: once the pleurectomy/decortication was completed and the lung re-expanded to check for air leaks, two 32-Fr chest tubes were placed anteriorly and posteriorly to the pleural cavity, and the thoracotomy wound was closed. We performed a hyperthermic pleural lavage using sterile water mixed with 10% povidone-iodine (dilution 1/10; Panion & BF Biotech Inc., Taipei, Taiwan), heating to 43 °C using a continuous hyperthermia system (Rand, via Statale, Italy) for 1 hour.

Adjuvant therapy protocol

Adjuvant chemotherapy was started 6–8 weeks after surgery, when the patient had recovered sufficiently, and the wounds had healed satisfactorily. The regimen consisted of a combination of pemetrexed (500 mg/m²) and cisplatin (75 mg/m²). The intent was to administer four to six cycles of chemotherapy with pemetrexed and cisplatin and then continue with single-agent pemetrexed every 3 weeks until disease progression or intolerance. Most patients were treated as outpatients at our institution and received their treatment every 3 weeks in the chemotherapy unit. Patients were followed-up in the outpatient clinic regularly and had PET-CT or chest CT arranged every 3–4 months to monitor their response to treatment or disease progression. Those relapsing after multimodality therapy were offered second-line treatment, and radiotherapy was offered over the thoracotomy wound for the prevention of wound recurrence, or as a palliative measure when patients were diagnosed with relapse.

Follow-up and statistics

Standard follow-up included an office visit and chest CT every 3 months. Patient demographics and treatment variables are described as frequencies and percentages. Survival was calculated from the time of surgery, not from time of enrollment, diagnosis, or initiation of any other treatment. Moreover, survival was defined as the time from surgery to death due to any cause or last live patient contact. Survival was estimated using the Kaplan–Meier method. All statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

The patient characteristics are summarized in Table 1. All patients received curative intent radical pleurectomy/decortication with minimal residual tumor (R1) resection and intraoperative adjuvant therapy. There was one surgical mortality due to uncontrolled bleeding during the operation, and the other 16 patients received adjuvant radiotherapy around the operation wound and any residual lesion marked intraoperatively, followed by adjuvant chemotherapy. The final histopathology showed that 10 patients had epithelioid mesothelioma (58.8%), one had a pleomorphic subtype of epithelioid MPM (5.9%), two had biphasic mesothelioma (11.8%), and four had sarcomatoid mesothelioma (23.5%). Furthermore, eight patients had N0 disease (47.1%), two had N1 disease (11.8%), and seven had N2 disease (41.2%). Additionally, the IMIG classification stage was I in seven patients (41.2%) and III in 10 patients (58.8%).

Excluding the surgical mortality case, at the last follow-up, the median follow-up time was 10 months (range, 2–73 months). At the end of this study, two patients were alive with stable disease. Furthermore, the overall median survival was 14.0 months (95% Confidence Interval [CI], 5.9–22.0), the 1-year survival was 55.6%, and the 2-year survival rate was 31.7% (Figure 1). The pleomorphic subtype of epithelioid MPM was classified into biphasic and sarcomatoid subtypes owing to very poor prognoses in our study. For the epithelioid type, the median survival was 20.0 months (95% CI, 0–41.89), while the 1-year survival rate was 76.2% and the 2-year survival rate was 45.7%. This median survival was significantly better than that associated with biphasic and sarcomatoid type mesotheliomas, which is only 5.0 months (95% CI, 0–10.13). Additionally, only one sarcomatoid type patient survived longer than 1 year (Figure 2).

In terms of surgical methods, because of the lack of randomization and potential selection bias, it was very difficult to determine which intraoperative adjuvant therapy was better in this study.

Discussion

This study analyzed the outcomes and overall survival rates in patients undergoing cytoreductive lung-sparing decortication pleurectomy surgery and intraoperative adjuvant therapy for MPM. To the best of our knowledge,

Table 1. HITHOC, hyperthermic intrathoracic chemotherapy; PDT, photodynamic therapy.

No.	Sex	Age (years)	Side	Preoperative Chemotherapy	Intraoperative Adjuvant tx	Pathology	Stage	Overall Survival (months)	Status (Dead/Alive)
1	F	56	L	N	PDT	Epithelioid	IIIB	32	Dead
2	M	58	L	N	PDT	Sarcomatoid	IIIB	2	Dead
3	M	65	R	N	PDT	Epithelioid	IB	73	Dead
4	M	66	R	N	HITHOC	Sarcomatoid	IIIB	2	Dead
5	M	54	L	N	HITHOC	Sarcomatoid	IIIA	25	Dead
6	M	65	R	N	PDT	Epithelioid	IIIB	0	Dead
7	F	66	R	N	HITHOC	Biphasic	IB	5	Dead
8	M	71	L	N	HITHOC	Epithelioid	IIIB	14	Dead
9	M	58	L	N	PDT	Epithelioid	IB	40	Dead
10	M	70	R	N	HITHOC	Epithelioid	IIIB	8	Dead
11	M	53	R	N	HITHOC	Sarcomatoid	IIIB	3	Dead
12	M	69	R	N	HITHOC	Pleomorphic	IIIA	6	Dead
13	M	62	L	C (12M)	HITHOC	Epithelioid	IB	12	Dead
14	M	83	L	N	HITHOC	Epithelioid	IA	20	Dead
15	F	61	L	N	HITHOC	Biphasic	IIIA	17	Dead
16	M	60	L	N	HITHOC	Epithelioid	IB	12	Alive
17	M	54	L	N	HITHOC	Epithelioid	IB	8	Alive

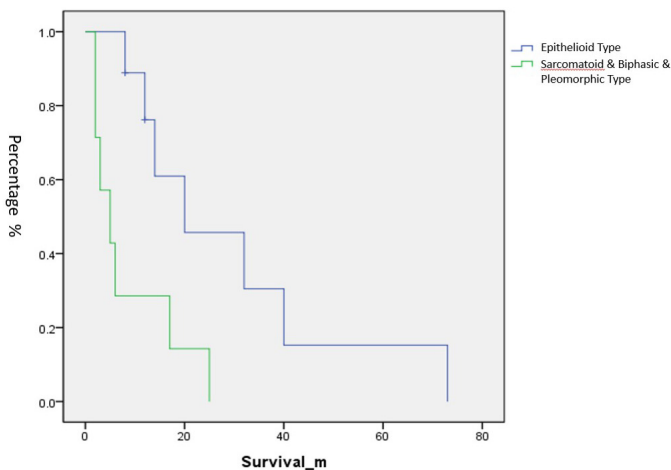


Figure 1. Overall mean survival of the patients.

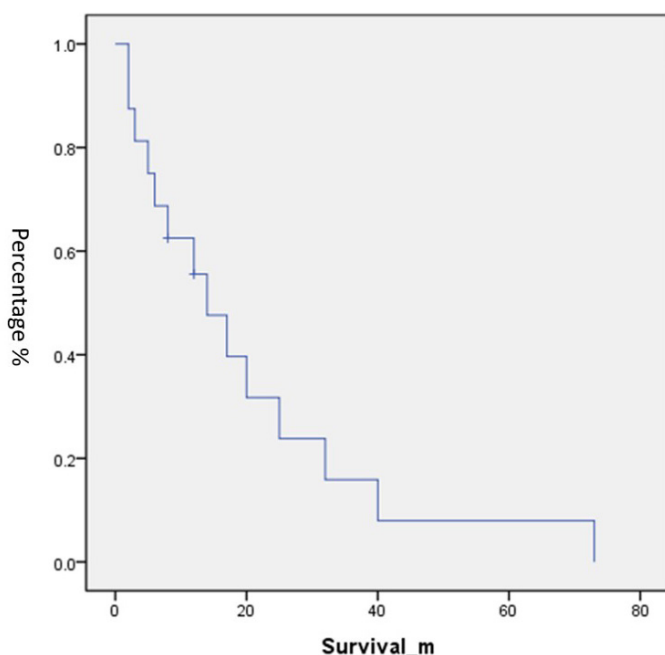


Figure 2. Overall mean survival of the mesothelioma types.

this is the first report from a single center in Taiwan devoted to lung-sparing decortication pleurectomy with intraoperative adjuvant therapy for MPM, a rare primary pleural malignancy. According to previous research, the number of Taiwanese male patients with MPM reached a peak from 2012 to 2016, with approximately 44–50 newly diagnosed patients per year, and the number of female patients with MPM reached a peak of approximately 15–17 patients per year between 2016 and 2020; additionally, it is estimated that there will be 659 new patients over the next 30 years (2017–2046) [4]. Owing to the small number of patients (approximately 40–50 newly diagnosed patients per year), rapid disease progression, and poor survival rate, most patients with MPM in Taiwan are treated with palliative chemotherapy, and the average survival is approximately 9 months [5].

Our hospital has been developing surgical treatment protocols for pleural cancer since 2012. In 2009, our team surgeon (Dr. Y. S. Hsieh) introduced the lung-sparing radical decortication/pleurectomy surgical technique and intraoperative PDT, based on a previous protocol. Photodynamic drugs (Porfimer sodium) are not approved for MPM in Taiwan; therefore, each time PDT is performed, IRB approval must be obtained for its off-label use. Moreover, HITHOC was performed with povidone-iodine according to a previously described manner; however, we used a continuous hyperthermia system (Rand, via Statale, Italy) to maintain a 43 °C thermostatic control for 1 hour to avoid overheating that may cause heat damage or a lower than

desirable temperature. Both methods are not covered by national health insurance in Taiwan, and patients must pay for this themselves. These methods were explained well to the patients, including the costs of adjuvant therapy, and they subsequently chose the method of treatment themselves.

Our MPM program was performed by a multimodality team including thoracic surgeons, pulmonologists, oncologists, radio-oncologists, radiologists, and pathologists, and the program adhered to multimodality treatment guidelines. Although we treated most MPM patients in Taiwan, MPM patient numbers in Taiwan are much lower than that of a high-volume center. Among the 17 patients, except for the patient who died of massive blood loss during surgery, all other surgeries were performed successfully. As experienced in other countries, sarcomatoid type MPM has a poor prognosis; therefore, we have not performed surgery on patients with sarcomatoid type MPM in the past years. The overall median survival was 14.0 months (95% confidence interval [CI], 5.9–22.0), the 1-year survival was 55.6%, and the 2-year survival rate was 31.7%. Although our outcome is not satisfactory compared with those reported by the best high-volume centers in the world [10,11], the results are still better than the results obtained from chemotherapy alone in Taiwan. In fact, one of our patients survived about 6 years. We provide an alternative to palliative chemotherapy alone in the treatment of patients with MPM in Taiwan.

Conclusion

To our knowledge, this is the first report from a single center in Taiwan devoted to lung-sparing decortication pleurectomy with intraoperative adjuvant therapy for malignant pleural mesothelioma. Although our hospital did the most operations for patients with malignant pleural mesothelioma in Taiwan, we were still far away from being a high-volume center in the world. The outcome is not satisfactory, but still slightly better than that of patients who received chemotherapy alone, especially those with the epithelial subtype disease. One of our patients survived for more than 6 years. We provide an option for the treatment of patients with malignant pleural mesothelioma in Taiwan.

Key Findings

Although the outcomes of lung-sparing decortication pleurectomy with intraoperative adjuvant therapy for malignant mesothelioma are not satisfactory, they are better than that of patients who receive chemotherapy alone.

What is known and what is new?

The incidence of Malignant Pleural Mesothelioma (MPM) has been increasing in Taiwan over the past few decades. It is expected to peak by 2030.

Median survival for patients with the epithelioid type of MPM was significantly better than for other sub-types (20.0 months vs. 14.0 months).

What is the implication, and what should change now?

Lung-sparing decortication pleurectomy with intraoperative adjuvant therapy is an alternative to palliative chemotherapy alone for the treatment of patients with MPM in Taiwan, and it may increase survival time in patients with the epithelioid type.

Ethical Statement

This research was approved by the Taoyuan General Hospital Institutional Review Board (TYGH111065). The requirement for informed consent was waived (TYGH111065).

Reporting Checklist

The authors have completed the STROBE reporting checklist.

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Conflict of Interest

None declared.

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