Extended pleurectomy/decortication and hyperthermic intraoperative intrapleural cisplatin perfusion for malignant pleural mesothelioma

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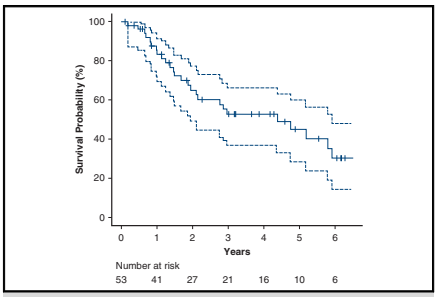
ABSTRACT

Objective: To evaluate the efficacy of multimodality treatment including extended pleurectomy/decortication (P/D) and hyperthermic intraoperative chemotherapy (HIOC) with cisplatin for malignant pleural mesothelioma (MPM), we investigated the pharmacokinetics of platinum, adverse events after HIOC, and survival outcome.

Methods: Fifty-three patients with pathologically diagnosed MPM (cT1-3N0-1M0, excluding sarcomatoid) underwent an extended P/D and HIOC (cisplatin 80 mg/m^2 in saline 2 L, 42°C, 60 minutes) since 2011. The protocol includes postoperative 4 cycles of cisplatin and pemetrexed. Platinum concentrations in the perfusate (before and after) and the serum (1, 2, 4, 8, 24, 48, 72 hours after perfusion) were measured in 10 patients. Mortality and morbidity, especially adverse events of renal function, were investigated, and survival and affecting factors were examined.

Results: All patients obtained macroscopic complete resection and pathologic staging revealed as follows: T1/2/3/4: 12/8/23/10, N0/1: 36/17, stage 1A/1B-3A/3B: 12/31/10, respectively. Platinum concentrations in the perfusate indicated that 28% of the dose remained in the pleural cavity, and the maximum concentration in the serum was 0.91 μg/mL. Six patients (11%) showed elevated max-creatinine (>2 mg/dL) postoperatively. Two patients (4%) received renal-replacement therapy, and one was weaned before discharge. There was no 30-day mortality and one in-hospital death (1.9%). Forty-six patients (87%) received multiple cycles of perioperative systemic chemotherapy. Median overall survival (OS) and disease-free survival (DFS) were 52.4 months and 18.7 months. Patents with stage 1A demonstrated a 5-year OS of 67.3% and a median DFS of 67.1 months, and patients with stage 1B-3A demonstrated a 5-year OS of 50.1% and a median DFS of 20.4 months. Univariate analysis showed histological subtype, p-T, p-stage, and multimodality treatment as significant factors affecting OS. Multivariate analysis revealed histology, p-stage, and multimodality as independent.

Conclusions: Extended P/D and HIOC with cisplatin for MPM is acceptable with limited acute kidney injury. This multimodality protocol provides promising favorable survival for stage 1A-3A disease. (JTCVS Open 2023;16:977-86)



Multimodality treatment including P/D and HIOC for MPM provided median OS of 52 months.

CENTRAL MESSAGE

Multimodality treatment for MPM consisting of P/D, HIOC (cisplatin 80 mg/m^2 in 2 L saline, 42°C, 1 h), and systemic chemotherapy resulted in limited acute kidney injury and favorable overall survival.

PERSPECTIVE

In multimodality treatment for MPM, HIOC combined with cytoreductive surgery has been applied with certain nephrotoxicity. HIOC with low-dose cisplatin demonstrated low Cmax of platinum in the serum, and the multimodal protocol consisting of extended P/D, HIOC, and systemic chemotherapy provides low incidence of AKI and favorable survival in patients with p-stage 1A-3A.

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Abbreviations and Acronyms

AKI = acute kidney injury
CT = computed tomography
DFS = disease-free survival
HIOC = hyperthermic intraoperative chemotherapy
MCR = macroscopic complete resection
MPM = malignant pleural mesothelioma
OS = overall survival
P/D = pleurectomy/decortication
RRT = renal-replacement therapy
s-CRE = serum creatinine

Malignant pleural mesothelioma (MPM) is a rare but aggressive malignancy of the pleura with a dismal prognosis. Median survival of standard-of-care chemotherapy is 12 to 14 months, and 16 months particularly for epithelioid subtype.[1,2] Recent advances in chemotherapy with immune checkpoint inhibitors demonstrated a median survival of 18 months.[2] A nationwide database analysis showed that surgery-based multimodality therapy was associated with improved survival and may offer therapeutic benefits among selected patients.[3] Although multimodality protocols including macroscopic complete resection (MCR), systemic chemotherapy, and radiotherapy showed prolonged survival,[4,5] locoregional recurrence occurs in a majority of patients.[6,7] Therefore, modalities for more effective local control have been investigated.[8,9]

In lung-sparing surgery for MPM, local control treatments include extra-beam radiation therapy and intraoperative intracavitary therapies. Postoperative hemithoracic intensity-modulated pleural radiotherapy has been delivered under the risk of radiation pneumonitis.[10,11] Photodynamic therapy,[12] heated povidone–iodine lavage,[13] and hyperthermic intraoperative chemotherapy (HIOC)[8,9] were administered as intraoperative intracavitary therapies. HIOC poses the advantage of a high-local concentration of cytotoxic anticancer drug with limited side effects. Regional hyperthermia increases the penetration depth, enhances the cytotoxicity of the drug, and exerts direct antineoplastic effects by inducing potent apoptosis of tumor cells.[14,15] The main role of HIOC is to eliminate the microscopic residual cancer cells, which cannot be removed by extended surgical cytoreduction, in the pleural cavity.

We have examined HIOC with cisplatin since we started extended pleurectomy/decortication (P/D) for patients with MPM in 2011. We previously reported an interim result of the protocol including P/D, HIOC, and systemic chemotherapy indicating promising survival.[16] In this study, we examined the pharmacokinetics of cisplatin perfusion, adverse events of HIOC, especially renal function, and acute and long-term results of the patients accrued.

METHODS

This study was a retrospective analysis of all consecutive patients with MPM who were prospectively enrolled in multimodality treatment including extended P/D, HIOC, and postoperative systemic chemotherapy in Tokyo Medical and Dental University. From 2010 to 2022, we enrolled 53 patients who underwent a P/D for MPM. Before 2014, the majority with MPM underwent an extrapleural pneumonectomy, and 4 patients who could not tolerate extrapleural pneumonectomy underwent a P/D, but after 2014 all patients with MPM underwent a P/D as cytoreductive surgery. The indication included pathologically proven MPM excluding sarcomatoid subtype, surgically resectable (T1-3N0-1) without distant metastasis, tolerable cardiopulmonary reserve, and Eastern Cooperative Oncology Group performance status 0–1.

Preoperative assessment included thoracoabdominal computed tomography (CT), magnetic resonance imaging of the brain, and positron emission tomography scan. Pathologic diagnosis was obtained through video-thoracoscopic biopsy or CT-guided biopsy and confirmed with an appropriate panel of immunohistochemical stains. Staging laparoscopy was examined to exclude penetrating diaphragm invasion when suspected. A pulmonary function test was examined to verify the predicted forced expiratory volume in 1 second of more than 1 L, and preoperative echocardiography was employed as an assessment for radical surgery to mainly exclude heart dysfunction.

Surgical Procedure and Multimodality Treatment

The surgical procedure of extended P/D is described elsewhere in detail.[10] To summarize, via a posterolateral thoracotomy through the sixth costal space, the extrapleural plane was dissected normally from the apical regions first. After the apex was reached, the dissection plane proceeded caudally to mediastinal extrapleura, with care taken not to injure great vessels. An additional ninth or tenth intercostal space was usually opened to view the entire diaphragm. Pericardium and diaphragm adjacent to the pleura were excised, when needed, and reconstructed with Gore-Tex patches (W. L. Gore & Associates Inc) later. The extrapleural dissection was carried out to the lung at the hilar reflection. Then, whole visceral pleura including interlobar fissure was dissected from the lung parenchyma to the hilar reflection. When tumors invaded lung parenchyma, an ultrasonic scalpel (Ethicon) was used to liberate the specimen with a parenchymal margin in recent series. Both the parietal and visceral pleura were removed and the pleurectomy was completed. Systemic dissection of the hilar and mediastinal nodes was routinely performed. After the pleurectomy, the pleural space was perfused with a solution of cisplatin (80 mg/m^2) in 2 L of saline maintained at 42 °C for 1 hour using a roller pump with heat generator. The inflow and outflow catheters were placed in the caudal and cephalad positions. A plastic adhesive drape created a seal around the thoracotomy incision. Body temperature was monitored with a rectal probe not to exceed 39 °C. After 1 hour of perfusion, the whole perfusate was removed from the thoracic space and discarded. Then, parenchymal air leak was controlled with direct sutures and fibrin-based glue. Before chest closure, two 24-F chest tubes were placed at the apex and base of the pleural cavity.

Four cycles of intravenous chemotherapy, cisplatin 60 mg/m^2 and pemetrexed 500 mg/m^2, were planned as protocol. The first cycle was scheduled to start within 5 to 10 weeks after the P/D and the following cycles were to repeat every 4 weeks.

Follow-up

Patients were seen on ambulatory visit in 3-months intervals. A CT of chest and abdomen or positron emission tomography scan was obtained every 4 months, or when complains occurred. Date of recurrence was considered to be the first radiographic study on which recurrence was demonstrable. Patients were treated for recurrence on an individualized basis. Modalities and agents included gemcitabine, vinorelbine, pemetrexed,

cisplatin, carboplatin, and local treatments of surgical resection and extra-beam radiotherapy. Immune checkpoint inhibitors were used for patients with recurrence after 2017 when the national health insurance permitted. The median follow-up duration was 55 months.

Pharmacokinetics and Analytical Method

The pharmacokinetics of cisplatin was examined in 10 patients (mean bovine serum albumin 1.74 ± 0.12). Heparinized blood samples (5 mL) for platinum concentration were obtained at 1, 2, 4, 8, 24, 48, and 72 hours after cisplatin perfusion. The blood was centrifuged immediately, and plasma samples to measure total platinum concentrations were stored at −20°. Five milliliters of the perfusion solution was collected before and after HIOC. To measure protein-unbound (free) platinum in the perfusion solution, 1 mL of the solution was centrifuged using an Amicon Centrifree 4104 (Amicon Corp) at 1980*g* for 20 minutes. The concentrations of free platinum and total platinum were determined by flameless atomic absorption spectrometry.[17] While using the concentrations before and after the perfusion, the rate (%) of residual platinum dose in the pleural cavity was defined as $[C_{before}–C_{after}]/C_{before} \times 100$.

Patient characteristics, operative parameters, pathologic stages, and completeness of multimodality treatment were analyzed. MCR was defined as no residual visible or palpable cancer.[18] Postoperative mortality and morbidity, especially renal function, were examined. Predictors of renal failure were investigated; associations between perioperative parameters and the incidence of acute kidney injury (AKI) were analyzed with the Student *t* test. Operative mortality is defined as the death of any reason within 30 days or death without hospital discharge after surgery. Overall survival (OS) was defined as the time from surgery to death from any cause or last patient contact. Disease-free survival (DFS) was defined as the time from surgery to the date of recurrence, death from any cause, or last patient contact. OS and DFS were estimated by the method of Kaplan–Meier. The log-rank test was used to test equality over the strata of selected clinical indications. Univariate and multivariate analyses were examined with Cox proportional hazard model. Statistical significance was set at 0.05. Data were analyzed using SPSS 27.0 (IBM Corp) and EZR version 1.54 (Saitama Medical Center), a graphical user interface for R (The R Foundation for Statistical Computing).

The protocol was approved by Tokyo Medical and Dental University institutional review board (R2013-020, November 25, 2013) and registered to UMIN-CTR (UMIN000016056). Informed consent was obtained from all patients.

RESULTS

The mean age of 53 patients was 67.2 years (range, 45-77 years), and there were 47 men (89%). Twenty-five (47%) patients had a right-side disease. The protocol was to treat patients de novo. However, 5 patients (9%) received preoperative platinum-based chemotherapy in other hospitals and were referred to our department for surgery. All patients were scheduled to receive P/D with HIOC and postoperative systemic chemotherapy.

All patients obtained MCR. Operating time was 666 ± 101 minutes, and blood loss was 3054 ± 1560 mg. Patient characteristics and pathologic TNM staging are shown in Table 1.

Platinum concentrations in the perfusate before and after the perfusion were 37.3 ± 5.5 μg/mL and 26.9 ± 3.9 μg/mL, respectively. This demonstrated 28% of the platinum in the perfusate remained in the pleural cavity after perfusion. Platinum concentrations, total platinum, and free platinum in the serum after perfusion are shown in Figure 1. The total platinum at the end of perfusion showed a maximum concentration of 0.91 ± 0.28 μg/mL and decreased with time for several days. Free platinum at the end of perfusion was 0.57 ± 0.18 μg/mL, and decreased to undetected beyond 4 hours after perfusion.

Changes of serum creatinine (s-CRE) level, preoperative, postoperative maximum, and at discharge, in each patient are demonstrated in Figure 2. Six patients (11%) showed elevated max-CRE (>2 mg/dL) postoperatively; one was oliguric, and 5 were non-oliguric. The patient with oliguria and another patient without oliguria required renal-replacement therapy (RRT) (hemodialysis or continuous hemodialysis and filtration during extracorporeal membranous oxygenation), and the other patients recovered without RRT. At discharge, 2 patients (4%) remained s-CRE >2 mg/dL, and one of them continued hemodialysis. Statistical analyses identified a significant association between the incidence of AKI (CRE >2) and preoperative s-CRE ($P = .021$). However, there was no significant association between the incidence of AKI and OP time or intraoperative blood loss.

Complications are summarized in Table 2. There was no 30-day mortality and one in-hospital death (1.9%). The cause of in-hospital death was nonocclusive mesenteric ischemia on postoperative day 70 after the patient was weaned from a respirator for respiratory failure. Other complications included arrhythmia in 17 patients (32%), prolonged air leak of more than 7 days in 16 patients (30%), and pneumonia/atelectasis in 12 patients (23%). Respiratory failure in 3 patients (6%) required respirator support, and one of them required additional extracorporeal membrane oxygenation, which were all eventually weaned from. Reoperations were needed for (1) prolonged air leak in 5 patients (9%); with smaller skin incision through third to fifth intercostal space multiple air leaks were closed with direct sutures and fibrin glue on postoperative days 11 to 31, resulting in chest tube removal within several days; (2) diaphragmatic hernia in 4 patients (8%); each was due to rupture of anastomosis of residual diaphragm and reconstructed with a 2-mm thick Gore-Tex patch on postoperative days 4 to 23; (3) lung abscess with aspergillus in 1 patient; and (4) empyema in 1 patient. Median postoperative hospital stay was 24 days.

Forty-five patients (85%) received postoperative chemotherapy, and eventually 46 patients (87%) received multiple cycles of perioperative systemic chemotherapy. They were regarded as completion of multimodality treatment. One patient with a microscopic positive margin at the thoracic vertebral (Th4) body received additional postoperative irradiation of 60 Gy.

TABLE 1. Patient and tumor characteristics for 53 patients with malignant pleural mesothelioma who underwent extended pleurectomy/decortication and hyperthermic intraoperative chemotherapy

Characteristics	n		%
Sex			
Male	47		89
Female	6		11
Age, y			
<70	31		58
>70	22		42
Side			
Right	25		47
Left	28		53
Symptom			
Absent	20		38
Present	33		62
Histology			
Epithelioid	45		85
Biphasic	8		15
p-T			
1	12		23
2	8		15
3	23		43
4	10		19
p-N			
0	36		68
1	17		32
UICC p-stage (1B/2/3A)			
1A	12		23
1B	20	┐	38
2	2	31 (= Total)	4
3A	9	┘	17
3B	10		19
Multimodality			
Systemic chemotherapy	46		87
Preoperative		5	9
Postoperative		45	85
Radiation therapy	1		2
None	7		13

UICC, Union for International Cancer Control.

Among 52 patients who survived the surgery, 35 patients (67%) experienced recurrence. First relapse sites were local in 23 (44%; neopleural thickening/mass 9, chest wall mass 9, lymphadenopathy 8, pericardium 3), distant in 3 (19%; abdomen 2, bone 1), and both local (neopleural thickening/mass 7, chest wall mass 1, lymphadenopathy 1, mediastinum 1) and distant (abdomen 7, bone, 1, contralateral thorax 1) in 9 (17%). Treatments for recurrence were surgical resection 23 times in 9 patients (17%) (chest wall resection 11 times in 7 patients, lymphadenectomy 11 times in 3 patients, removal of surface soft tissue twice in 2 patients, pulmonary resection once, and resection of jejunum once), cure-intent irradiation (lung, lymph node, chest wall, including surgical stump) of 13 times in 10 patients (19%), systemic chemotherapy in 25 patients (48%), palliative radiotherapy in 3 patients (6%), and supportive care in 6 patients (12%).

Median OS in all 53 patients was 52.4 months, and 2- and 5-year survivals were 65.2% and 45.0%, respectively (Figure 3, *A*). Median DFS in all patients was 18.7 months, and 2- and 5-year DFS were 39.2% and 20.9%, respectively (Figure 3, *B*). Survival analyses according to staging revealed that among patients with stage 1A, median DFS was 67.1 months and 5-year OS was 67.3%, respectively. Among patients with stage 1B-3A, median DFS was 20.4 months. However, median and 5-year OS was 69.5 months and 50.1%, respectively, although among patients with stage 3B median DFS and OS were 9.5 months and 16.4 months, respectively (Figure 4). Univariate analysis of factors affecting OS identified histologic subtype, p-T factor, p-stage, and accomplishment of multimodality treatment as significant factors. Multivariate analysis revealed histology, p-stage, and multimodality treatment as independent significant factors (Table 3).

DISCUSSION

Rusch and colleagues[19] reported that cisplatin 100 mg/m^2 in 100 mL of saline instilled into the pleural cavity after P/D was rapidly absorbed systemically in 1 hour and that the concentration was greater in the pleural fluid than in the plasma. Recent review of the literature showed a number of intraoperative intrapleural cisplatin perfusions, with a dose range of 50 to 300 mg/m^2 in the perfusate for a duration of 60 to 90 minutes under around 42 °C temperature, respectively, were reported with certain effectiveness, median survivals of 11 to 35 months.[20] In one study that examined the use of cisplatin perfusion in a group of patients with MPM with a favorable risk profile, HIOC led to significantly longer DFS (27.1 vs 12.8 months) and OS (35.3 vs 22.8 months) than the comparison group.[21] However, approximate one half of the patients who received high-dose (175-225 mg/m^2) HIOC experienced AKI, and a greater rate of RRT was required in a later analysis.[22] The effectiveness of HIOC needs to be balanced against its toxicities. Whereas a few previous studies have evaluated the pharmacokinetics of cisplatin in the perfusate and the serum.[14,23,24]

We investigated cisplatin pharmacokinetics by measuring the concentration of the perfusate and the serum under a single-dose protocol (80 mg/m^2 in 2 L of saline). The concentration change of the perfusate before and after perfusion indicated that approximately 30% of perfused cisplatin was left in the pleural cavity. The perfused cisplatin should have moved to the decorticated lung parenchyma or the surface of the pleural cavity due to the concentration gradient between the perfusate and the adjunct tissues. Then, the platinum was absorbed into the serum through lung parenchyma or pleural

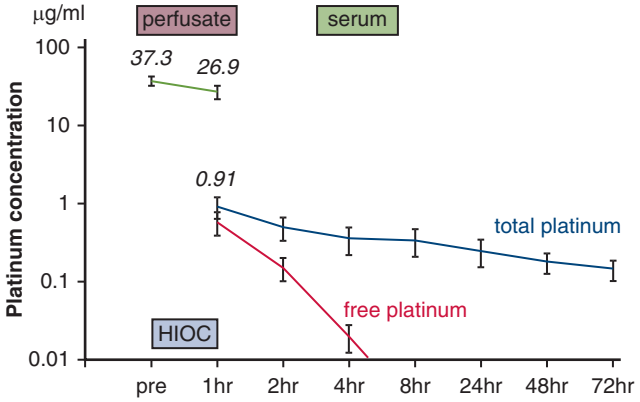


FIGURE 1. Semilogarithmic plot of the mean concentration–time curves of platinum in the perfusate and the serum before and after cisplatin perfusion. *HIOC*, Hyperthermic intraoperative chemotherapy.

cavity's surface. Total platinum concentrations in the serum of our series showed that maximum concentration of 0.91, and area under the concentration–time curve appeared to be lower than those administered similar dose intravenous drip in the literature.[25-28] Measuring platinum concentrations could reveal platinum doses of consistent intravenous administration and predict the safety of intrapleural cisplatin perfusion.

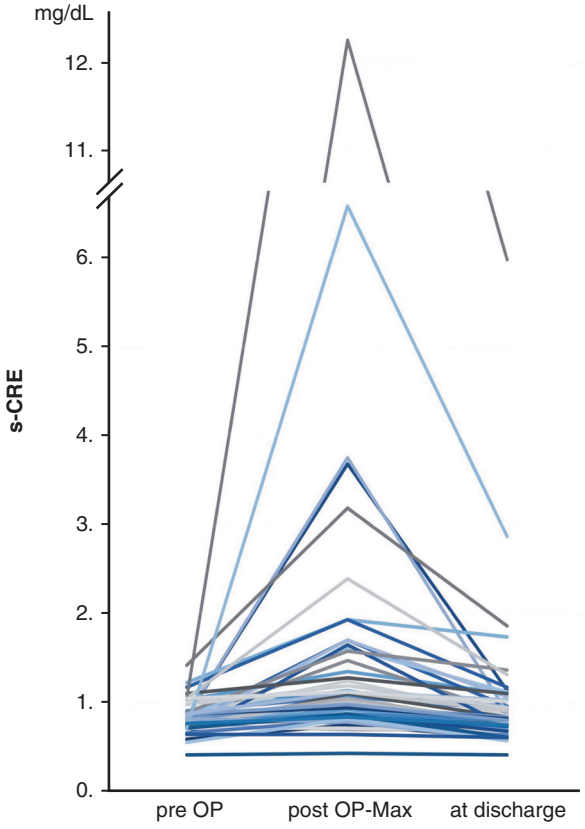


FIGURE 2. Changes in serum creatinine level; preoperative, postoperative maximum, at discharge, in each patient were depicted. *s-CRE*, Serum creatinine; *OP*, operative.

TABLE 2. Postoperative complications

Complications	n (%)
Arrythmia	17 (32)
Prolonged air leak (>7 d)	16 (30)
Pneumonia/atelectasis	12 (23)
Pleuritis/empyema	6 (11)
Acute kidney injury	6 (11)
Diaphragmatic hernia	4 (8)
Congestive heart failure	3 (6)
Respiratory failure	3 (6)
Chylothorax	2 (4)
Tube drainage, d	13.0 ± 9.7

AKI is common after major surgery and has been associated with increased length of stay and mortality.[29,30] Proximal tubules are at risk of injury, caused by ischemia and nephrotoxicity. Intraoperative hypotension, decreased renal blood flow, or exposure to cytotoxic effects of absorbed cisplatin cause nephrotoxicity.[31] Grade 4 nephrotoxicity requires RRT. In our series, 6 patients (11%) showed elevated s-CRE (>2 mg/dL), and 5 of them preserved urine output. Two patients (4%) received RRT; One with oliguria and high s-CRE level (8 postoperative day) received hemodialysis twice a week and continued after discharge. The other was attributed to vancomycin use for pneumonia and received continuous hemodialysis and filtration (23 postoperative day) during extracorporeal membrane oxygenation for respiratory failure, from which the patient was weaned later. Eventually 1 patient (2%) experienced nephrotoxicity requiring persistent RRT due to low-dose cisplatin HIOC.

In survival analyses, a median OS of 52.4 months in all cohorts was a favorable long-term survival comparing recent literatures.[20,32-34] This might be because of complete MCR in all patients, 87% accomplishment of the multimodality treatment, and inclusion of HIOC in the protocol. It is difficult to evaluate the specific effect of a single modality in the multimodality setting. Considering the median DFS of 18.7 months, the treatment for recurrence should have led to prolonged OS. In our series, locoregional treatments, surgical resection, and/or cure-intent irradiation for oligometastases were performed total 36 times in 11 patients. Patients who received a local treatment for recurrence demonstrated significantly longer post-recurrent survival than those with chemotherapy alone (n = 17) (median postrecurrence survival; 43.3 vs 9.1 months, $P = .0115$), which should be brought by lung-preserved surgery for MPM.

Analyses of factors affecting survival identified histologic subtype, staging (p-T factor and p-stage), and

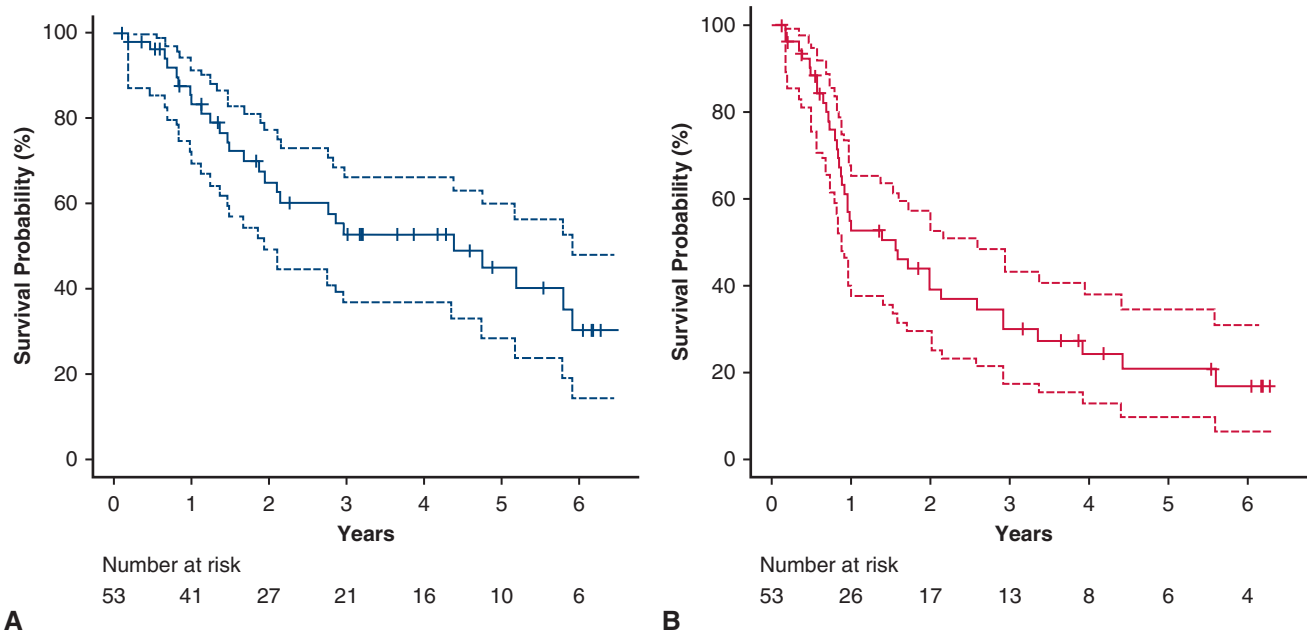


FIGURE 3. Overall survival (A) and disease-free survival (B) of all intent to treat patients (n = 53). Kaplan–Meier curve and 95% confidence interval.

accomplishment of multimodality treatment, which were revealed as independent factors in multivariate analysis. Epithelioid histology and multimodality treatment were previously reported as favorable factors.[3,4] Pathologic staging in our cohort predicted stratification of postoperative survivals: patients with stage 1A (T1N0) showed a DFS of more than 60 months, resulting in favorable long-term OS. Patients with stage 1B-3A (T2-3N0-1), whose number was limited and OS and DFS in each stage showed no significant difference, demonstrated a DFS of 20.4 months. However, median OS reached more than 60 months. They were the candidates for possible cure with repetitive

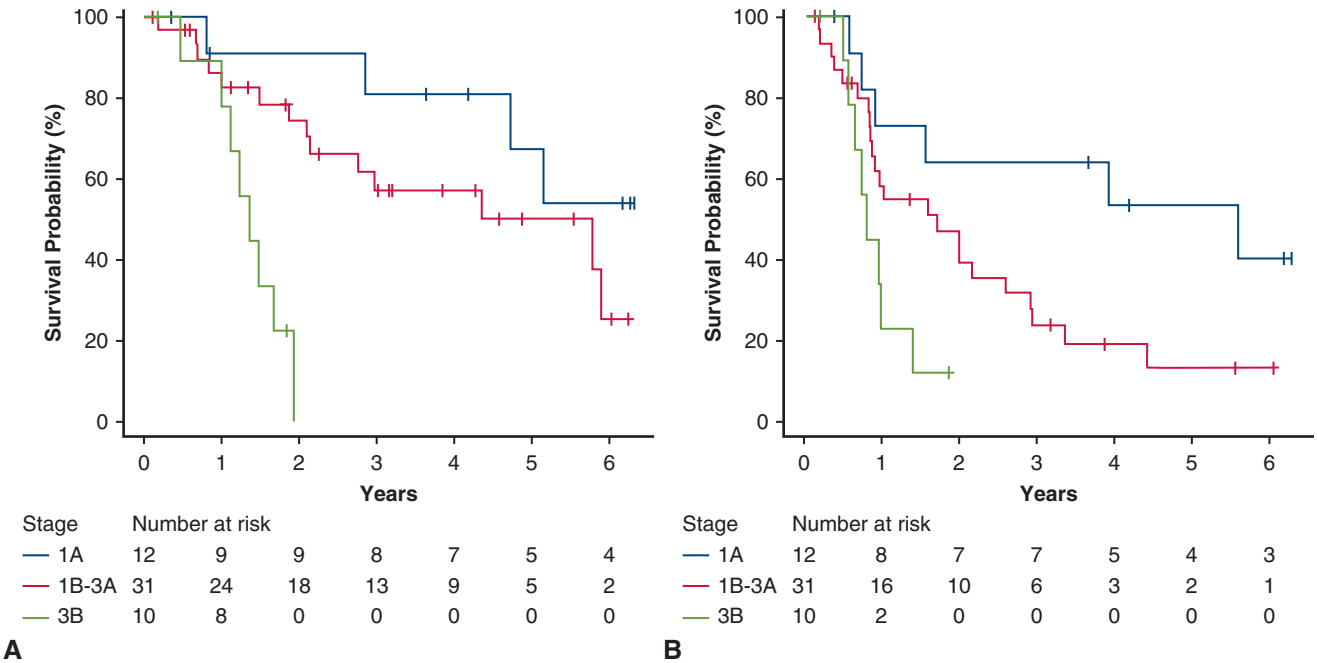


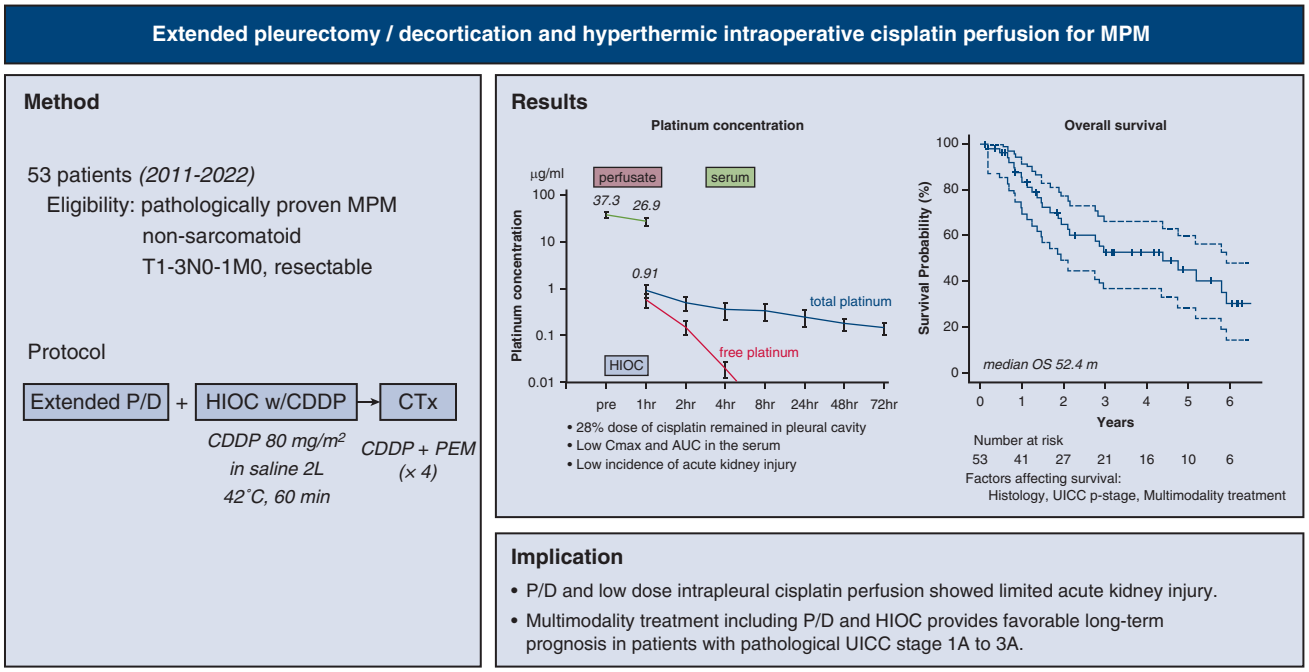
FIGURE 4. Overall survival (A) and disease-free survival (B) sorted by UICC staging 1A (n = 12)/1B-3A (n = 31)/3B (n = 10). Kaplan–Meier curve. The 95% confidence intervals are shown separately in Table E1.

TABLE 3. Analysis of association of overall survival with patient factors (Cox model)

Factors	Category	Univariate analysis			Multivariate analysis		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Sex	M/F	0.732	0.352-1.518	.401	0.786	0.156-3.957	.771
Age	<70/>70	1.166	0.534-2.544	.700	1.708	0.688-4.241	.249
Side	Rt/Lt	1.185	0.810-4.067	.148			
Symptom	−/+	0.849	0.390-1.846	.679			
Histology	E/B	4.602	1.726-12.275	.002	4.087	1.469- 11.371	.007
p-T	1/2/3/4	1.950	1.212-3.138	.006			
p-N	0/1	1.365	0.603-3.091	.456			
UICC p-stage	1A/1B-3A/3B	3.581	1.687-7.602	<.001	3.286	1.440-7.499	.005
Multimodality	−/+	0.266	0.097- 0.724	.010	0.241	0.077- 0.751	.014

HR, Hazard ratio; *CI*, confidence interval; *M*, male; *F*, female; *Rt*, right; *Lt*, left; *E*, epithelioid; *B*, biphasic; *UICC*, Union for International Cancer Control.

anticancer treatment. While patients with stage 3B (T4N0-1) demonstrated poor prognosis, median DFS of 9.5 months and median OS of 16.4 months. They appeared not to have received benefits from invasive surgery. Pathologic T4 was diagnosed with the excised specimen postoperatively—penetrating pericardial invasion, invasion to aorta, vertebra, or multiple chest walls.[35] Considering the poor postoperative prognosis, we would exclude these patients from surgery, or put them on previous chemotherapy followed by cyto-reduction surgery when downstaged. Accurate staging would be obtained before invasive surgery.



MPM: malignant pleural mesothelioma, P/D: pleurectomy/decortication, HIOC: hyperthermic intraoperative chemotherapy, CTx: chemotherapy, CDDP: cisplatin, PEM: pemetrexed, Cmax: maximum concentration, AUC: area under the concentration-time curve, OS: overall survival

FIGURE 5. Study methods, results, and imprecations. *MPM*, Malignant pleural mesothelioma; *P/D*, pleurectomy/decortication; *HIOC*, hyperthermic intraoperative chemotherapy; *CDDP*, cisplatin; *CTx*, chemotherapy; *PEM*, pemetrexed; *Cmax*, maximum concentration; *AUC*, area under the concentration–time curve; *UICC*, Union for International Cancer Control.

There are several limitations to our study. Generalizability is limited because this report is from a single institution that performs a technically demanding, complex surgical procedure under the multimodality protocol. The number of patients was limited, and patients of each subclassified stage were insufficient to analyze statistically, which could explain no survival difference among pathologic nodal status. The pharmacokinetics study of a single dose could not quantify outcomes or risk factors, although the obtained data were reproducible. Finally, postrecurrence chemotherapy was not consistent throughout the study period. Novel immune-oncology drug became available for recent recurrence despite limited benefits.

In summary, extended P/D and HIOC with cisplatin for MPM is acceptable with limited AKI (Figure 5). Multimodality treatment with this protocol provides promising DFS for stage 1A and favorable survival with repetitive anticancer treatment for stage 1B-3A.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: malignant pleural mesothelioma, pleurectomy/decortication, hyperthermic intraoperative intrapleural chemotherapy, cisplatin, concentration, acute kidney injury, survival

TABLE E1. The 95% CIs for the 2 survival curves shown in Figure 4

Overall survival			Disease-free survival		
Time, y	Survival probability (%) (95% CI)		Time, y	Survival probability (%) (95% CI)	
Stage 1A			Stage 1A		
Baseline	100.0	(100.00-100.00)	Baseline	100.0	(100.00-100.00)
1	90.9	(50.8-98.7)	1	72.7	(37.1-90.3)
2	90.9	(50.8-98.7)	2	63.6	(29.7-84.5)
3	80.8	(42.3-94.9)	3	63.6	(29.7-84.5)
4	80.8	(42.3-94.9)	4	53.0	(20.9-77.3)
5	67.3	(27.7-88.5)	5	53.0	(20.9-77.3)
6	53.9	(17.6-80.2)	6	39.8	(11.0-68.0)
Stage IB-3A			Stage IB-3A		
Baseline	100.0	(100.00-100.00)	Baseline	100.0	(100.00-100.00)
1	82.3	(62.6-92.3)	1	54.3	(34.5-70.5)
2	74.2	(53.3-0.869)	2	38.8	(21.0-56.4)
3	57.2	(35.8-73.8)	3	23.3	(9.6-40.4)
4	57.2	(35.8-73.8)	4	18.6	(6.5-35.7)
5	50.1	(27.6-69.0)	5	12.4	(2.7-30.0)
6	25.0	(5.0-52.8)	6	12.4	(2.7-30.0)
Stage 3B			Stage 3B		
Baseline	100.0	(100.00-100.00)	Baseline	100.0	(100.00-100.00)
1	88.9	(43.3/98.4)	1	22.2	(3.4-51.3)
2			2		
3			3		
4			4		
5			5		
6			6		

CI, Confidence interval.