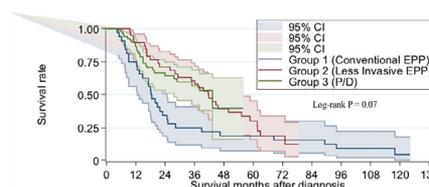




Surgical Risk and Survival Associated With Less Invasive Surgery for Malignant Pleural Mesothelioma

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We compared less invasive surgery with conventional surgery for malignant pleural mesothelioma (MPM). We retrospectively reviewed consecutive patients with MPM who received surgery at Hyogo College of Medicine between July 2004 and April 2016. Patients underwent multimodal treatment comprising chemotherapy (neoadjuvant and/or adjuvant) and surgery with or without 54 Gy hemithoracic radiotherapy. Patients were grouped into 3 groups according to the surgery intended: Conventional extrapleural pneumonectomy was intended in Group 1 (until August 2009); less invasive extrapleural pneumonectomy was intended in Group 2 (after September 2009); pleurectomy/decortication was intended in Group 3 (after September 2012). We included 152 patients (median age 64 [37–71] years; 131 men, 21 women), mostly with epithelioid subtypes (91.4%). Of them, 149 (98.0%) underwent neoadjuvant chemotherapy and 117 (77.0%) underwent surgery (60 had extrapleural pneumonectomy and 57 had pleurectomy/decortication). Macroscopic complete resection was achieved in 94.9% (111/117), and the mortality rates at 30 and 90 days were 1.7% (2/117) and 3.4% (4/117), respectively. The overall median survival time and progression-free survival for all 152 patients were 34.9 and 17.4 months. The overall median survival time for Groups 1, 2, and 3 were 18.5, 41.9, and 43.4 months, respectively. The progression-free survival for Groups 1, 2, and 3 were 12.0, 24.5, and 21.8 months, respectively. Compared with conventional surgical techniques, less invasive surgery for MPM yielded lower surgical risks and comparable or improved survival.



The overall median survival for Groups 1, 2, and 3 were 18.5, 41.9, and 43.4 months, respectively.

Central Message

Surgery that is less invasive than conventional extrapleural pneumonectomy could achieve lower surgical risk without compromising survival in patients with malignant pleural mesothelioma.

Perspective Statement

Patients with resectable mesothelioma typically have low survival despite the need for aggressive surgery. We showed that less invasive surgery could result in comparable overall survival rates to conventional invasive surgery.

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Abbreviations: CT, computed tomography; EPP, extrapleural pneumonectomy; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; MPM, malignant pleural mesothelioma; MST, median survival time; P/D, pleurectomy/decortication; PFS, progression-free survival

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INTRODUCTION

Malignant pleural mesothelioma (MPM) is associated with a very poor prognosis.¹ At present, multimodality therapy comprising chemotherapy and surgery, with or without radiotherapy, is the strategy of choice for resectable disease.² The 2 surgeries used for MPM are extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D), and the goal of both is to achieve macroscopic complete resection.^{3,4} Although EPP is theoretically more radical than P/D, in 2008, a large-scale retrospective study revealed favorable survival in P/D over EPP.⁵ Consequently, arguments have arisen as to whether the invasiveness of EPP can still be justified,^{6–8} and efforts have been made to develop less invasive techniques that do not compromise survival.^{9–14}

We switched to less invasive EPP after 5-year experience of conventional EPP. Then, 3 years later, we moved to P/D, seeking for further lower invasiveness. We report our 12-year experience with less invasive surgery for resectable MPM.

PATIENTS AND METHODS

Study Design

This was a retrospective cohort study at single institution. We reviewed the data for all 152 consecutive patients registered in the database of the Hyogo College of Medicine MPM Surgery Program between July 2004 and April 2016. According to the initial surgical intent, patients were divided into 3 groups. Patients in whom conventional EPP surgery was intended from 2004 to 2009 were classified as Group 1. Patients in whom less invasive EPP surgery was intended after 2009 were classified as Group 2. Patients in whom P/D or extended P/D was intended were classified as Group 3. All eligible patients were included in the program after providing informed consent. This study was approved by the institutional review board of Hyogo College of Medicine (HCM-IRB 0044, March 22, 2006).

Eligibility Criteria

Eligibility criteria were age ≤75 years for EPP or ≤80 years for P/D, histologically confirmed diagnosis of any type of MPM, clinical stage T1-3N0-1M0 disease, an Eastern

Cooperative Oncology Group performance status of 0–1, no major comorbidity, and written informed consent. Respiratory reserve was calculated by pulmonary function tests and quantitative ventilation/perfusion scans, and we required a predicted postoperative forced expiratory volume in 1 s of at least 1 L. Patients with sarcomatoid histology were excluded from registration after 2012. Otherwise, patients were excluded from the program if they had previously undergone treatment for MPM, had serious concomitant disorders, or had pathologically proven N2 disease. Patients were also excluded from surgery, regardless of resectability, if disease progression had occurred despite neoadjuvant chemotherapy.

Multimodality Therapy and Treatment Protocol

Multimodal therapy was intended for all patients. The changes in surgical technique over the study period are summarized in Table 1. Major complications of chemotherapy, surgery, or radiotherapy were graded according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0) guidelines.¹⁵ Chemotherapy, surgery, and radiotherapy were performed as follows.

Chemotherapy

Patients included until the end of 2006 (n = 9) underwent neoadjuvant chemotherapy with a variety of regimens. Thereafter, all patients received platinum plus pemetrexed.

Conventional EPP Surgery (2004–2009)

Conventional EPP was defined as en bloc resection of the lung and the parietal and visceral pleura with or without resection of the ipsilateral diaphragm or pericardium. We employed posterolateral thoracotomy at the fifth or sixth costal bed with division of the anterior costal arch, adding another thoracotomy if required. Division of the anterior costal arch provided a wide and continuous exposure of the pleural cavity which facilitated safe and radical dissection of the pericardium and the diaphragm.¹⁶ En bloc resection of skin, chest wall, and adjacent ribs, along with previous biopsy sites, was mandated. The diaphragm was reconstructed in the anatomical position using a 2-mm Gore-Tex patch (GORE-TEX Soft Tissue Patch 13150S; W.L. Gore & Associates, Inc., Arizona). The

Table 1. Changes in Surgical Technique

	Group 1 (n = 32)	Group 2 (n = 39)	Group 3 (n = 81)
Thoracotomy	Fifth or sixth costal bed	Sixth or seventh costal bed	Seventh costal bed
Use of VATS	Supplementary	Essential	Essential
Division of anterior costal arch	Yes	No	No
Rib resection at previous port sites	Yes	No	No
Diaphragm/pericardium resection	If required	If required	Avoid with maximal efforts
Preoperative stage			
I	6 (18.8%)	16 (41.0%)	34 (42.0%)
II	17 (53.1%)	14 (35.9%)	32 (39.5%)
III	9 (28.1%)	9 (23.1%)	15 (18.5%)

VATS, video-assisted thoracoscopic surgery.

pericardium was reconstructed with 1 or 2 sheets of 0.1-mm Gore-Tex patch (PRECLUDE Pericardial membrane IPCM102; W.L. Gore & Associates, Inc.) with care taken to avoid constriction of cardiac motion.

Revised Less Invasive EPP Surgery (2009 Onward)

A less invasive EPP procedure was introduced in 2009 (Table 1). The main purpose of this refinement was to preserve the rigidity of chest cavity. To complete all the surgical procedure through a single thoracotomy without dividing anterior costal arch, thoracotomy level was moved from fifth to seventh or eighth costal bed. Since the above changes led to loss of direct vision to the apical area, monitor vision with video-assisted thoracoscopy was mandated. Video-assisted thoracoscopy was also applied to parietal pleurectomy at the costophrenic angle. To preserve the rigidity of chest cavity, adjacent ribs at previous port sites were not resected, but only skeletonized and left intact.

P/D Surgery (2012 Onward)

P/D was introduced in September 2012, and since then it has been our policy to select the least invasive surgical procedure for achieving macroscopic complete resection.^{18,19} In this study, P/D was defined as complete resection of the parietal and visceral pleura, regardless of the existence of visible tumor²⁰; otherwise, the operation was classified as R2 resection. Resection of the diaphragm, pericardium, or lung parenchyma was only added if required. In patients undergoing P/D, maximal efforts were made to avoid patch reconstruction of the diaphragm or pericardium, because we speculated that an artificial patch would not adhere to the decorticated lung parenchyma, which would result in prolonged air leakage. Cotton gloves were quite useful because they provided delicate finger manipulation with strong grip in dissecting thin and fragile parietal and visceral pleura from the diaphragm, pericardium, and lung parenchyma. Visceral pleurectomy was performed basically by direct eye vision, not by monitor vision. Conversion from P/D to EPP was decided only when diffuse tumor invasion to the pulmonary parenchyma was found during surgery.

Radiotherapy

A 54 Gy adjuvant hemithoracic irradiation was performed within 12 weeks of EPP.

Measurements and Outcomes

Chest computed tomography (CT), brain magnetic resonance imaging, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), exercise electrocardiography, echocardiography, and quantitative pulmonary ventilation/perfusion scans were mandated before registration. Extended surgical staging was performed if histologic confirmation was required for suspected extensive disease. Twenty-one patients underwent mediastinoscopy, contralateral thoracoscopy, or laparoscopy. Tumors were staged according to version 7 of the International Mesothelioma Interest Group staging system.¹⁷ Chest CT or FDG-PET/CT was used for prospective observation every 3 months or until death. Local recurrence was defined as tumor relapse in the ipsilateral hemithorax or in the mediastinum, and distant recurrence was defined as tumor recurrence in the contralateral hemithorax, abdomen, or another extrathoracic location. If patients relapsed, appropriate treatment was given according to their condition and preference.

Statistical Analysis

We calculated survival periods from the date of first pathologic diagnosis to date of death, and progression-free survival (PFS) was calculated from the date of pathologic diagnosis. Analysis was based on data updated on January 31, 2017. We used the Kaplan-Meier method to estimate the survival and compared the survivals between groups by Log-rank test. Variables potentially confounding survival were adjusted including age (≥ 65 vs < 65), gender, performance status (0 vs 1), preoperative cancer stage (0–II vs III), epithelioid, and macroscopic complete resection. These factors were included in the multivariable Cox proportional hazard models and hazard ratios (HRs) were estimated. STATA/SE version 14.2 software (STATA Corporation, College Station, TX) was used for statistical analyses. Statistical significance was set at two-tailed $P < 0.05$.

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 2. One hundred and fifty-two patients were included and the median age was 64 years (range 37–71). Men accounted for 86.2% (131). The tumor histologic types were epithelioid ($n = 139$), biphasic ($n = 11$), and sarcomatoid ($n = 2$).

	Group 1 ($n = 32$)	Group 2 ($n = 39$)	Group 3 ($n = 81$)	P Value
Median age, years (range)	62 (47–71)	63 (37–71)	66 (42–77)	0.002
Male gender, n (%)	24 (75.0%)	34 (87.2%)	73 (90.1%)	0.108
Right-sided, n (%)	15 (46.9%)	17 (43.6%)	52 (64.2%)	0.059
Performance status >1 , n (%)	3 (9.4%)	5 (12.8%)	3 (3.7%)	0.145
Histology (epi/bi/sar)	28/2/2	38/1/0	74/7/0	0.26
IMIG c-stage (I/II/III)	6/17/9	16/14/	34/32/15	0.521

Of the 152 patients, 149 (98%) proceeded to neoadjuvant chemotherapy with platinum plus pemetrexed ($n = 140$) or other regimens ($n = 9$), and the remaining 3 underwent EPP without neoadjuvant chemotherapy (Fig. 1). Neoadjuvant chemotherapy was discontinued in 2 patients because they developed hepatic dysfunction or a respiratory disorder, so 147 patients completed neoadjuvant chemotherapy. Of these, 124 proceeded to surgery, and the remaining 23 did not because of progressive disease ($n = 12$) or because they refused to provide consent ($n = 11$). Of the 127 patients who proceeded to surgery, with ($n = 124$) and without ($n = 3$) neoadjuvant chemotherapy, 117 completed surgery and 10 received exploratory thoracotomy because of unexpected tumor extension. Of 117 patients who underwent surgery, 26 patients in Group 1 had conventional EPP, 34 patients in Group 2 and 5 patients in

Group 3 had less invasive EPP, and 57 patients in Group 3 had P/D. After introduction of P/D in September 2012, less invasive EPP was performed as the primary choice of surgical technique ($n = 2$) or after conversion from P/D ($n = 5$).

Finally, 88 of the 152 patients (57.9%) completed surgery plus both the neoadjuvant and adjuvant treatments: 31.2% in Group 1 (10/32), 59.0% in Group 2 (23/39), and 67.9% in Group 3 (55/81).

Surgical Results

Macroscopic complete resection was achieved in 94.9% (111/117) of patients who completed surgery: 88.5% in Group 1 (23/26), 100% in Group 2 (29/29), and 95.2% in Group 3 (59/62) (Table 3). Four patients had R2 resection with macroscopic residual tumors of the chest wall ($n = 2$), aorta ($n = 1$), or lung parenchyma ($n = 1$). Two other patients had dense inflammatory adhesions between part of the visceral pleura and lung parenchyma, making complete visceral pleurectomy technically difficult. Because these latter 2 patients had insufficient cardiopulmonary reserve for EPP, they underwent incomplete visceral pleurectomy with no residual tumor on the pulmonary parenchyma, and were classified as having R2 resection.

One patient in Group 1 died of bleeding from the descending aorta on postoperative day 15. Two patients in Group 1 and 1 in Group 3 died of acute respiratory distress syndrome on postoperative days 48, 72, and 30, respectively. The overall postoperative mortality rates at 30 and 90 days for patients undergoing operation were 1.7% (2/117) and 3.4% (4/117), respectively. The 30-day surgical mortality rates were 3.8%, 0%, and 1.6% for Groups 1, 2, and 3, respectively; the corresponding 90-day surgical mortality rates were 11.5%, 0%, and 1.6%. After adjuvant chemotherapy, another patient in Group 1 died of interstitial pneumonia, but no patient had other grade 4 or higher adverse events related to chemotherapy or radiotherapy. Within 6 months of surgery, death occurred in 8 (30.8%), 1 (3.4%), and 2 (3.2%) patients in Groups 1, 2, and 3, respectively. Of these, 4 deaths in Group 1 were tumor-related, but the others were not.

The surgery-related adverse events are summarized in Table 3. Grade 3 or higher adverse events occurred in 12 patients in Group 1 (46.2%), 10 patients in Group 2 (34.5%), and 18 patients in Group 3 (29.0%). Reoperation was required in 6 patients in Group 1 (23.1%), 8 patients in Group 2 (27.6%), and 7 patients in Group 3 (11.3%). Two patients in Group 3 underwent completion EPP because they developed uncontrollable lung abscesses on postoperative days 10 and 50, respectively. Prolonged air leakage, defined as an air leak lasting 7 days or longer, developed in 27 patients in Group 3 (43.5%); of these, 12 received pleurodesis, 4 required reinsertion of chest tubes, and 3 underwent rethoracotomy.

Survival

There was one censored case in Group 2, who refused surgery and lost follow-up after completion of neoadjuvant

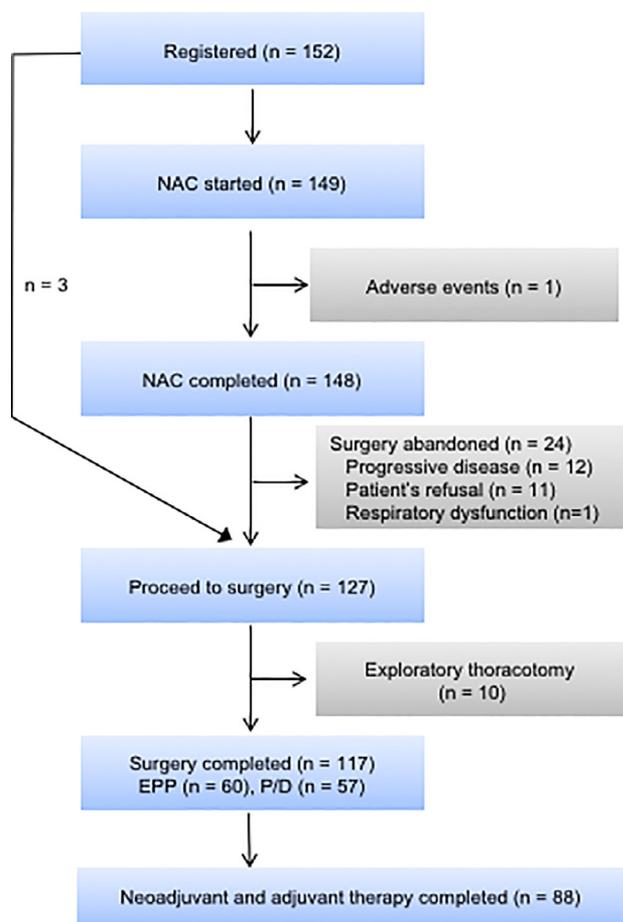


Figure 1. Patients' characteristics. Of the 152 registered patients, 3 underwent EPP without preoperative treatment, and the remaining 149 received neoadjuvant chemotherapy. Surgery was completed in 117 patients (60 EPP and 57 P/D) with a 94.9% (111/117) macroscopic complete resection rate. Completion of neoadjuvant chemotherapy, surgery, and adjuvant treatment with either radiotherapy or chemotherapy was achieved in 58% (88/152) of the registered patients. Abbreviations: EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortication.

Table 3. Surgical Results in Whom Surgery Was Completed

	Group 1 (n = 26)	Group 2 (n = 29)	Group 3 (n = 62)	P Value
Operation time (min), median (range)	524 (379–769)	430 (229–676)	509 (362–882)	<0.0001
Blood loss (g), median (range)	1765 (600–9060)	1320 (365–6380)	1545 (480–7648)	0.396
Average number of resected ribs (range)	2.4 (1–5)	1.0 (1–2)	1.0 (1–1)	<0.0001
Patch reconstruction of diaphragm, n (%)	25 (96.1%)	25 (86.2%)	22 (35.5%)	<0.0001
Patch reconstruction of pericardium, n (%)	26 (100%)	24 (82.8%)	28 (45.2%)	<0.0001
Macroscopic complete resection, n (%)	23 (88.5%)	29 (100%)	59 (95.2%)	0.153
NAC, surgery, and adjuvant treatment completed, n (%)	10 (38.5%)	23 (79.3%)	55 (88.7%)	<0.0001
IMIG p-stage (I/II/III/IV)	0/5/17/4	5/6/18/0	18/11/29/4	0.053
30-day mortality, n (%)	1 (3.8%)	0 (0%)	1 (1.6%)	
90-day mortality, n (%)	3 (11.5%)	0 (0%)	1 (1.6%)	
6-month mortality, n (%)	8 (30.8%)	1 (3.4%)	2 (3.2%)	
Prolonged air leakage (>7 d)	NA	NA	27 (43.5%)	
Patients with Gr ≥3 AEs	12 (46.2%)	10 (34.5%)	18 (29.0%)	
Reoperation	6 (23.1%)	8 (27.6%)	7 (11.3%)	
Bleeding	1 (3.8%)	1 (3.4%)	0	
Patch dislocation	2 (7.7%)	2 (6.9%)	1 (1.6%)	
Bronchopleural fistula	2 (7.7%)	0	0	
Cardiac tamponade	0	1 (3.4%)	0	
Persistent air leak	0	0	3 (4.8%)	
Empyema/lung abscess	1 (3.8%)	4 (14.0%)	2 (3.2%)*	
Esophageal injury	0	0	1 (1.6%)	
Arrhythmia, heart failure	5 (19.2%)	8 (27.6%)	10 (16.1%)	
Pneumonia/empyema	3 (11.5%)	6 (20.7%)	5 (8.1%)	
ARDS/interstitial pneumonia	3 (11.5%)	1 (3.4%)	5 (8.1%)	
Tracheostomy	1 (3.8%)	0	2 (3.2%)	
Delirium	0	1 (3.4%)	3 (4.8%)	
Cerebral infarction	0	0	1 (1.6%)	
Pulmonary embolism	0	0	1 (1.6%)	
Renal dysfunction	0	1 (3.4%)	1 (1.6%)	

AE, adverse event; NAC, neoadjuvant chemotherapy.

*These 2 patients required pneumonectomy due to lung abscess.

chemotherapy. The median follow-up after diagnosis for survivors was 29.2 months (range 4.0–124.1 months). The overall median survival time (MST) and PFS for all patients (n = 152) was 34.9 months (95% confidence interval [CI] 23.8–43.4) and 17.4 months (95% CI 15.2–23.3), respectively. The MSTs for Groups 1, 2, and 3 were 18.5 (95% CI 12.5–24.8), 41.9 (95% CI 28.0–55.2), and 43.4 months (95% CI 27.5–in calculable), respectively (Fig. 2). The PFSs for Groups 1, 2, and 3 were 12.0 (95% CI 8.3–15.4), 24.5 (95% CI 15.9–32.3), and 21.8 months (95% CI 15.4–25.5), respectively (Fig. 3). There was no significant difference in both OS and PFS among Groups (Online Tables 1 and 2).

Survivals of patients in whom surgery was completed were as follows (Table 4). Overall median survival for all surgical patients (n = 117), Group 1 (n = 26), Group 2 (n = 29), and Group 3 (n = 62) were 43.4 months, 17.7 months, 45.6 months, and 43.4 months, respectively. Median PFS for all surgical patients, Group 1, Group 2, and Group 3 were 23.8 months, 12.1 months, 28.9 months, and 25.5 months, respectively.

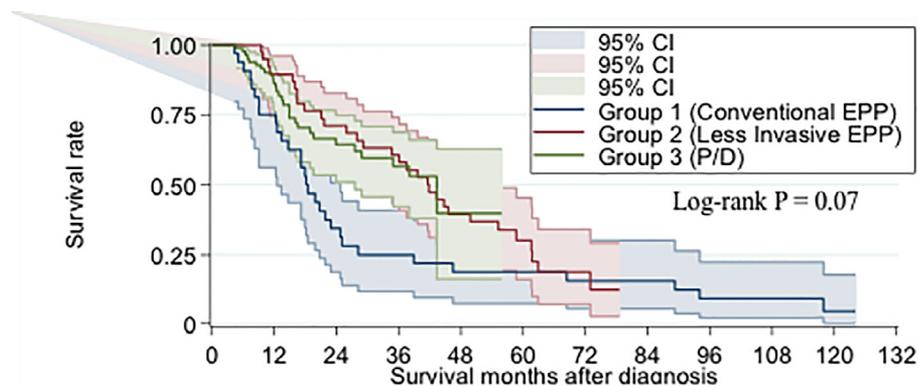
Local recurrence occurred in 75.0%, 48.2%, and 85.6% in Groups 1, 2, and 3, respectively (Table 5 and Online Table 3).

There was no significant difference in recurrence patterns among Groups 1–3.

DISCUSSION

This study describes the results of multimodality therapy in 152 patients with MPM at Hyogo College of Medicine over 12 years. The initial 5 years (Group 1, conventional EPP) produced unacceptable outcomes, with 30- and 90-day surgical mortalities of 3.8% and 11.5%, respectively, a surgical morbidity of 46.2%, and an MST of 18.5 months. Improved surgical risks and survivals were obtained in Group 2 patients in whom less invasive EPP was intended: no 30- and 90-day surgical mortalities and an MST of 41.9 months. Switching from less invasive EPP to P/D did not compromise the results: 30- and 90-day surgical mortalities and MST in Group 3 (P/D) were 1.6%, 1.6%, and 43.4 months, respectively.

Although some of the surgical insult in the initial period (Group 1) could not be separated from EPP, we thought that the massive chest wall damage caused by multiple resections of the rib cage could be managed. Thus, conversion from conventional EPP to the less invasive EPP surgery focused on preserving chest wall rigidity (Group 2). MPM surgery requires good



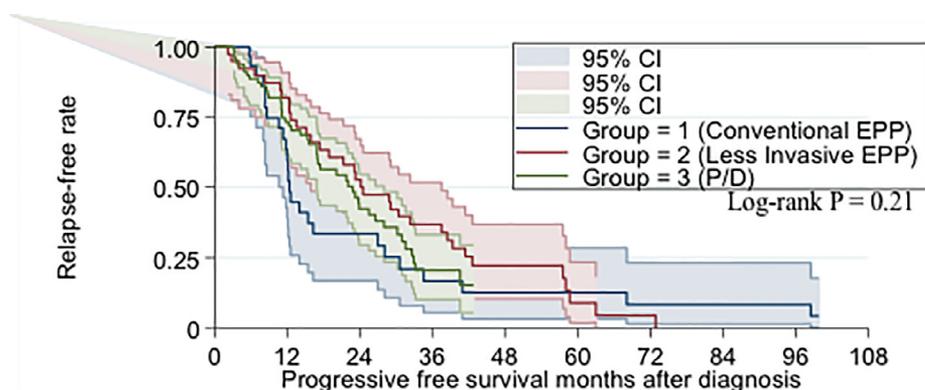
Interval		0 month	12 months	24 months	36 months	48 months	60 months	72 months	84 months	96 months	108 months	120 months
Group 1 (Conventional EPP)	Number	32	24	11	8	6	6	5	5	3	2	1
	Survival rate 95% Confidence interval		0.56 - 0.87	0.19 - 0.51	0.12 - 0.41	0.08 - 0.34	0.08 - 0.34	0.06 - 0.30	0.06 - 0.30	0.02 - 0.22	0.02 - 0.22	0.004 - 0.18
Group 2 (Less Invasive EPP)	Number	39	34	27	23	15	8	3				
	Survival rate 95% Confidence interval		0.74 - 0.96	0.54 - 0.83	0.43 - 0.74	0.24 - 0.54	0.16 - 0.45	0.07 - 0.34				
Group 3 (P/D)	Number	81	62	30	18	2						
	Survival rate 95% Confidence interval		0.76 - 0.92	0.51 - 0.75	0.42 - 0.69	0.16 - 0.63						

Figure 2. Overall survival by groups. For Group 1, overall 1- and 2-year survival rates were 75.0% and 34.4%, respectively; for Group 2, the respective survival rates were 89.5%, and 71.1%; and for Group 3, the respective survival rates were 86.0% and 64.3%. The overall median survival times for Groups 1, 2, and 3 were 18.5, 41.9, and 43.4 months, respectively. There was no significant difference in overall survival among the 3 groups.

visibility and access from the apical area down to the costophrenic angle at the level of the kidney, which simple thoracotomy is barely able to provide. Use of video-assisted thoracoscopic surgery and abandoning direct visualization of the apical area enabled a single thoracotomy to be performed at lower intercostal spaces. Because the hemithorax is shaped like a cone, thoracotomy at a lower intercostal space produced longer, wider, and easier openings to the chest cavity, without

the need to add anterior costal arch division or a second thoracotomy.

Conversion to the less invasive EPP surgery contributed to lower mortality and morbidity, as well as to the dramatic reductions in mortality within 6 months of surgery (ie, 30.8% for Group 1 and 3.4% for Group 2). We speculate that improved visibility and easier manipulation at the lower chest cavity allowed more precise manipulation around the



Interval		0 month	12 months	24 months	36 months	48 months	60 months	72 months	84 months	96 months
Group 1 (Conventional EPP)	Number	32	16	8	4	3	3	2	2	2
	Progressive free survival rate 95% Confidence interval		0.39 - 0.75	0.17 - 0.51	0.05 - 0.33	0.05 - 0.33	0.03 - 0.29	0.03 - 0.29	0.01 - 0.23	0.01 - 0.23
Group 2 (Less Invasive EPP)	Number	39	31	20	13	7	2	1		
	Progressive free survival rate 95% Confidence interval		0.66 - 0.91	0.36 - 0.67	0.22 - 0.52	0.10 - 0.37	0.02 - 0.23	0.004 - 0.18		
Group 3 (P/D)	Number	81	49	21	7					
	Progressive free survival rate 95% Confidence interval		0.62 - 0.82	0.29 - 0.55	0.10 - 0.33					

Figure 3. Progression-free survival by groups. There was no significant difference in median PFS among Groups 1, 2, and 3 (12.0 months for Group 1, 24.5 months for Group 2, and 21.8 months for Group 3, respectively). Abbreviations: MST, median survival time; PFS, progression-free survival.

Table 4. Survivals in Whom Surgery Was Completed

	Groups 1 + 2 + 3 (n = 117)	Group 1 (n = 26)	Group 2 (n = 29)	Group 3 (n = 62)
Overall survival (mo)				
1-year (95% CI)	88.8 (93.4–81.6)	69.2 (83.3–47.8)	89.7 (96.5–71.3)	96.8 (99.2–87.7)
2-year (95% CI)	66.8 (75.0–56.8)	38.5 (56.3–20.4)	72.4 (85.1–52.3)	77.4 (87.0–62.5)
3-year (95% CI)	59.7 (68.7–49.3)	30.8 (48.5–14.6)	69.0 (82.5–48.8)	67.9 (80.1–50.9)
Median (95% CI)	43.4 (34.9–58.7)	17.7 (9.0–28.2)	45.6 (25.9–61.7)	43.4 (38.1–incalculable)
PFS (mo)				
1-year (95% CI)	76.6 (83.3–67.8)	53.8 (70.6–33.3)	86.2 (94.6–67.3)	81.5 (89.3–69.1)
2-year (95% CI)	48.6 (57.8–38.6)	30.8 (48.5–14.6)	58.6 (74.0–38.8)	57.4 (69.9–42.2)
3-year (95% CI)	28.8 (38.2–19.9)	15.4 (31.5–4.8)	41.4 (58.3–23.7)	25.3 (40.2–12.6)
Median (95% CI)	23.8 (17.3–30.2)	12.1 (8.0–21.8)	28.9 (15.9–39.3)	25.5 (21.8–31.5)

pericardium, diaphragm, and peritoneum, resulting in improved early postoperative survival. There was a striking difference in completion rates of all the scheduled treatments, that is, neoadjuvant plus adjuvant therapies (38.5% for Group 1 vs 79.3% for Group 2). We further speculate that relatively stable postoperative condition in Group 2 resulted in improved completion rate of scheduled treatments, and was translated into improved survival.

Although the less invasive EPP surgery led to improvements in postoperative status and survival, it was inevitable that patients would have poor postoperative cardiopulmonary reserve following EPP. Therefore, lung-sparing surgery was considered a possible solution to this problem, but we were concerned that introducing such a technique might compromise survival. In September 2012, encouraged by accumulating data showing favorable outcomes after lung-sparing surgery,^{5,9,10} we decided to employ P/D surgery for all eligible patients. At 4.5 years since its introduction, our results show that P/D surgery has provided similar surgical mortality/morbidity and postoperative survival to the less invasive EPP surgery.

There is a lack of consensus about the appropriate extent of surgical resection in MPM surgery. Some, including ourselves, prefer to keep resection to a minimum when achieving macroscopic complete resection,^{11,12,21–23} whereas others always resect the diaphragm and pericardium, regardless of tumor invasion.^{24–26} When seeking to avoid possible R2 resection in P/D surgery, it seems inconsistent to resect the diaphragm and/or pericardium when there is no visible tumor invasion, especially given the risk of leaving tumor cells in spared lung parenchyma. In the present study, overall survival and PFS at 1, 2, and 3 years were similar for Groups 3 and 2. Therefore, we

think that efforts to preserve the lung parenchyma, diaphragm, and pericardium do not compromise how radical surgery can otherwise be, even though no definitive conclusion can be given at this moment.

It seems that, similar to surgery for lung cancer,²⁷ Japanese centers operate earlier for patients with MPM when compared with US and European centers.^{28,29} Given that most of the literature on P/D surgery has described its use for advanced MPM, the present study adds a new perspective that complements existing research. However, it is unclear whether our experience with less invasive, organ-sparing techniques can be applied directly to patients with more advanced MPM.

There are several limitations to the present study. First, we performed a retrospective analysis of prospectively collected data in a single center. Selective bias of patients according to the retrospective study may have distorted the results of the current analysis. We also have a problem of external validity with the study in a single center. Second, unknown confounding factors might affect the survival periods between these operations. Third, we did not include a sufficiently long follow-up period for patients who underwent P/D surgery. Fourth, we did not have access to data regarding the pre- and postoperative cardiopulmonary function or quality of life of patients.

In conclusion, we showed that introducing less invasive surgical techniques could decrease surgical risks without compromising survival. However, further study is needed in a randomized controlled trial to confirm our hypothesis.

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Table 5. Relapse Pattern

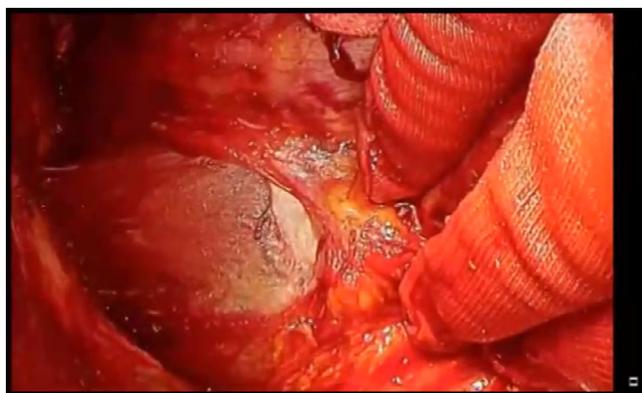
	Group 1	Group 2	Group 3
Local only	11 (55.0%)	9 (31.0%)	22 (78.6%)
Distant only	5 (25.0%)	15 (51.7%)	4 (14.3%)
Local and distant	4 (20.0%)	5 (17.2%)	2 (7.1%)

SUPPLEMENTARY MATERIAL

The following is the supplementary data to this article:



Video 1. Left P/D. Pleurectomy/decortication was performed in a 63-year-old male with cT1N0M0 epithelioid mesothelioma after 3 course of induction chemotherapy with cisplatin and pemetrexed. A single thoracotomy with resection of the seventh rib was given. Extrapleural dissection in the apical area was performed through thoracoscopic vision. The parietal pleura was completely dissected from the diaphragm, the pericardium, and the phrenic nerve, using cotton gloves and sponge sticks. Then, the parietal and visceral pleura was opened with scissors. Visceral pleurectomy was performed by holding the cut end of the pleura with cotton gloves, and peeling it off from the pulmonary parenchyma, preferably without touching. Finally, the pleura was cut at the interlobar fissure and the hilum, and was removed en bloc.



Video 2. Details of the dissection techniques at the diaphragm and the pericardium. Less invasive EPP was performed in a 48-year-old male with right malignant pleural mesothelioma of epithelioid subtype. Operation was performed through a single seventh rib bed thoracotomy with assistance of a thoracoscope. The diaphragm, pericardium, and the phrenic nerve were totally preserved and no patch reconstruction was required.

REFERENCES

1. Takuwa T, Hasegawa S: Current surgical strategies for malignant pleural mesothelioma. *Surg Today* 46:887–894, 2016

2. Scherpereel A, Astoul P, Baas P, et al: Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. *Eur Respir J* 35:479–495, 2010
3. Sugarbaker D: Macroscopic complete resection: The goal of primary surgery in multimodality therapy for pleural mesothelioma. *J Thorac Oncol* 1:175–176, 2006
4. Rusch V, Baldini E, Bueno R, et al: The role of surgical cytoreduction in the treatment of malignant pleural mesothelioma: Meeting Summary of the International Mesothelioma Interest Group Congress, September 11–14, 2012, Boston, Mass. *J Thorac Cardiovasc Surg* 145:909–910, 2013
5. Flores R, Pass H, Seshan V, et al: Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: Results in 663 patients. *J Thorac Cardiovasc Surg* 135:620–626, 2008. 626 e1–e3
6. Treasure T, Lang-Lazdunski L, Waller D, et al: Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: Clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol* 12:763–772, 2011
7. Rena O, Casadio C: Extrapleural pneumonectomy for early stage malignant pleural mesothelioma: An harmful procedure. *Lung Cancer* 77:151–155, 2012
8. Taioli E, Wolf A, Flores R: Meta-analysis of survival after pleurectomy decortication versus extrapleural pneumonectomy in mesothelioma. *Ann Thorac Surg* 99:472–480, 2015
9. Nakas A, Trousse D, Martin-Ucar A, et al: Open lung-sparing surgery for malignant pleural mesothelioma: The benefits of a radical approach within multimodality therapy. *Eur J Cardiothorac Surg* 34:886–891, 2008
10. Bolukbas S, Manegold C, Eberlein M, et al: Survival after trimodality therapy for malignant pleural mesothelioma: Radical pleurectomy, chemotherapy with cisplatin/pemetrexed and radiotherapy. *Lung Cancer* 71:75–81, 2011
11. Lang-Lazdunski L, Bille A, Lal R, et al: Pleurectomy/decortication is superior to extrapleural pneumonectomy in the multimodality management of patients with malignant pleural mesothelioma. *J Thorac Oncol* 7:737–743, 2012
12. Friedberg J, Culligan M, Mick R, et al: Radical pleurectomy and intraoperative photodynamic therapy for malignant pleural mesothelioma. *Ann Thorac Surg* 93:1658–1667, 2012
13. Batirel H, Metintas M, Caglar H, et al: Adoption of pleurectomy and decortication for malignant mesothelioma leads to similar survival as extrapleural pneumonectomy. *J Thorac Cardiovasc Surg* 151:478–484, 2016
14. Sharkey A, Tenconi S, Nakas A, et al: The effects of an intentional transition from extrapleural pneumonectomy to extended pleurectomy/decortication. *Eur J Cardiothorac Surg* 49:1632–1641, 2016
15. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm-ctc_40; 2009
16. Kameyama K, Huang C, Hayashi E, et al: Extended posterolateral-subcostal thoracotomy for extrapleural pneumonectomy: A surgical approach for radical operation of pleural mesothelioma. *Interact Cardiovasc Thorac Surg* 3:201–203, 2004
17. Rusch V: A proposed new international TNM staging system for malignant pleural mesothelioma from the International Mesothelioma Interest Group. *Lung Cancer* 14:1–12, 1996
18. Hasegawa S: Extrapleural pneumonectomy or pleurectomy/decortication for malignant pleural mesothelioma. *Gen Thorac Cardiovasc Surg* 62:516–521, 2014
19. Hasegawa S, Okada M, Tanaka F, et al: Trimodality strategy for treating malignant pleural mesothelioma: Results of a feasibility study of induction pemetrexed plus cisplatin followed by extrapleural pneumonectomy and postoperative hemithoracic radiation (Japan Mesothelioma Interest Group 0601 Trial). *Int J Clin Oncol* 21:523–530, 2016
20. Rice D, Rusch V, Pass H, et al: Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma. A consensus report of the International Association for the Study of Lung Cancer

- International Staging Committee and the International Mesothelioma Interest Group. *J Thorac Oncol* 6:1304–1312, 2011
21. Flores R: Pleurectomy decortication for mesothelioma: The procedure of choice when possible. *J Thorac Cardiovasc Surg* 151:310–312, 2016
 22. Bolukbas S, Eberlein M, Kudelin N, et al: Factors predicting poor survival after lung-sparing radical pleurectomy of IMIG stage III malignant pleural mesothelioma. *Eur J Cardiothorac Surg* 44:119–123, 2013
 23. Lang-Lazdunski L, Tan C, Treasure T: Extrapleural pneumonectomy for malignant mesothelioma: Should pericardium be resected routinely? *J Thorac Cardiovasc Surg* 129:1202, 2005. author reply 1202–1203
 24. Sharkey A, Bilancia R, Tenconi S, et al: The management of the diaphragm during radical surgery for malignant pleural mesothelioma. *Eur J Cardiothorac Surg* 50:311–316, 2016
 25. Wolf A, Daniel J, Sugarbaker D: Surgical techniques for multimodality treatment of malignant pleural mesothelioma: Extrapleural pneumonectomy and pleurectomy/decortication. *Semin Thorac Cardiovasc Surg* 21:132–148, 2009
 26. Yan T, Boyer M, Tin M, et al: Extrapleural pneumonectomy for malignant pleural mesothelioma: Outcomes of treatment and prognostic factors. *J Thorac Cardiovasc Surg* 138:619–624, 2009
 27. Committee for Scientific Affairs TJAfTSMasuda M, Okumura M, et al: Thoracic and cardiovascular surgery in Japan during 2014: Annual report by the Japanese Association for Thoracic Surgery. *Gen Thorac Cardiovasc Surg* 64:665–697, 2016
 28. Hasegawa S: Early mesothelioma revisited. *Int J Clin Oncol* 17:30–32, 2012
 29. Hasegawa S, Kondo N, Matsumoto S, et al: Practical approaches to diagnose and treat for T0 malignant pleural mesothelioma: A proposal for diagnostic total parietal pleurectomy. *Int J Clin Oncol* 17:33–39, 2012