

Diaphragm and lung-preserving surgery with hyperthermic chemotherapy for malignant pleural mesothelioma: A 10-year experience

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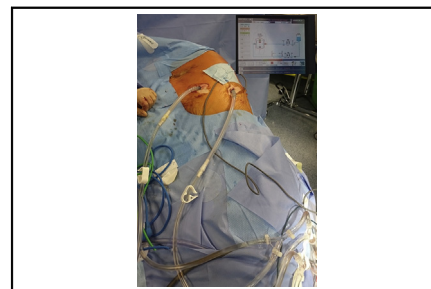
ABSTRACT

Background: The best surgical treatment for malignant pleural mesothelioma is still under a debate, but recent evidence points toward a less-invasive approach to reduce morbidity and mortality. We reported our 10-year experience of a limited surgical approach associated with hyperthermic intrathoracic chemotherapy (HITHOC).

Material and Methods: Between 2005 and 2014, patients with epithelioid or biphasic malignant pleural mesothelioma were treated with lung–diaphragm–pericardium-sparing pleurectomy associated with double-drug HITHOC; at least 3 cycles of adjuvant chemotherapy were then administered. The primary outcome examined was the feasibility of the procedure, whereas secondary outcomes were overall survival and disease-free interval.

Results: Among 49 patients, 41 were male. Median age was 68 years (35–76 years). Histology was epithelioid in 43 cases. Pathologic stage I, II, III, and IV occurred in 12, 14, 20, and 3 cases, respectively. No intraoperative complications or postoperative mortality occurred, whereas morbidity rate was 46.9%. Median hospital stay was 8 days (5–45 days). Actuarial median overall survival was 22 months and a 1-, 2-, and 5-year survival accounted for 79.6%, 45.7%, and 9.9%, respectively. Disease-free survival after surgery was 62%, 37.5%, and 18.5% at 1, 2, and 5 years, respectively. Risk factors analysis for overall survival confirmed a significant role for early stages, epithelioid histology, and fibrinogen serum levels.

Conclusions: Cytoreductive surgery associated with HITHOC and adjuvant chemotherapy appears feasible and safe, with no mortality and low morbidity. Preserving lung and diaphragmatic function might warrant an acceptable long-term outcome. (*J Thorac Cardiovasc Surg* 2017; ■:1–10)



Lung and diaphragm-sparing surgery associated with hyperthermic intrathoracic chemotherapy leads to good long-term results.

Central Message

Using cytoreductive surgery with hyperthermic intrathoracic chemotherapy and adjuvant chemotherapy for malignant pleural mesothelioma, we preserved lung and diaphragmatic function, which might achieve acceptable long-term outcomes despite incomplete resection.

Perspective

The best surgical option for malignant pleural mesothelioma is still uncertain, but lung-sparing procedures are acquiring an increasing consensus. We report the results of a 10-year experience using pleurectomy and focal decortication associated with local hyperthermic chemotherapy with a total sparing of lung and diaphragmatic function and promising long-term oncologic outcomes.

See Editorial Commentary page XXX.

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Malignant pleural mesothelioma (MPM) is an aggressive disease arising from the mesothelial cells of the parietal pleura. Its incidence is strictly connected to direct or indirect asbestos exposure with a long latency period that can be up to 40 years¹; a peak number of cases of mesothelioma is expected to occur in the next decade. Treatment for mesothelioma is still under debate: chemotherapy using cisplatin in association with pemetrexed has shown better



Scanning this QR code will take you to a procedural video and supplemental file.



Abbreviations and Acronyms

CI	= confidence interval
CT	= computed tomography
DFI	= disease-free interval
EPD	= extended pleurectomy and decortication
EPP	= extrapleural pneumonectomy
HITHOC	= hyperthermic intrathoracic chemotherapy
HR	= hazard ratio
MCR	= macroscopic complete resection
MPM	= malignant pleural mesothelioma
NLR	= neutrophil/lymphocyte ratio
OS	= overall survival
P/D	= pleurectomy and decortication
PLR	= platelet/lymphocyte ratio

results² in controlling the disease; furthermore, different surgical approaches have been proposed.³ Usually, all the available therapies are used in a multimodality setting, but unfortunately none of them, both alone or combined, are able to warrant satisfactory long-term outcomes, and prognosis is still very disappointing.³

In particular, great debate regarding the role of surgery is currently ongoing. Although extrapleural pneumonectomy (EPP) was more extensively performed in cases of resectable MPM in the 1990s and at the beginning of the last decade, more recently pleurectomy and decortication (P/D) and extended pleurectomy and decortication (EPD) increasingly have been used.⁴ EPP accounts for an en-bloc resection of pleura, ipsilateral pericardium, hemidiaphragm, and the entire lung, whereas P/D and EPD allow sparing of lung parenchyma by the resection of parietal and visceral pleura with or without ipsilateral pericardium and hemidiaphragm.⁵ Despite no clear and consistent evidence, lung-sparing techniques might reduce the postoperative mortality and morbidity and increase the possibility for the patient to complete the multimodality treatment. Macroscopic complete resection (MCR) is usually considered the goal of surgery,⁶ but many reports describe similar long-term results in patients treated with chemotherapy alone or with nonradical surgery.^{7,8}

Hyperthermic intrathoracic chemotherapy (HITHOC) combines the sensitizing effects of hyperthermia and the local effect of chemotherapy drugs; the local cytotoxic effects of chemotherapy are strengthened by the effect of the high temperature, which makes cancer cells more vulnerable to drugs, allowing a deeper penetration of chemotherapies.⁹ In thoracic surgery, HITHOC has been reported for the treatment of primary and secondary pleural tumors using different protocols, doses, and type of drugs.¹⁰⁻¹³

Since 2005, we started a new treatment protocol for MPM that consists of pleurectomy and partial decortication with HITHOC. This study reports our 10-year experience,

focusing on feasibility, safety, long-term outcomes, and prognostic factors.

MATERIALS AND METHODS

All medical records of patients undergoing surgery and HITHOC for MPM in our institution during the period between March 2005 and December 2014 were reviewed. Approval for this retrospective study was obtained from our Institutional Ethical Committee. All patients gave full consent regarding data collection and its use in clinical studies; moreover, they gave their consent to update database information. Standardized perioperative care was used in all cases, as per protocol (Appendix E1). The results were then retrospectively collected.

The primary objective of this study was to confirm the feasibility of HITHOC immediately after partial pleurectomy by analyzing intraoperative complications, morbidity, and mortality particularly in regard to adverse events related to chemotherapy agents. The secondary objectives were to analyze long-term survival and to evaluate the pattern and timing of disease recurrence.

Preoperative Assessment and Selection Criteria

All patients had a histologic diagnosis of epithelial or biphasic MPM obtained via a thoracoscopic procedure. In no cases was pleurodesis using talc or any other chemical agent performed. All specimens were analyzed or verified by a dedicated team of pathologists, according to the World Health Organization criteria.

All patients affected by MPM who met inclusion criteria were treated following the same protocol and the same type of procedure during the study period at our institution; no alternative surgical procedures were offered to patients.

Selection criteria for surgery and HITHOC were clinical International Mesothelioma Interest Group stage I to III, age between 18 and 75 years, performance status ≤ 3 per the Eastern Cooperative Oncology Group scale, platelets count $>100,000/L$, hemoglobin level $>10\text{ g/dL}$, white cell count $>4000 \times 10^3/L$, absence of cardiac or neuropathic diseases, and absence of concomitant infection or pregnancy. All patients were discussed by a multidisciplinary team; clinical N2 were excluded if a bulky lymphadenopathy or a multistation N2 disease was observed on the computed tomography (CT) scan. Invasive lymph node staging (namely endobronchial ultrasound or mediastinoscopy) was not required in our workup protocol.

In all cases, a chest radiograph and recent chest and abdomen CT scans were performed; conversely, positron emission tomography scanning was done only when required by the referring oncologist and not on a routine basis. Magnetic resonance imaging of the chest was performed only if a chest wall invasion was suspected on the CT scan or in cases of localized chest pain. Preoperative assessment consisted of complete blood analysis, D-dimer blood dosage, liver function tests, renal function tests, including creatinine clearance test, respiratory function tests, cardiological evaluation, including echocardiography, and lower-limb echo-Doppler.

To reduce the possibility of a renal impairment due to HITHOC, all patients received a standardized amount of fluid from the day before surgery until postoperative day 5 (2000 mL the day before surgery, at least 3000 mL the day of surgery, and 2000 mL from postoperative day 1 until postoperative day 5), together with proton-pump inhibitors, diuretics, antibiotics, corticosteroids, and low-molecular-weight heparin.

Surgical Technique

A posterior-lateral thoracotomy is routinely performed at the fifth/sixth intercostal space. The operative procedure consists of a complete parietal and mediastinal pleurectomy and the resection of the greater lesions on the visceral pleura; diaphragm and pericardium are always spared, with the aim of achieving an MCR or at least an extensive debulking with minimal impairment of the lung function. Lymph node sampling was routinely

performed. At the end of the surgical resection, once satisfactory lung expansion was verified, two 28- or 32-Fr intercostal drains were placed in the pleural space, one at the apex and one on the diaphragm, respectively, working as outflow and inflow drainage during the perfusion. A temperature probe was also placed into the pleural cavity, and the thoracotomy was eventually closed (Video 1). Operative time was defined as the time between skin incision and the end of the perfusion. All patients were extubated at the end of the procedure.

Devices and Perfusion Technique

Perfusion was run with patients in lateral decubitus and the lung was not ventilated. In all procedures, a dedicated perfusion system, Performer LRT (Rand, Medolla, MO, Italy), with software for locoregional hyperthermic oncological treatments, was used to perform HITHOC. The volume of perfusion, preloaded in the machine, was calculated in liters, based on the value of the body surface and then doubled to keep the same proportion of chemotherapy agents among all patients. After the connection of the device to inflow and outflow drainages, pleural space was gradually filled with the preloaded isotonic saline solution at a temperature of 38°C; careful attention was paid to fill the entire pleural space until no air was coming out from the tubes. The temperature was then progressively increased to obtain an intrathoracic target temperature of 42.5°C; once the target temperature was reached, chemotherapeutic agents were added into the system and perfusion was then continued for 60 minutes. We use 2 chemotherapeutic drugs: cisplatin (dose, 80 mg/m²) and epirubicin (25 mg/m²). Blood pressure, cardiac frequency, oxygen saturation, and core and chest cavity temperatures were continuously monitored and recorded the entire perfusion time. At the end of the perfusion, inflow and outflow drains were exchanged to empty the pleural space, temperature probes were removed, and the lung was ventilated again.

Postoperative Management

Broad-spectrum antibiotic therapy was administered until removal of the chest drain and low-molecular-weight heparin administration was continued until discharge. Blood count, liver and renal function tests, and D-dimer blood levels were monitored daily for the first 5 postoperative days. Morbidity, 30-day, and 90-day mortality and postoperative stay were recorded. Any adverse event was stratified with the Common Terminology Criteria for Adverse Events, version 4.03.

Adjuvant Treatments and Follow-up

The final pathology report was first discussed by a multidisciplinary team and then with the patient. At least 3 cycles of adjuvant chemotherapy (cisplatin 80 mg/m² and pemetrexed 500 mg/m²) were scheduled for all patients, and follow-up was carried out with chest and abdominal CT every 6 months; prophylactic radiotherapy and further systemic or local treat-

ments were administered according to the choice of the referring oncologists. Follow-up information (vital status, adverse events after discharge, and their severity and presence of any recurrence) was gathered by the authors from the referring oncologist and by a direct call to the patients or to their relatives.

Statistical Analysis

Statistical analysis was performed with SPSS software version 18.0 for Windows (SPSS, Chicago, Ill). Continuous variables were expressed in terms of median and interquartile range, whereas categorical variables were expressed in terms of frequency.

Overall survival (OS) was estimated with Kaplan-Meier estimator with a 95% confidence interval (CI). Survival was calculated from the date of surgery to last follow-up (December 2015) or death. Disease-free interval (DFI) was based on the cumulative incidence estimate with death considered as a competing risk, and it was calculated from the date of surgery to the first evidence of recurrence. Mortality after documented recurrence or progression was considered to be disease-related unless a clear different cause was proved.

Survival comparison between groups of patients undergoing surgical resection with HITHOC was performed with the log-rank test for categorical variables and Cox regression for continuous variables. Considering the recent results emphasizing the role of inflammation on the onset of MPM,¹⁴ we decided to analyze the impact of inflammatory markers on OS. Preoperative fibrinogen and albumin levels were calculated as continuous variables, whereas platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) cutoffs were chosen on the basis of past published experiences (200 and 4, respectively).^{15,16} Multivariable analysis with the Cox proportional hazards model was applied to identify predictors for OS. Prognostic factors that were significant at the univariate analysis were used to perform a multivariate analysis. A *P* value <.05 was considered statistically significant.

RESULTS

This study included 49 patients (41 male, 8 female), with a median age of 68 years (range 35-76). Histologic diagnosis was obtained by a thoracoscopic procedure performed at our division in all but 2 cases. The median interval between the thoracoscopic procedure and the P/D plus HITHOC procedure was 33 days (range, 7-90 days). Before surgery, no patients presented with known cardiovascular diseases or hepatic or renal function alterations. Demographic, clinical, and surgical features are summarized in Table 1.

The surgical procedure consisted of pleurectomy and partial decortication, and in 4 cases a wedge resection of the lung was necessary. The pericardium and diaphragm were always spared. The median operative time, including preparation of the perfusion circuit and perfusion time, was 240 minutes (range, 160-315).

Pathology

The seventh edition of International Mesothelioma Interest Group mesothelioma classification was used to stage the disease.¹⁷ Histology was epithelioid in 43 cases and biphasic in 6 cases. Pathologic stage I, II, III, and IV was presented in 12 (4 stage IA and 8 stage IB), 14, 20, and 3

Diaphragm and Pericardium preserving Pleurectomy and partial Decortication with HITHOC for treatment of Malignant Pleural Mesothelioma: a 10 year experience

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VIDEO 1. The main steps of our surgical technique of pleurectomy and focal decortication followed by hyperthermic intrathoracic chemotherapy are shown. Video available at: <http://www.jtcvsonline.org>.

TABLE 1. Demographic, clinical, and surgical features of all patients

Features	n (%) or IQR
Sex	
Male	41 (83.7)
Female	8 (16.3)
Median age, y (IQR)	68 (11)
Side	
Right	29 (50.2)
Left	20 (49.8)
Median body mass index (IQR)	25.9 (4.4)
Median preoperative pulmonary function test (IQR)	
FEV1, L	2.20 (1.3)
FEV1, %	56 (16)
FVC, L	2.4 (0.9)
FVC, %	58 (17)
Comorbidities	40 (82)
Diabetes	12 (24.5)
Hypertension	31 (63.3)
Pulmonary disease (COPD or asthma)	25 (51.02)
Other cardiovascular disease	3 (6.12)
Previous cancer	7 (14.3)
ECOG	
0	32 (65.3)
1	17 (34.7)
Histology	
Epithelioid	43 (87.8)
Biphasic	6 (12.2)
Smoking	
Smoker/ex-smoker	16 (32.7)
Nonsmoker	24 (49.0)
Missing data	9 (18.4)
Asbestos exposure	
Positive	23 (46.9)
Negative	7 (14.3)
Uncertain/missing data	19 (38.8)
Median number of lymph node resected (IQR)	11 (3.6)
Median number of N2 lymph node station resected (IQR)	3 (1)
pT	
T1a	4 (8.2)
T1b	8 (16.3)
T2	18 (36.7)
T3	16 (32.7)
T4	3 (6.1)
pN	
N0	39 (79.6)
N1	0 (0.0)
N2	10 (20.4)
Pathologic IMIG stage	
IA	4 (8.2)
IB	8 (16.3)
II	14 (28.6)
III	20 (40.8)
IV	3 (6.1)

IQR, Interquartile range; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group performance status; IMIG, International Mesothelioma Interest Group.

cases, respectively. All stages IV were due to a T4 tumor that unexpectedly involved the chest wall.

Morbidity and Mortality

No intraoperative complications occurred, and HITHOC perfusion was successfully completed in all cases; in one case perfusion was stopped after 45 minutes due to technical problems. Median hospital stay was 8 days (range, 5-45). No thermal intolerance and no anesthesiologic complications occurred during the perfusion period. The core temperature never exceeded 38°C. Moreover, neither hemodynamic nor respiratory instability was observed. No patient experienced signs or symptoms related to the toxicity of the chemotherapy used. Reversal of anesthesia was always performed at the end of the procedure, and no patient needed to be hospitalized in the intensive care unit.

Postoperative complications appeared in 23 patients (46.9%; 95% CI, 30-59) (Table 2); the most common cause of morbidity was anemia, which occurred in 17 cases (34.7%), of whom 13 required a blood transfusion with a median number of red cell unit used of 2.5 (range, 1-11); 1 of those patients required reoperation to check hemostasis. Only 4 patients were affected by prolonged air-leaking (more than 5 days, 8.1%); only one case of postoperative empyema was observed, which finally resolved with chest drain and antibiotic therapy. All postoperative complications are summarized in Table 2.

All patients successfully completed the first 3 cycles of adjuvant therapy with cisplatin and pemetrexed. The

TABLE 2. Description of all postoperative complications

Type of complication(s)	CTCAE 4.03	Number of patients
Prolonged air leak*	3	2
Anemia without need for transfusion	2	4
Anemia with need for transfusion	3	Nine, of whom 1 required a surgical hemostasis
Wound dehiscence†	2	2
Fever (>38.5°C for at least 24 h)	1	1
Syncope	3	1
Ischemic cerebral vascular accident and anemia with need for transfusion	2	1
Anemia with need for transfusion and prolonged air leak	3	2
Anemia with need for transfusion, wound dehiscence and empyema†	3	1

CTCAE, Common Terminology Criteria for Adverse Events version 4.03. *Longer than 5 days. †Diastases of the ribs during the postoperative follow-up control, which was not visible on postoperative radiographs.

administration of the adjuvant radiotherapy was decided by the referring oncologist according to the N status, pathologic stage, and patient clinical conditions; among the whole cohort, 3 patients received a 60-Gy adjuvant radiotherapy. Grade 2 and grade 3 toxicity occurred in one case each, but all patients were able complete their planned adjuvant radiation.

Oncologic Outcomes

At a median follow-up of 68.5 months (range, 13-127), 14 patients were still alive. We had no cases of mortality in the first 90 postoperative days (95% CI, 0-7.2). Median OS of the entire cohort was 22 months with 30 and 90 days and 1-, 2-, and 5- year survival of 100%, 100% 79.6%, 45.7%, and 9.9%, respectively (Figure 1); 27 patients died after a recurrence of the disease; in 3 cases death was due to chemotherapy toxicity (treatments administered for recurrence), and 5 patients died due to causes not related to the disease or treatments. Concurrently, DFI was 62%, 37.5%, and 18.5% at 1, 2, and 5 years, respectively, and recurrence occurred in 39 patients (79.6%); precise information about the site of recurrence was missing in 4 cases. Recurrences were mainly local (ipsilateral chest wall, diaphragm or pericardium, drain wounds), accounting for 23 cases, whereas in 4 cases the recurrence was exclusively distant (mediastinal nodes or any other systemic localization) and in 8 cases was both local and distant.

Prognostic Factors

On the log-rank analysis (Table 3), age older 65 years, sex, side, Eastern Cooperative Oncology Group score, and postoperative complications were not significant factors influencing OS. Conversely, the histology resulted a very strong prognostic factor where epithelioid MPM had a significant better prognosis rather than biphasic ($P = .022$); moreover, early stage (I and II) MPM had a median OS of 35 months, significantly better compared with advanced

stages (III and IV, 17 months; $P = .049$). With regard to the univariate analysis of inflammatory markers, preoperative fibrinogen level, PLR, and NLR resulted significant risk factors affecting OS and showed a significant impact on OS in the univariate analysis.

Multivariate analysis (Table 4) showed that the epithelioid histology, early stages, and low fibrinogen serum levels were associated with a better prognosis (hazard ratio [HR], 0.341; 95% CI, 0.120-0.968, $P = .043$; HR, 0.303; 95% CI, 0.123-0.749, $P = .010$; and HR, 1.007; 95% CI, 1.004-1.011, $P < .001$, respectively).

DISCUSSION

The role of surgery in mesothelioma treatment has not yet been fully established. EPP, EPD, and P/D are currently the surgical approaches that are most frequently proposed, but indications and outcomes of these approaches are inconsistent, varying according to different experiences.^{18,19} Lung preservation seems to be a fundamental factor to increase both patients' indication to surgery and their compliance to a multimodality treatment.²⁰ In our experience, both lung and diaphragm were spared in all cases, and all patients successfully completely the planned multimodality treatment.

MCR is usually considered the goal of mesothelioma surgery,⁶ even if a real R0 resection is not anatomically possible according to the common oncologic parameters, as the anatomical features of the pleura do not allow one to reach a disease-free margin regardless of the type of procedure performed.²¹ R1 resection is considered the gold standard for mesothelioma surgery, which is usually performed in the frame of a multidisciplinary scheme of therapies. Sharkey and colleagues²² recently reported the experience of their group in the management of diaphragm after radical surgery for mesothelioma (both EPP and EPD). They observed that diaphragm invasion was not an independent prognostic factor, although their conclusions are that, in case of doubt, diaphragm resection should be performed to stay on the safe side, and their data question the necessity of a routine phrenectomy. In our study, we reported our 10-year experience in mesothelioma surgery; our aim was to look at mesothelioma surgery from a different perspective: our main target was to perform a MCR or to leave a small quantity of disease (minimal R2) but always preserve pulmonary and diaphragmatic function. HITHOC was applied with the aim to extend the radicality of our surgical resection by the local effect of chemotherapy agents on residual tumor. This choice of action aimed to guarantee a plausible better performance status after surgery, allowing the patients to undergo adjuvant therapies or different treatments for recurrences.

Cisplatin has been demonstrated to be an effective drug for mesothelioma, and several papers report its use in an intrapleural setting. Sugarbaker¹² recently reported a

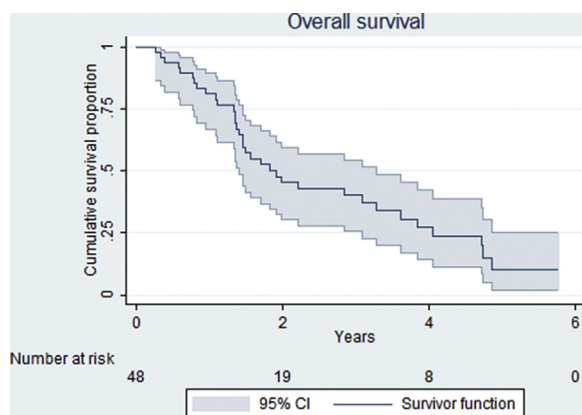


FIGURE 1. Overall survival of the entire cohort of patients. CI, Confidence interval.

TABLE 3. Univariate analysis of risk factors influencing OS

Risk factor	Median OS (months)	Lower CI	Upper CI	Log-rank (P value)
Age, y				.804
<65	23	1.92	44.08	
≥65	18	9.88	26.11	
Age (continuous variable)	NA	0.97	1.06	.501
Sex				.991
Male	22	16.12	27.87	
Female	43	0	93.53	
Side				.799
Right	20	2.96	37.04	
Left	22	15.86	28.13	
ECOG				.563
0	22	17.05	26.95	
≥1	18	5.16	30.83	
FEV1 (continuous variable)	NA	0.02	2.04	.106
Postoperative complications				.402
Yes	26	11.41	40.59	
No	17	14.27	19.73	
Histology				.022
Epithelioid	23	5.21	40.77	
Biphasic	10	0.39	19.60	
IMIG stage				.049
Early (I-II)	35	16.53	53.57	
Late (III-IV)	17	14.17	19.83	
Fibrinogen, mg/dL (continuous variable)	NA	1.004	1.009	<.001
Albumin, g/dL (continuous variable)	NA	0.22	1.28	.151
PLR				.001
<200	36	13.46	58.54	
≥200	17	13.68	20.32	
NLR				.030
< 4	23	4.77	41.23	
≥4	18	13.58	22.42	

Analysis was calculated with log-rank test for categorical variables and Cox regression for continuous variables. Significance was considered for $P < .05$, 95% CI. P values in bold indicate statistical significance. Fibrinogen, albumin, NLR, and PLR refer to preoperative serum levels. OS, Overall survival; CI, confidence interval; NA, not available; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in 1 second; IMIG, International Mesothelioma Interest Group; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio.

retrospective study comparing the oncologic outcomes of patients affected by MPM with good prognostic factors treated with EPP or P/D with and without the use of HITHOC after surgery; results showed a better median OS

for patients receiving HITHOC surgery (35.3 months vs 22.8 months) and, in particular, better outcomes were observed with HITHOC for patients with a nodal involvement. A more recent report of Ishibashi and coworkers²³

TABLE 4. Multivariate analysis of risk factors influencing overall survival

	Hazard ratio	95% CI		P value
		Inferior	Superior	
Epithelioid histology	0.341	0.120	0.968	.043
Early stage (I and II)	0.303	0.123	0.749	.010
Fibrinogen (continuous variable)	1.007	1.004	1.011	<.001
PLR <200	0.523	0.164	1.668	.273
NLR <4	0.944	0.358	2.488	.907

Analysis was calculated with Cox regression models. Significance was considered for $P < .05$ for a CI between 5% and 95%. P values in bold indicate statistical significance. Fibrinogen, albumin, NLR, and PLR refer to preoperative serum levels. CI, Confidence interval; PLR, platelet/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio.

TABLE 5. Results of studies using surgery for malignant pleural mesothelioma

Author	Number of patients	Inclusion criteria	Type of surgical treatment	Median OS, mo (95% CI)	90-d mortality	Morbidity (any grade)
Rusch and colleagues, 2012 ¹⁸	1708	Stage I-IV Any histology	EPP: 1125 P/D: 479	Stage I EPP: 40 (29-58) Stage II EPP: 23 (19-26) Stage III EPP: 16 (15-18) Stage IV EPP: 12 (10-14) Stage I P/D: 23 (20-29) Stage II P/D: 20 (18-25) Stage III P/D: 19 (16-23) Stage IV P/D: 15 (11-19)	NA	NA
Rena and Casadio, 2012 ²⁰	77	Stage I-II Epithelioid	EPP: 40 P/D: 37	Stage I EPP: 28 (16-41)* Stage II EPP: 18 (10-36)* Stage I P/D: 32 (17-45)* Stage II P/D: 23 (2-40)*	EPP: 5% P/D: 0%	EPP: 62% P/D: 24%
Flores, 2008 ³⁴	663	Stage I-IV Any histology	EPP: 385 P/D: 278	Stage I EPP: 22 Stage II EPP: 19 Stage III EPP: 10 Stage IV EPP: 4 Stage I P/D: 46 Stage II P/D: 18 Stage III P/D: 13 Stage IV P/D: 9	EPP: 7% P/D: 4%	EPP: 27% P/D: 14.7%
Ploenes, 2013 ³⁶	48	Stage I-IV Any histology	EPP: 25 P/D: 23	EPP: 22 P/D: 29	EPP: 4% P/D: 0%	EPP: 48% P/D: 8%
Bedirhan, 2013 ³⁷	76	NR Any histology	EPP: 31 P/D: 25 EPD: 20	EPP: 17 P/D: 15 EPD: 27	EPP: 12.9% P/D: 4% EPP: 0%	All cases: 48%
Lang-Lazdunski, 2012 ³⁸	76	Stage I-IV Any histology	EPP: 22 P/D + hyperthermic pleural lavage with povidone-iodine: 54	EPP: 12.8 (7.8-17.7) P/D: 23 (14.1-31.9)	EPP: 4.5% P/D: 0%	EPP: 68% P/D: 27.7%
Nakas, 2011 ³⁹	165	Stage III-IV Any histology	EPP: 98 P/D: 67	EPP: 14.7 (12.2-17.2) P/D: 13.4 (9.7-17.1)	EPP: 7% P/D: 3%	EPP: 67.68% P/D: 29.4%

(Continued)

TABLE 5. Continued

Author	Number of patients	Inclusion criteria	Type of surgical treatment	Median OS, mo (95% CI)	90-d mortality	Morbidity (any grade)
Okada, 2008 ⁴⁰	65	Stage I-IV Any histology	EPP: 31 P/D: 34	EPP: 13 P/D: 17	EPP: 3.2% P/D: 0%	EPP: 48% PD: 15%
Sugarbaker, 2014 ⁴¹	529	Stage I-IV Epithelioid	EPP: 529	18	EPP: 5%	NA
Bovolato and colleagues, 2014 ⁷	503	Stage I-IV Any histology	EPP: 301 P/D: 202	EPP: 18.8 (17.2-20.9) P/D: 20.5 (18.2-23.1)	EPP: 6.9% P/D: 6%	EPP: 21.6% P/D: 10.4%
Current study	49	Stage I-IV Epithelioid Biphasic	P/D + HITHOC: 49	P/D + HITHOC: 22 (13.4-30.6) Stage I-II: 35 (17-53) Stage III-IV: 17 (14-20)	0% (CI, 0-7.2)	46.9% (CI, 30-59)

OS, Overall survival; CI, confidence interval; EPP, extrapleural pneumonectomy; NA, not available; P/D, pleurectomy and decortication; EPD, extended pleurectomy and decortication; HITHOC, hyperthermic intrathoracic intraoperative chemotherapy. *Range.

compared the DFI after EPP or P/D both associated with HITHOC with cisplatin; despite the very small cohort of patients with significant differences in pathologic stage, they noticed a significant better DFI after P/D.

The pharmacokinetics of HITHOC using cisplatin alone or in association with anthracyclines have been investigated by several authors,^{9,24-27} confirming its feasibility and its low systemic exposure; doxorubicin has shown to have a quite low penetration factor into the tissues compared with cisplatin; moreover, direct cardiac toxicity of doxorubicin has been discussed, but no clear evidence is available and results are inconsistent. Concurrently, the dosage of drugs used for HITHOC is very variable based on single-institution protocols; dosages of cisplatin have been reported to be up to 225 mg/m² when used alone, and doxorubicin is usually administered at a dose of 80 mg/m².¹⁰ Hyperthermia seems to play a key role in the local control of the disease, enabling drugs to penetrate more deeply into the tissue and to enhance their cytotoxic effects. Schaaf and colleagues²⁸ recently studied the in vitro effects of temperature during hyperthermic intraperitoneal chemotherapy, confirming that 40°C is the ideal threshold to obtain a benefit in terms of OS and DFI; Ratto and colleagues⁹ and Matsuzaki and colleagues²⁹ confirmed the adjuvant effect of hyperthermia; nevertheless, a recent in vitro study³⁰ questioned its role, stressing the importance of the use of a combination of drugs.

In our study, the same combination of drugs and dosage (cisplatin 80 mg/m² and epirubicin 25 mg/m²) was administered to all patients with perfusion at a target temperature of 42.5°C for 60 minutes, according to our protocol. To date, no case of systemic toxicity due to drugs has been experienced.

Postoperative mortality and morbidity are serious drawbacks of EPP and EPD. In fact, these operations are burdened with a relatively high mortality: a recent meta-analysis found a mortality rate ranging from 3.7% to 7.6% for EPP³¹ and 4% for EPD or P/D³²; moreover, the major complication rate was almost 50% in EPP and

up to 43% in EPD-P/D.³³ In our experience, no case of mortality was observed in the first 90 days from surgery, and our complication rate was 46.9%, comparable with other experiences. In particular, among the 22 patients who experienced complications, only 14 had a severe complication (classified as stage 3 according to Common Terminology Criteria for Adverse Events, version 4.03; no stage 4 complications were registered). It is clear that MPM cannot be considered a purely surgical disease; in fact, surgery cannot achieve a R0 resection in any case, due to anatomical features, and it is always part of a multimodality treatment³; moreover, patients are very likely to need treatments for recurrence. From this perspective, any surgical procedure should offer an extensive resection of the tumor, attempting to preserve performance status and respiratory function, offering a low postoperative complication profile. It is hard to quantify the impact of a diaphragm and pericardium resection on postoperative morbidity and mortality, but retrospective series has shown that invasive procedures such as EPP do not have any survival benefit compared with P/D, that they have a high mortality rate, and that one third of patients are generally unable to complete the multimodality treatment. Moreover, extended resections have a clear selection bias because only patients with an acceptable preoperative performance status are able to undergo these procedures. Lastly, in some reports no difference in terms of OS has been found between patients treated with multimodality treatment including EPP or EPD and those who received only systemic treatments.^{7,8,34} Our approach seems to fit all these criteria, and in our small cohort of patients, oncologic results seem to be at least comparable with those which were previously reported (Table 5).

Consistent with the literature,³ local recurrence was the main pattern of failure that we noticed in our experience. The treatment of recurrence was generally decided by the referring oncologist after multidisciplinary discussion;

systemic therapy or immunotherapy was the treatment of choice as well as radiotherapy.

In 1 case, we performed a chest wall resection for recurrence. Abdominal recurrences are one main pattern of failure after resection of the diaphragm.³⁵ Consistent with the literature, in our cohort, only 1 case was reported to have an intra-abdominal recurrence, whereas in 4 cases the diaphragm was the site of recurrence. Not surprisingly, these data might confirm that diaphragm resection can cause a neoplastic seeding of the peritoneum, which might be prevented if the diaphragm is preserved.

In the analysis of prognostic factors, we confirmed the role of inflammatory markers; high fibrinogen levels were first described as an important prognostic factor for MPM by Ghanim and colleagues,¹⁴ and we observed a strict relationship with OS also in our cohort. This strict relationship has been proven for several malignancies and it might be explained either as a result of the immune response against the tumor or to the increased autocrine growth stimulation. NLR and PLR showed to have a good prognostic value in literature, but this was not confirmed in our report. Nonetheless, the impact of all these prognostic factors on the choice of the therapy is still very limited, and further perspective, randomized trials are needed to assess their use in daily clinical practice.

Our study has some limitations. First, it is a retrospective study, and the relatively small cohort of patients as well as the selection criteria might limit the strength of our conclusions; second, there was no objective postoperative assessment of quality of life and pulmonary function. This would have been useful to investigate the long-term outcomes after our procedure; moreover, a clear definition of R1 or minimal R2 resection was not always available in the operative reports, and it was therefore impossible to define it clearly. Finally, our protocol included 3 cycles of adjuvant chemotherapy with cisplatin and pemetrexed, but any further therapies or treatments in case of recurrence were then decided according to the referring oncologist's preference. In conclusion, pleurectomy and focal decortication with a systematic sparing of the diaphragm and pericardium associated with HITHOC is a feasible and safe procedure leading to satisfactory long-term results. Although larger, controlled studies are needed to confirm our promising outcomes, this experience confirms that the preservation of lung and diaphragm, and a low postoperative rate of high-grade morbidity or mortality might be a more important argument than a macroscopic radicality for oncologic results after surgery.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: malignant pleural mesothelioma, pleurectomy, decortication, hyperthermic intrathoracic chemotherapy

APPENDIX E1. HYPERTHERMIC INTRATHORACIC INTRAOPERATIVE CHEMOTHERAPY PROTOCOL

Inclusion Criteria

1. Histologic diagnosis of epithelial or biphasic malignant pleural mesothelioma.
2. Clinical International Mesothelioma Interest Group stage I-III.
3. Age between 18 and 75 years.
4. Performance status ≤ 3 according to Eastern Cooperative Oncology Group scale,
5. Blood analysis:
 - Platelets count $>100,000 \mu\text{L}$
 - Hemoglobin level $>10 \text{ g/dL}$
 - White blood cells $>4000 \cdot 10^3 \mu\text{L}$
6. Absence of cardiac or neuropathic disease.
7. Absence of concomitant infection.
8. Absence of pregnancy.

Preoperative Evaluation

1. Blood analysis:
 - Hemochromocytometric test (complete blood count)
 - Blood chemistry test (glucose, electrolytes)
 - Coagulation test (prothrombin time [PT], activated partial thromboplastin time [aPTT], international normalized ratio [INR], fibrinogen, and D-dimer)
 - Evaluation of liver and kidney function (serum glutamic oxaloacetic transaminase [GOT], glutamic pyruvic transaminase [GPT], gamma-glutamyl transferase [GGT], albumin, protein electrophoresis, blood urea nitrogen [BUN], creatinine and creatinine clearance)
2. Cardiac evaluation
 - Electrocardiogram
 - Echocardiography with ejection fraction evaluation
 - Exercise stress test if requested by cardiologist
3. Pulmonary evaluation
 - Chest radiograph
 - Pulmonary function tests
 - Arterial blood gas analysis
 - Six-minute walking test if requested by pneumologist

DAY 1

Start sequential hydration 24 hours before the surgery:

- Saline solution (500 cL) with the addition of dexamethasone (8 mg) and ranitidine (50 mg)
- Sodium lactate solution (1000 cL)
- Saline solution (500 cL) with the addition of furosemide (20 mg)

Antithrombotic prophylaxis with low-molecular-weight heparin (LMWH) according to the patient's weight.

DAY 0 (OPERATIVE DAY)

Intraoperative monitoring:

- Central venous catheter
- Nasogastric tube
- Urinary catheter
- Arterial pressure monitoring
- Temperature sensor
- Antithrombosis tights
- Isotonic solution

SURGICAL PROCEDURE AND HYPERTHERMIC INTRATHORACIC INTRAOPERATIVE CHEMOTHERAPY

Complete parietal and mediastinal pleurectomy and a partial decortication sparing the diaphragm and the pericardium is performed with the goal of achieving a macroscopic complete resection. Mediastinal lymph-node sampling is performed. A temperature probe is placed into the pleural cavity. Two 28- or 32-Fr intercostal drains are placed in the pleural space: one at the apex and one on the diaphragm, respectively working as outflow and inflow drainage during the perfusion.

We routinely use Performer LRT (Rand, Medolla, MO, Italy). The patient is left on lateral decubitus with collapsed lung throughout the procedure. First, the chest cavity is filled up through the lower drainage (inflow) with isotonic solution; the correct volume for each patient is assessed according to the body surface ($2\text{--}2.5 \text{ L/m}^2$). Body surface is calculated with the Mosteller formula. Once the chest cavity is filled, the apical drainage (outflow) is connected and the perfusion is started until the intrathoracic target temperature (42.5°C) is reached; drugs are then added to the perfusion as a bolus (epirubicin 25 mg/m^2 alone and cisplatin 80 mg/m^2 in 250 cL of saline solution). Chemotherapy drugs and solutions are prepared in the pharmacy department, and they are sent directly to the operating room in a closed, light-protected bag. From the time drugs are inserted in the circuit, perfusion is run for an additional 60 minutes so that the chest cavity is uniformly exposed to heat and chemotherapy. At the end of the perfusion, inflow and outflow drains are exchanged to empty the pleural space, temperature probes are removed, and lung is ventilated again.

Operative day intravenous hydration and therapies to start during surgery:

- Intravenous ceftriaxone (2 g)
- Saline solution (500 cL) with the addition of dexamethasone (16 mg) and ranitidine (50 mg)

- Saline solution (500 cL) with the addition of 20 mEq MgSO₄
- Saline solution (500 cL) with the addition of 20 mEq KCl
- Saline solution (500 cL) with the addition of furosemide (20 mg)
- Sodium lactate solution (500 cl)
- Saline solution (500 cL) with the addition of furosemide (20 mg)

Antithrombotic prophylaxis is performed with LMWH according to the patient's weight.

Elastomeric infusion pump for the administration of continuous intravenous analgesia (morphine up to a maximum of 30 mg); additional analgesic therapy is available by the patient's request (paracetamol 1000 mg or ketorolac 75 mg).

Postoperative blood analysis:

- Hemochromocytometric test (complete blood count)
- Blood chemistry test (glucose, electrolytes)
- Coagulation test (PT, aPTT, INR, fibrinogen, D-dimer)
- Evaluation of liver and kidney function (GOT, GPT, GGT, albumin, BUN, creatinine)

DAYS 1 TO 5 (POSTOPERATIVE DAYS)

Hydration and therapies:

- Ceftriaxone (2 g)
- Saline solution (500 cL) with the addition of dexamethasone (4 mg) and ranitidine (50 mg)
- Sodium lactate solution (1000 cL)
- Saline solution (500 cL) with the addition of furosemide (20 mg)

Antithrombotic prophylaxis with LMWH according to the patient's weight.

Elastomeric infusion pump for the administration of continuous intravenous analgesia.

Daily blood analysis:

- Hemochromocytometric test (complete blood count)
- Blood chemistry test (glucose, electrolytes)
- Coagulation test (PT, aPTT, INR, fibrinogen, D-dimer)
- Evaluation of liver and kidney function (GOT, GPT, GGT, albumin, BUN, creatinine)

Mobilization from the first postoperative day.

Chest radiograph on day 0-2-5 or when required for clinical conditions.

000 Diaphragm and lung-preserving surgery with hyperthermic chemotherapy for malignant pleural mesothelioma: A 10-year experience

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Using cytoreductive surgery with hyperthermic intrathoracic chemotherapy and adjuvant chemotherapy for malignant pleural mesothelioma, we preserved lung and diaphragmatic function, which might achieve acceptable long-term outcomes despite incomplete resection.