

MÉSOTHÉLIOMES MALINS DU PÉRITOINE

Malignant peritoneal mesothelioma: treatment with maximal cytoreductive surgery plus intraperitoneal chemotherapy

ARTICLE
ORIGINAL

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SUMMARY

Objective — To report survival results in patients with diffuse malignant peritoneal mesothelioma (MPM) treated with maximal cytoreductive surgery followed by immediate intraperitoneal chemotherapy, and to compare them with the median survival of 12-24 months obtained with the standard treatment based on systemic chemotherapy.

Patients and methods — Twenty-six patients underwent this new regional approach and a median follow-up of 55 months was achieved after this treatment. Complete cytoreductive surgery (residual disease <2 mm) was performed in all but one patient. Intraperitoneal chemotherapy was performed with hyperthermia (42-45°C) and oxaliplatin in 22 patients. The last 12 patients additionally received irinotecan. Data were prospectively verified and retrospectively analyzed.

Results — One patient died postoperatively (4%), and morbidity attained 54%. The median survival exceeded 100 months and the overall 5-year survival rate was 63%. This small series lacks the statistical power required to conduct a well-grounded study on prognostic factors, particularly as the completeness of the surgery is not analyzable here. However, the low-grade histological types had a better disease-free survival rate that was of borderline significance compared to their high-grade counterparts.

Conclusion — This new approach combining complete cytoreductive surgery considerably increases the survival of patients with MPM compared with the standard treatment based on systemic chemotherapy.

RÉSUMÉ

Mésothéliomes malins du péritoine : traitement par exérèse complète suivie de chimiothérapie intrapéritonéale

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Objectif — Rapporter les résultats en termes de survie de malades présentant un mésothéliome malin du péritoine (MPM) diffus, traités par résection chirurgicale maximale suivie de chimiothérapie intrapéritonéale, et les comparer à la médiane de survie de 12 à 24 mois obtenue par le traitement standard (basé sur la chimiothérapie systémique).

Malades et méthodes — Vingt-six malades ont été traités avec ce traitement régional et ont un recul médian de 55 mois après ce traitement. La chirurgie de réduction tumorale a été complète (résidu tumoraux < 2 mm) chez tous les malades sauf un. La chimiothérapie intrapéritonéale a été associée à une hyperthermie (42-45 °C) et à de l'oxaliplatine chez 22 malades. Les 12 derniers ont reçu en plus de l'irinotecan. Les données ont été enregistrées de manière prospective et analysées de manière rétrospective.

Résultats — Un malade est décédé en postopératoire (4 %), et la morbidité a été de 54 %. La médiane de survie a été supérieure à 100 mois et la survie globale à 5 ans a été de 63 %. La petite taille de cette série explique le manque de puissance de l'étude pronostique, ce d'autant plus que le critère « résection complète » n'est pas analysable. Cependant, les mésothéliomes de haut-grade avaient une survie sans récurrence presque significativement plus basse que les mésothéliomes de bas-grade.

Conclusion — Cette nouvelle approche combinant résection chirurgicale complète des lésions et chimiohyperthermie intrapéritonéale améliore nettement la survie des malades atteints d'un MPM en comparaison avec le traitement standard basé sur la chimiothérapie systémique.

Introduction

Malignant mesothelioma arises from the serosal lining of the pleural, peritoneal and pericardial cavities. Diffuse malignant peritoneal mesothelioma (MPM) accounts for 25% of cases, with a very low incidence in France (approximating 0.3/100,000) [1]. The role of asbestosis in its onset is unclear.

The most frequent clinical presentation is abdominal pain and distention caused by accumulation of tumors and ascitic fluid [2]. Exploratory coelioscopy is the most useful exploration method to obtain the diagnosis based on biopsy specimens and to provide a precise description of the extent of the disease. Macroscopically, MPM is characterized by thousands of whitish tumor nodules, variable in size and consistency that may coalesce to form plaques, masses or are layered out uniformly covering the entire peritoneal surface.

Histologically, the diagnosis is frequently difficult, and only specific immunostains (calretinin and WT-1 are positive mesothelial markers, and polyclonal CEA and Ber-EP4 are negative markers) [3] allow a definitive diagnosis of MPM. Moreover, one

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is frequently faced with a broad spectrum of architectural patterns from one microscopic field to another, making it difficult to classify each case as a distinct histological type.

Conventional treatment is a combination of systemic chemotherapy (similar to that administered for pleural mesothelioma) and palliative surgery, yielding a median survival uniformly close to one year [4-6]. However, it is well known that most MPM remain localized within the abdomino-pelvic cavity throughout their natural history, as evidenced in autopsy series [7]. It is therefore logical to consider that an aggressive local treatment could be more efficient. During the last 5 years, a cytoreductive surgical approach combined with HIPEC has been used by a few teams and has resulted in dramatically improved median survival approaching 5 years for patients undergoing such treatment [8-12].

The purpose of this report is to provide an analysis of the 26 patients with diffuse MPM that we treated with cytoreductive surgery and HIPEC.

Patients and methods

Patients

This study reviews, from a prospective database, data concerning 26 patients with histologically proven malignant peritoneal mesothelioma (MPM) who were treated with maximal cytoreductive surgery followed by immediate intraperitoneal chemotherapy from January 1996 to December 2005. These patients were included in different and successive clinical trials approved by our Institutional Review Board and by an independent Ethics Committee. All patients gave their signed informed consent. Eligibility criteria were as follows: histologically proven MPM, age <65 years, a good general status, adequate renal (creatinine <2.0) and hepatic (normal bilirubin level and prothrombin time) function, adequate hematological parameters (WBC >3000/mL and platelet count >75,000/mL), no systemic chemotherapy during the 30 days before treatment, and no evidence of extra-abdominal metastases.

Cytoreductive surgery

Complete cytoreductive surgery resecting all tumor deposits measuring >1 mm was our usual policy, before using intraperitoneal chemotherapy. The modality of this cytoreductive surgery has been described elsewhere [13]. Briefly, it consists in performing large peritonectomies and resection of any viscera which had been invaded by tumor deposits. The main factor limiting resectability is the extent of the disease on the small bowel. Intraoperatively, the extent of peritoneal disease was assessed with Sugarbaker's peritoneal score [17] which ranges from 1 to 39. This index takes into account the number of invaded areas amid a total of 13, and the maximal size of tumor nodules in 3 possible groups (<5 mm, 5 mm to 5 cm, >5 cm).

Immediate intraperitoneal chemotherapy

As the years went by, our trial modalities were modified, and we successively used 4 types of hyperthermic intraperitoneal chemotherapy (HIPEC) which are detailed in table I. Twenty-four patients were treated with HIPEC with cisplatin (N=2), oxaliplatin (N=10), and oxaliplatin plus irinotecan (N=12). The modalities and pharmacokinetics of these treatments have previously been described [14, 15]. Briefly, after complete reductive surgery, HIPEC was performed over 30 min at a minimal temperature exceeding 42°C (range: 42°C-45°C), with an open technique (Coliseum technique), and a closed circuit with 2 in-drains and 2 out-drains, without Y connectors, and with 2 pumps with a flow rate of 1 L/min for each pump. An intravenous perfusion of leucovorin (20 mg/m²) and 5-fluorouracil (400 mg/m²) was delivered before HIPEC, over 1 hour in patients receiving oxaliplatin alone or oxaliplatin ± irinotecan

Table I. – Intraoperative parameters of patients. Modalities of peritoneal chemotherapy.

Données opératoires et modalités de la chimiothérapie intrapéritonéale.

Intraoperative Parameters			
	Mean ...SE	Median	Range
Peritoneal score	22±7	20	12-39
Nb of resected organs	4.2±1.6	4	1-8
Nb of circular anastomoses ^a	1.2±1.2	1	0-5
Nb of lateral sutures ^a	2.1±1	2	0-5
Duration of surgery (min)	472±106	408	280-720
Intraoperative blood loss	958±820	750	100-3000

Peritoneal chemotherapy (clinical trial development)	
Type	Nb of patients
EPIC with doxorubicin (5 mg/m ²) + cisplatin (15 mg/m ²)	2
HIPEC with cisplatin (200 mg/m ²)	2
HIPEC with oxaliplatin (460 mg/m ²)	10
HIPEC with oxaliplatin (360 mg/m ²) + irinotecan (360 mg/m ²)	12

^a: Digestive sutures.

EPIC: early postoperative intraperitoneal chemotherapy in 1 L/m² of ringer solution (lasting 5 days). HIPEC: hyperthermic intraperitoneal chemotherapy.

Completeness of cytoreduction: no residue = 17 (65%), residue <2 mm = 8 (31%), residue measuring 3 mm = 1 (4%).

(22 patients) in order to potentiate the activity of oxaliplatin and irinotecan [14, 15]. The first two patients were treated with early postoperative chemotherapy (EPIC) containing cisplatin over 5 days, from day 0 to day 4 according to the initial schedule of Sugarbaker et al. but without hyperthermia [16].

Follow-up and evaluation

Complications were scored using a scale of 1-to-5, according to a previously published grading system [18]. *Grade 0* corresponds to cases with no complications. *Grade 1*: complications are those requiring no intervention or minor interventions such as oral antibiotics, bowel rest, or basic monitoring. *Grade 2*: complications are those requiring moderate interventions such as intravenous medications (e.g. antibiotics or anti-arrhythmics), TPN, prolonged tube feeding, or chest tube insertion. *Grade 3*: complications are those requiring readmission to hospital, a surgical intervention, or a radiological intervention. *Grade 4*: complications are those producing chronic disability, organ resection, or enteral diversion. *Grade 5*: complications result in death.

Patients were evaluated every 3 months for 2 years, then every 6 months for 3 years, with a physical examination, measurement of tumor markers if initially elevated and CT-scan of the chest, abdomen and pelvis. Patients were considered to be in remission until they had radiographic evidence of a recurrence.

Histological categorization of tumors

The histological diagnosis of MPM was based on the following panel of immunostains: calretinin and WT-1 were used as positive mesothelial markers, and polyclonal CEA and Ber-EP4 were negative markers, eliminating carcinomatosis [19]. Tumors were classified as epithelial, sarcomatoid and biphasic (mixed epithelial and sarcomatoid components) according to the World Health Organization classification [3]. MPM were then subdivided into low-grade tumors (tubulo-papillary and adenomatoid) and high-grade tumors (solid epithelial and sarcomatoid types), according to the predominant pattern [9].

ABBREVIATIONS:

MPM : Malignant peritoneal mesothelioma
 HIPEC : Hyperthermic intraperitoneal chemotherapy
 EPIC : Early postoperative intraperitoneal chemotherapy
 WBC : White blood count

Statistical analysis

Patients were prospectively recorded in a specific database. Postoperative mortality was analyzed not only during the 30 days following HIPEC, but until the patient was discharged from hospital. The exact status of each patient was known on the date of the analysis of the series (October 2006). No patient was excluded from survival analyses (including postoperative deaths). The Chi-square test or Fisher's exact test, when appropriate, were used for univariate comparisons. Survival curves were calculated with the Kaplan-Meier method and compared with the Log-Rank test. Differences were considered significant at $P=0.05$.

Results

Preoperative data

Fourteen male and 12 female patients underwent cytoreductive surgery followed by immediate intraperitoneal chemotherapy, with or without hyperthermia. The mean age was 46 ± 8.2 years (range: 14-59). Previous exposure to asbestos was found only in 5 male patients. Symptoms were mainly increased abdominal girth (54%) and abdominal pain (31%). In 15% of cases, symptoms were incidentally discovered. In all cases, the diagnosis of MPM was made by laparoscopy which led to a biopsy.

There were 12 cases (46%) of low-grade MPM (tubulopapillary type [11] and multicystic type [1]) and 14 cases (54%) of high-grade MPM (epithelial type [13] and byphasic type [1]). Preoperative systemic chemotherapy was administered to 16 patients (including the 14 with high-grade MPM), over three months with pemetrexed-cisplatin (N=9) or tomudex-oxaliplatin (N=5), resulting in decreased ascites in 9 out of 12 patients who developed this complication. The other 10 patients did not receive preoperative chemotherapy because they were considered as having a low-grade tumor. Nine of these 12 patients received the same chemotherapy after surgery because they had high-grade tumor and because they presented reduction or stabilization of their tumor under preoperative chemotherapy.

Intraoperative data

The peritoneal score concerning the extent of the disease, resected organs and the main intraoperative parameters are reported in table I. The completeness of cytoreductive surgery was considered maximal in 25 patients: there was no visible residual tumor deposit in 17 patients (65%) and tumor deposits smaller than 2 mm in diameter in 8 patients (31%). Resection of all tumor deposits exceeding 2 mm was performed in all but one patient. That patient had thick and diffuse mesothelioma covering the entire peritoneal surfaces and 8 liters of ascites had to be extracted weekly from the peritoneal cavity. After cytoreductive surgery resecting 2/3 of these surfaces but leaving tumor deposits measuring 3-4 mm in diameter, HIPEC was performed with a palliative intent to try to relieve this debilitating build-up of fluid in the abdomen.

Postoperative course

Mortality was 4%: one patient suddenly died at day 14 having developed Ogilvie's syndrome.

Grade 3-4 morbidity was 54%. Fourteen patients experienced a complication (hemorrhage: 3, deep abscess: 2, hematological toxicity: 2, rhabdomyolysis: 2, lung infection: 2, pulmonary embolism: 1, digestive fistula: 1, ureteral fistula: 1). Four of them required another operation.

The mean duration of hospitalization was 28 ± 18 days (median: 23, range: 13-92).

Survival rates and study of prognostic factors:

At a median follow-up of 54 months (range: 6 to 129), median actuarial overall survival has not yet been reached, but exceeds 100 months. The median disease-free survival is 40 months. Survival curves are reported in figure 1. The 1-through-5-year estimates of overall and disease-free survival rates are presented in table II. In spite of the small number of patients, an analysis was performed to identify prognostic factors associated with overall survival and disease-free survival. The grade seems to have no significant impact on overall-survival (figure 2), but almost had an impact ($P=0.09$) on disease-free survival (figure 3). Gender had no significant impact (figure 4) on disease-free survival rate, nor did the peritoneal score (figure 5). The patient whose disease was incompletely resected with uncontrolled ascites before surgery, no longer had clinical ascites two years after this regional treatment.

Discussion

This article reports on a small series of patients suffering from an unfamiliar and rare disease. The incidence of MPM can be evaluated as a quarter of the cases of pleural mesotheliomas, i.e. approximately 230 cases per year in France [1]. Our survival results obtained with aggressive local therapy combining complete cytoreductive surgery and HIPEC are encouraging, with median survival exceeding 100 months, whereas conventional treatment mainly based on systemic chemotherapy results in a

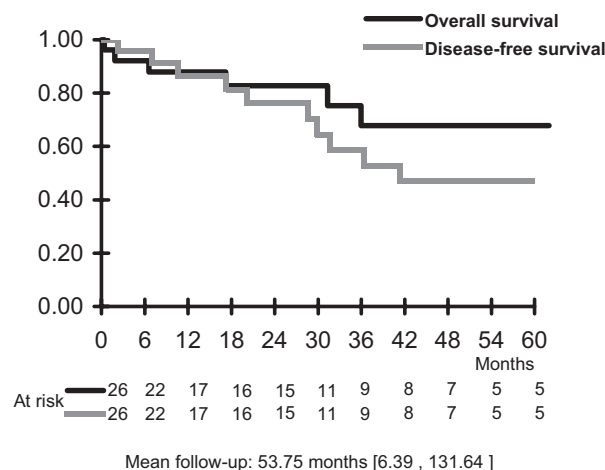


Fig. 1 – Overall and disease-free survival rates of the 26 patients.
Survie globale et survie sans récurrence des 26 malades traités.

Table II. – Outcome after regional treatment in patients with Malignant Peritoneal Mesothelioma.
Évolution après traitement régional des malades avec mésothéliomes malins du péritoine.

Parameter	Overall survival	95% CI	Disease free survival	95%CI
Median	>100 months		40 months	
1-year	88%	70-96%	86%	67-95%
2-year	83%	63-93%	76%	55-90%
3-year	68%	44-85%	53%	31-73%
4-year	68%	44-85%	47%	27-68%

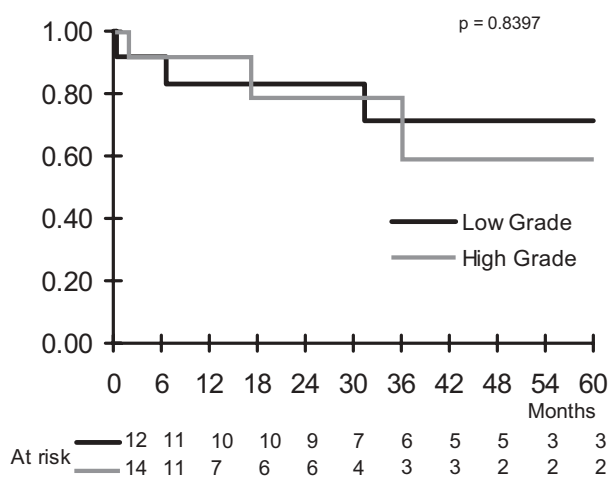


Fig. 2 – Overall survival rates according to the grade of malignant mesothelioma.
Survies globales en fonction du grade histologique.

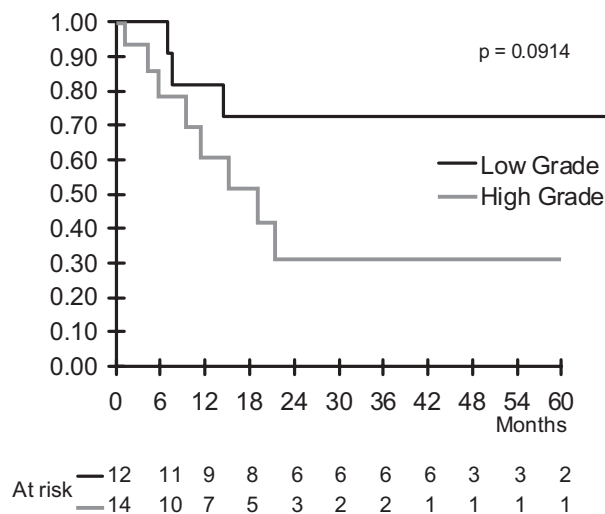


Fig. 3 – Disease-free survival rates according to the grade of malignant mesothelioma.
Survies sans récurrence en fonction du grade histologique.

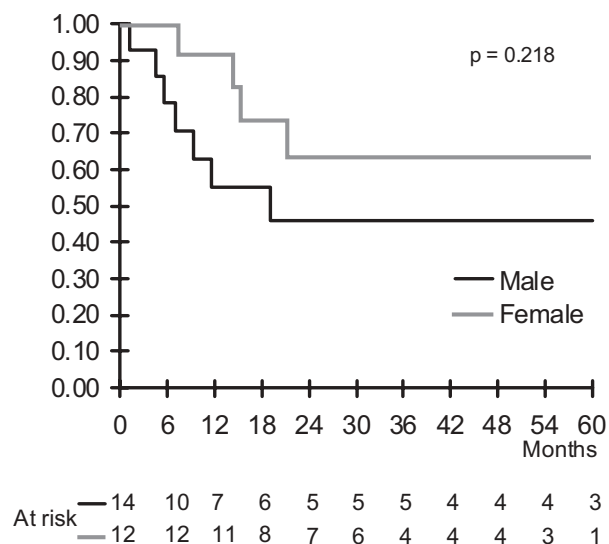


Fig. 4 – Disease-free survival rates according to patient gender.
Survies sans récurrence en fonction du sexe.

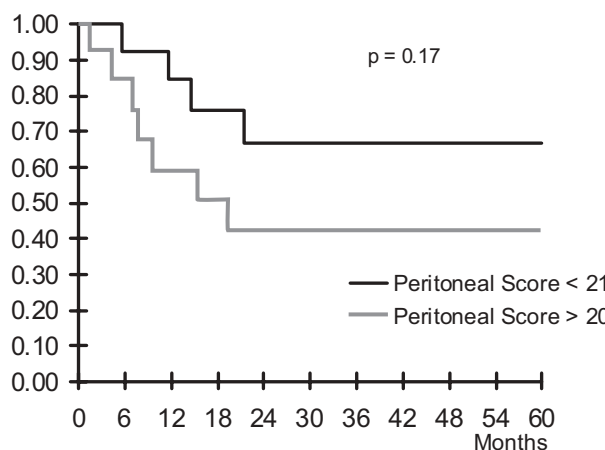


Fig. 5 – Disease-free survival rates according to the Peritoneal Score.
Survies sans récurrence en fonction du score d'extension intrapéritonéale.

median survival duration comprised between 12 and 24 months with the most recent agents (premetrexed, raltitrexed, oxaliplatin and vinorelbine) (table III).

Our favorable results confirm those published earlier by other groups using the same local approach [8-12] (table IV): median survival ranged from 35 to 100 months and 5-year survival ranged from 29% to 63%. The discrepancy in results between series is mainly due to differences in the completeness of cytoreductive surgery and the HIPEC techniques. Mortality ranged from 0 to 6% and morbidity from 27% to 54% [8-12], which is acceptable, given the results obtained.

Only selected patients can undergo this new approach. Patients with a poor general status, and those presenting huge and diffuse peritoneal disease are not eligible. This is why it is not completely relevant to compare these good results to those obtained with conventional therapy. In addition, if the completeness of cytoreductive surgery is the main explanation for the good results obtained in our study, it is difficult to appreciate the real benefit of intraperitoneal oxaliplatin and a high intraperitoneal temperature of between 45°C (in-drains) and 42.5°C (out-drains).

It was not possible to analyze prognostic factors adequately because our series is small and also because the completeness of cytoreductive surgery, which is the preponderant factor [8-12], was performed in all but one patient. The second classic prognostic factor is the histological type of MPM [20]. However, as only approximately 5% of patients had a sarcomatoid or a biphasic histologic type, this criterion is not a useful prognostic indicator in most of the patients. As in the WHO classification [3], we divided the epithelial type into high-grade and low-grade entities and ascertained that it impacted significantly on disease-free survival in our series. Possibly, a high mitotic count (greater than 20 per 50 high-power microscopic fields) and nuclear grade 3 (large nuclei, irregular chromatin pattern with clear and prominent nuclei) are more appropriate for differentiating patients with a good prognosis from those with a poor prognosis [21]. Finally, the usual best survival among female patients does not appear to be significant in our series, probably due to the limited sample size of our study.

In conclusion, as in the case of peritoneal pseudomyxoma [22] and colorectal peritoneal carcinomatosis [23, 24], this new

Table III. – Median survival of diffuse malignant peritoneal mesothelioma treated with conventional modalities.

Médianes de survie des mésothéliomes diffus du péritoine traités selon les modalités classiques.

Authors	Year	No. of patients	Median survival (months)
Markman et al. [4]	1992	19	9
Neumann et al. [5]	1999	74	12
Eltabbali et al. [6]	1999	15	12.5

Table IV. – Survival results of cytoreductive surgery combined with intraperitoneal chemotherapy for MPM.

Survies obtenues avec une chirurgie de réduction tumorale maximale combinée à une chimiothérapie intrapéritonéale, pour mésothéliomes malins du péritoine.

Author	Year	No Pts	Median survival (months)	5-year survival rate (%)
Sugarbaker [8]	2006	100	52	46
Alexander [9]	2003	49	92	59
Deraco [10]	2006	49	NA	57
Glehen [11]	2003	15	36	29
Loggie [12]	2001	12	34	33
Present series	2006	26	100	63

NA: median survival was not reached.

approach combining complete cytoreductive surgery with HIPEC allows a dramatic increase in the survival of selected patients with MPM. Mortality and morbidity are similar to that of any type of extended digestive surgery. We still need to widen our knowledge of prognostic factors and mainly biomolecular factors in this rare disease, and finally determine the exact role of systemic chemotherapy in these patients.

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