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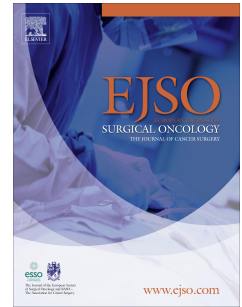
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Multicystic Peritoneal Mesothelioma: Outcomes and Patho-Biological Features in a Multi-Institutional Series Treated by Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC).

Original article.

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**Running title:** Multicystic Peritoneal Mesothelioma

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**Keywords:** multicystic peritoneal mesothelioma; cytoreductive surgery; peritonectomy; hyperthermic intraperitoneal chemotherapy; HIPEC.

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## ABSTRACT

**Aim** This retrospective multi-institutional study addresses the role of surgical cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of multicystic peritoneal mesothelioma (MCPM). MCPM is an uncommon tumour with uncertain malignant potential and no current standard therapy. Additionally, poorly defined pathological and biological features of this disease were investigated.

**Methods** Twelve patients with MCPM underwent 14 procedures of cytoreduction and HIPEC in two Italian referral centres. Nine patients had recurrent disease after previous debulking (one operation in six patients, two in two, four in one). Biological markers related to mesothelioma origin and clinical features were assessed by immunohistochemical studies.

**Results** Median follow-up was 64 months (range 5–148). Optimal cytoreduction (residual tumour nodules  $\leq 2.5$  mm) was performed in all the procedures. One grade IV postoperative complication (NCI/CTCAE v.3.0) and no operative death occurred. All the patients are presently alive with no evidence of disease, including two patients who underwent the procedure twice, due to locoregional disease recurrence. Five- and ten-year progression-free survival was 90% and 72%, accounting for a statistically significant difference ( $P = .0001$ ) with progression-free survival following previous debulking surgery (median 11 months; range 2–31). All cases showed low proliferative activity assessed by mitotic rate and Ki-67 expression.

**Conclusions** MCPM is a borderline tumour with a high propensity to local-regional recurrence. Definitive tumour eradication by means of cytoreduction and HIPEC seems more effective than debulking surgery in preventing disease relapse. Low mitotic rate and poor Ki-67 expression might be related to the peculiar behaviour of MCPM.

## INTRODUCTION

Tumours originating from the mesothelial cells lining the abdominal cavity cover a wide spectrum of biological aggressiveness. Among them, adenomatoid tumour is a benign lesion that mostly involves the genital tract and very unlikely recurs after local excision.[1] At the other extreme, diffuse malignant peritoneal mesothelioma is a locally aggressive and rapidly lethal malignancy.[2] Multicystic peritoneal mesothelioma (MCPM) is an exceedingly rare lesion with uncertain malignant potential and an enigmatic natural history.[3-7]

Approximately 150 cases of MCPM have been reported in the medical literature since it was first described by Mennemeyer and Smith in 1979.[8] According to the available information, MCPM most commonly occurs in the abdomino-pelvic cavity of reproductive age women with no history of asbestos exposure. The disease shows an indolent clinical behaviour in most cases. However, early recurrences requiring multiple surgical interventions[5-7], transformation into truly malignant disease[9], lymph-node involvement[10] and even death[4] have been described.

*The conceptual and methodological paradigm for the management of peritoneal surface malignancies is currently evolving from end-stage conditions with only palliative options to local-regional disease amenable to intensive treatment.* Accordingly, an innovative treatment strategy has emerged, involving aggressive cytoreductive surgery to remove all the visible peritoneal tumour, in combination with intra-operative local-regional chemotherapy to treat the microscopic residual disease.[2,11-13] This combined approach has become a treatment option for malignant peritoneal mesothelioma in the last decade. Median survival has dramatically improved reaching approximately five years, as compared to 9-13 months in the historical case-series treated by debulking surgery and/or palliative systemic chemotherapy.[2]

In few international centres, MCPM has been included among the indications for surgical cytoreduction and intraperitoneal chemotherapy. However, only a small number of patients undergoing combined treatment has been reported in the literature.[14-17] Furthermore, the biology of peritoneal mesothelioma has been addressed only in recent years and the features of rare sub-variants, such as MCMP, are still largely unknown. The present paper reports the collaborative effort of two Italian centres to assess safety and effectiveness of the combined treatment. Additionally, pathological and biological features of MCMP, including lymph-nodal involvement, serum and cellular marker expression, were analyzed together with their prognostic significance.

## PATIENTS AND METHODS

All the patients were treated according to clinical protocols approved by the Institutional Ethics Committee of each participating institution. The informed consent form was signed by each patients. Standardized clinical data on consecutive patients were collected from prospective institutional databases and entered into a central database. Additional information was retrieved from medical charts. The same author reviewed all the information to ensure a uniform interpretation of data. The exact number of patients from each hospital is not stated due to confidentiality issues.

### Data form

A standard data form was created to retrieve information on patient characteristics (sex, age, performance status), clinical history (exposure to asbestos, presenting symptoms, methodology for diagnosis, previous therapies), operative treatment (number of peritonectomy procedures and multivisceral resections, completeness of surgical cytoreduction, methodology for intraperitoneal chemotherapy), pathological data (histological features, special studies, lymph-node metastases), length of hospital stay, grade III/IV postoperative complications according to the National Cancer Institute Common Terminology Criteria (<http://ctep.cancer.gov/forms/CTCAEv3.pdf>), and follow-up (date of last control, disease status, occurrence and treatment of disease relapse).

### Inclusion criteria

Pathological diagnosis of MCPM was made by specialized pathologists in each institution, based on haematoxylin/eosin slides showing typical morphological features and appropriate immunohistochemical studies.[1] Patients were managed by cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC). In both institutions, eligibility criteria for combined treatment included: age  $\leq 75$ ; performance status  $\leq 2$  according to the Eastern Cooperative Oncology Group (ECOG);[18] no significant co-morbidities; peritoneal disease amenable to potentially complete surgical cytoreduction and no extra-abdominal or hepatic metastases at preoperative computed tomography (CT)-scan.

### Operative treatment

The extent of peritoneal involvement was rated at surgical exploration using the peritoneal cancer index (PCI). PCI is a semi-quantitative score which combines lesion size (LS-0/3) with disease distribution in 13 abdomino-pelvic regions (PCI 0/39).[19]

Cytoreductive surgery was performed according to the technique described by Sugarbaker.[20] Briefly, the goal of the surgical cytoreduction was to remove all the visible tumor by means of diaphragmatic, parietal and pelvic peritonectomy with greater and lesser omentectomy. Depending on disease involvement of visceral surfaces, local excision and electro-coagulation of small localizations or multi-visceral resections were performed, including cholecystectomy, splenectomy, sigmoid, right or total colectomy and hysterectomy with salpingo-oophorectomy in women.

The completeness of cytoreduction (CCR) was rated at the end of the procedure, as follows: CCR-0= no visible residual disease; CCR-1= residual disease  $\leq 2.5$ mm; CCR-2= residual disease  $>2.5$ mm and  $\leq 25$ mm; CCR-3= residual disease  $>25$ mm.[21]

All HIPEC procedures were performed intra-operatively, but with many variations in exposure techniques, drugs, drug doses, duration (60-90 minutes), intraperitoneal temperatures (40-42.5°C), perfusate volume (3.4-6 L), and flow rates (600-1000 mL/min.). Nine HIPEC procedures were performed using the closed-, one the open- and four an original semi-closed-abdomen technique.[21] The combination of cisplatin (45 mg/L) and doxorubicin (15 mg/L) was used in ten procedures, according to the results of a formal phase I study.[22] Two patients were treated with cisplatin alone (a total of 100 and 120 mg, respectively), one with cisplatin (25 mL/m<sup>2</sup>/L) plus mitomycin-C (3.3 mL/m<sup>2</sup>/L), and one with mitomycin-C (35 mg/m<sup>2</sup>). Dose reduction up to 30% was applied to patients treated with prior systemic chemotherapy and/or extensive cytoreductive surgery.

Patients were followed postoperatively with physical examination, thoracic/abdominal CT scan, and serum marker measurements every three to six months. No patient was lost at follow-up. Postoperative disease progression was confirmed at surgical exploration or by CT-scan/ultrasound-guided biopsy.

### Statistics

Overall and progression-free survival was calculated from the day of cytoreduction and HIPEC to the time of death due to any cause or postoperative disease progression, according to the Kaplan–Meier method.[23] Patients with uneventful postoperative course were censored at the time of last follow-up visit. The two-tailed log-rank test was used to assess the significance of the comparison between survival distributions. P value  $<.05$  was considered significant. The following potential prognostic factors were tested with regard to overall and progression-free survival: sex, age at

diagnosis, diagnosis (incidental vs. symptomatic), interval diagnosis-HIPEC, previous surgery, previous systemic chemotherapy, ECOG performance score (0 vs.1-2), time-to-progression after the last treatment, PCI, presence of ascites, CCR, baseline CA125 and CA15.3, immunohistochemical studies, number of peritonectomy procedure ( $\leq 3$  vs.  $>3$ ), visceral resections, HIPEC drug schedule (cisplatin and doxorubicin vs. others), cisplatin total dose ( $\leq 100$ mg vs.  $>100$ mg). Continuous variables were categorized into two classes using their median value as cut-off.

## RESULTS

### Patient characteristics

From August 1995 to October 2009, 12 patients underwent 14 procedures of cytoreduction and HIPEC in two Italian tertiary referral centres. Some of these patients were reported previously.[15,24-25] Patient characteristics and clinical history before comprehensive treatment are summarized in Table 1. Eleven patients were females. No-one reported a documented history of asbestos exposure. Median age at diagnosis was 39 (range 22–63). One patient was affected by Glanzman's thrombasthenia. Abdominal pain was the most common presenting symptom and final diagnosis was established by laparotomy in most instances. Every patient complained of abdominal distension and/or pain at the time of cytoreduction and HIPEC.

Before combined treatment, nine patients underwent 14 surgical procedures for MCMP (one operation in six patients, two operations in two, and four operations in one); one of them received systemic carboplatin with gemcitabine. Two partial and one macroscopically complete excision were performed in the participating institutions before the initiation of their peritoneal malignancy treatment programs; PCI range was 10–14. CCR and PCI score were difficult to ascertain retrospectively in patients operated on elsewhere. They were all considered as having received debulking surgery. Disease progression invariably followed each of these 14 surgical attempts, with a median time-to-progression of 11 months (range 2–31).

### Operative outcomes

Operative procedures are displayed in Table 2. Median PCI was 10 (range 4–26). CCR-0 cytoreduction was accomplished in 12 operations and CCR-1 cytoreduction (residual disease  $\leq 2.5$ mm) in two. Twenty-three visceral resections were made during nine operations. Hysterectomy with bilateral salpingo-oophorectomy was the most commonly performed procedure, being carried out in 7 patients. Uterus and ovaries were removed in additional 3



women during previous operations. Conversely, genitalia could be spared in one reproductive age woman, according to patient will and limited disease involvement. Six colon resections were performed in four patients, and protective ileostomy in one. No operative death occurred. One grade IV small bowel perforation away from anastomotic sites required re-intervention and ileostomy. Both ileostomies were closed later.

### **Patho-biological features**

Pathological and biological features are shown in Table 3. Eleven patients showed typical MCPM morphology, with multiple variably sized cysts separated by fibrous/adipose septa and lined by a single layer of flattened to cuboidal mesothelial cells with no or little atypia. One patient showed a mixed multicystic and papillary well-differentiated pattern, consisting of delicate papillary structures with fibrovascular core covered by cuboidal mesothelial cells.

Intra-abdominal lymph-nodes were clinically suspicious and sampled by surgeons or pathologists in six patients. Pathological reports documented no metastatic involvement. In the remaining patients, no lymph-node was sampled or thought to be suspicious for metastatic disease.

Immunohistochemical studies were available for eight patients. In all cases, cytocheratins (CK) 5-6 and Wilm's Tumour (WT)-1 were positive and CEA and Ber-Ep4 negative. Calretinin was positive in only five patients. Mitotic count and percentage of cell expressing MIB-1 were low in all patients. Baseline serum CA125 and CA15.3 determinations were positive in one patient, respectively.

### **Survival and failure**

Median follow-up was 64 months (range 5-148). By the time of the present analysis, all the patients are alive with no evidence of disease, including two patients who underwent the procedure twice, due to postoperative recurrence. One of them developed a widespread intra-abdominal relapse (PCI=19) at 18 months; in the second patient, a small volume recurrence (PCI=4) was incidentally diagnosed at 68 months, during hernia repair operation. Both the patients are presently free of disease after 39 and 56 months, respectively, from re-intervention. Histological and immunohistochemical features at recurrence were not remarkably different from those seen at initial cytoreduction. Five- and 10-year Kaplan-Maier estimated progression-free survival were 90% and 72%. In figure 1, progression-free survival curves after cytoreduction and HIPEC and after 14 debulking operations carried out in nine patients before referral for combined treatment are shown; the difference was statistically significant ( $P<0.0001$ ). Seventeen months after combined treatment, a multiloculated para-adnexial lesion was detected by CT-scan and trans-vaginal ultrasound

in the woman with spared uterus and ovaries. Disease recurrence was suspected, but the patient refused any treatment or invasive diagnostic procedures.[24] Serial CT-scans demonstrated the spontaneous complete regression of the cysts and the patient is now considered free of disease.

Exploratory analysis of patient-, tumour- and treatment-related data showed no significant association with survival. Both the patients who recurred had typical MCPM; their nodes were pathologically negative. Both patients had positive calretinin and normal levels of serum CA125 and CA15.3.

## DISCUSSION

To our knowledge, this is the first multi-institutional study on multicystic peritoneal mesothelioma treated by surgical cytoreduction and HIPEC. The present analysis collected twelve patients, which represent a relatively large number of such an uncommon disease entity. Our data suggest that comprehensive treatment may result in long-term disease control and even definitive cure. Furthermore, operative complication rates were similar to those reported by specialized centres performing major gastrointestinal surgery.[26]

### **Rational basis for comprehensive treatment of multicystic mesothelioma**

Although the histological[7-8] and radiological[27] features have been extensively described, disagreement still exists regarding the natural history and treatment of choice of MCPM. Complete surgical resection has been favoured by some authors[3-5] and less aggressive approaches by others, due to the risk of infertility deriving from extensive pelvic surgery in women.[7] Radiation, systemic or intraperitoneal chemotherapy, laser vaporization, percutaneous cyst drainage, hormone-therapy, sclero-therapy, or simple observation have been used with uncertain results.[3-8] Cytoreductive surgery and HIPEC, aiming at complete tumour eradication, is a new concept. Cytoreduction to microscopic or sub-millimetric tumour provides the optimal conditions for HIPEC to target minimal residual disease. The intraoperative setting minimizes the risk of tumour cell entrapment that could give rise to disease recurrence.[2,11-17] This comprehensive strategy is successfully used to treat pseudomyxoma peritonei, a disease which shares with MCPM the low biological aggressiveness and tendency to recur after incomplete excision.[9,14-15] In the current study, drugs were chosen for HIPEC based on their suitability to intra-peritoneal administration and synergistic effect with heat. No data are available on their activity against MCPM, although cisplatin and doxorubicin are largely used in systemic and local-regional treatment of peritoneal mesothelioma.[2]

### **Cytoreduction and HIPEC versus debulking surgery**

Due to the rarity of MCPM, direct comparative studies of treatment efficacy are virtually unfeasible. In an effort to overcome these limitations, we compared in our patients the results of cytoreduction and HIPEC with those of traditional surgery: disease recurrence occurred after all the 14 debulking operations performed before referral for combined treatment (median time-to-recurrence 11 months) and after two of 12 cytoreductions with HIPEC (median follow-up 64 months). The highly significant survival difference ( $P < 0.0001$ ) strongly suggests the superiority of the comprehensive approach. Since the two treatments were compared in the same population, it may be assumed that prognostic factor distribution was well-balanced. Additionally, complete tumour removal was likely feasible at the time of previous debulking, as it was accomplished at the more recent cytoreduction. However, a bias could have occurred in this setting, since the presence of active disease was a condition for patients to undergo cytoreduction with HIPEC and only cases with disease progression after previous surgery were analyzed.

The nature of MCPM as a benign, malignant or even reactive process is still debated, because of the reported association with previous abdominal surgery, inflammation, or endometriosis.[2-7] Consequently, criticisms may involve the use of potentially life-threatening procedures, such as cytoreduction with HIPEC. However, it has to be acknowledged that conventional treatments have often been disappointing: Ross reported disease recurrence in 14 of 25 patients,[5] Katsube in 4 of 8[3] and Sawh in 5 of 12,[6] with median time-to recurrence of 26-48 months. Also in a recent literature review, relapse rate was about 50%.[7] Death related to MCMP was reported by Weiss and Tavassoli in two cases: a man who refused any treatment and died 12 years after diagnosis and a 6-month-old infant who died 11 months after partial resection of invasive intrahepatic MCPM with transition into malignant mesothelioma.[4] Malignant transformation developed over 10 years and 6 surgical attempts in a patient reported by Gonzalez-Moreno who underwent only partial cytoreduction with HIPEC,[9] and eventually died of disease progression.[27]

Literature data on cytoreduction and HIPEC for MCPM are summarized in table 4. To date, the study by Sugarbaker group is the only published case-series entirely devoted to MCPM.[14] The number of patients treated at the Washington Cancer Center has been recently updated to seven.[27] One of the participating institution reported four cases of MCPM together with papillary well-differentiated peritoneal mesothelioma.[15] Consistently with the present study, combined treatment was universally associated to favourable prognosis, except for the patient who had transition of MCMP into aggressive mesothelioma.[9,27]

### **Patho-biological features**

In an exhaustive clinico-pathological analysis of 62 patients undergoing combined treatment at the Washington Cancer Center, 6 cases of MCPM were classified as multicystic variant of epithelial malignant mesothelioma. The authors found that all MCPM cases met the criteria for malignancy because of a clear evidence of diffuse disease distribution throughout the abdomen, invasion into peritoneal surfaces, and lymphovascular involvement. The apparent discrepancy with previous publications reporting benign behaviour was explained by the advanced disease stage and massive tumour load seen in these patients treated at a highly specialized centre. Furthermore, cytoreductive surgery provided more extensive tumour sampling from many different anatomic sites.[28]

A set of biological markers related to mesothelioma origin and clinical features was investigated. Due to the retrospective nature of the present study, markers were not consistently assessed in all the patients. However, interesting information were provided. The Ki-67 antigen is a nuclear protein expressed during all phases of cellular cycle, but not in non-cycling cells (G0 phase). Immunohistochemical staining with Ki-67 of Mib-1 antibodies is an excellent marker of cellular proliferation and tumour aggressiveness.[30] Three independent studies showed low Ki-67 expression in peritoneal mesothelioma, with a median of 0.6% to 10% positive cells.(13,29-30)). Analogously, mitotic rate is generally low in malignant peritoneal mesothelioma, but higher proliferative activity correlates with poor outcome.[13] Ki-67 and mitotic rate were low in all our patients, as compared with the truly malignant counterpart, suggesting that poor proliferative activity may be related to the indolent MCMP behaviour.

Cytokeratin5/6, which is involved in cellular differentiation, the transcription factor WT-1 and calretinin, a vitamin-D-dependent protein involved in calcium signaling, are expressed by most mesothelioma and largely used for diagnosis.[1] CK5-6 and WT-1 were positive in all our patients. Calretinin was not expressed in 3 of 8 cases, although the biological meaning of this observation is not clear, since no prognostic significance was apparent. The poor expression of CA125 and CA15.3 in MCMP suggests that serum marker measurements is not useful in this setting.

### **Analysis of prognostic variables**

The results of the current study regarding potential determinants of outcome showed no correlation with survival, probably because of the small number of events and imbalance in prognostic variable distribution, such as optimal surgical cytoreduction.[2] Lymphatic involvement has been demonstrated to be an independent prognostic factor for malignant peritoneal mesothelioma.[2,13] Nodal metastases were described in the patient with malignant transformation

of MCPM,[9] and recently in a 35-year-old woman.[10] In the present series, all nodes were either pathologically negative or not clinically suspicious and not therefore sampled.

### **Conclusions**

In summary, both literature data and the present series suggest that MCPM is a locally aggressive and border-line malignant tumour capable of transition into an invasive and potentially lethal process, rather than a benign disease. Definitive tumour eradication by means of peritonectomy procedures and HIPEC seems to be the optimal treatment to prevent disease recurrence or malignant transformation.

**Conflict of interest statement** The authors have no potential conflict of interest to disclose.

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Table 1. Clinical characteristics of 12 patients with multicystic peritoneal mesothelioma

	<b>Sex</b>	<b>Age at diagnosis</b>	<b>Presenting symptom</b>	<b>Diagnosis</b>	<b>Previous treatments</b>	<b>Time to progression</b>
1	M	42	incidental	laparotomy	debulking	7 mo.
2	F	29	ileus	laparotomy	TAH, BSO debulking debulking debulking	11 mo. 18 mo. 24 mo. 31 mo.
3	F	35	abdominal pain	laparotomy	BSO, debulking	5 mo.
4	F	63	abdominal pain	laparotomy	TAH, BSO, omentectomy, small bowel and cecum resection syst. CBDCA +gemcitabine (6 courses)	9 mo.
5	F	56	abdominal pain	laparotomy	biopsy debulking	1 mo. 7 mo.
6	F	50	incidental	laparotomy	TAH, debulking	23 mo.
7	F	39	ascites	laparoscopy	biopsy	6 mo.
8	F	22	abdominal pain	laparotomy	partial omentectomy, debulking debulking	27 mo. 28 mo.
9	F	39	umbilical hernia	laparotomy	biopsy	-
10	F	52		laparoscopy	biopsy	-
11	F	36	bleeding	laparotomy	TAH left SO omentectomy, debulking	25 mo. 3 mo.
12	F	28	abdominal pain	laparotomy	biopsy omentectomy, left SO	7 mo. 12 mo.

TAH= total abdominal hysterectomy; BSO= bilateral salpingo-oophorectomy; CBDCA= carboplatin

Table 2. Four-teen procedures of cytoreduction and hyperthermic intra-peritoneal chemotherapy

<b>Procedure</b>	<b>Patients (n)</b>
<b>Peritonectomy</b>	
Right upper quadrant	7
Left upper quadrant	8
Pelvic	12
Greater omentectomy	11
Lesser omentectomy	7
<b>Visceral resection</b>	
Glisson's capsule resection	1
Cholecistectomy	-
Splenectomy	5
Right colectomy	3
Appendectomy	2
Sigmoidectomy	3
Small bowel resection	2
TAH-BSO	7
Protective ostomy	1
<b>Completeness of cytoreduction</b>	
No visible residual tumour	12
Residual tumour $\leq 2.5$ mm	2
Residual tumour $> 2.5$ mm	-
<b>PCI, median (range)</b>	10 (4-26)
<b>Median operative time, minutes (range)</b>	570 (390-750)
<b>Median ICU stay, days (range)</b>	18 (9-31)
<b>Median total hospital stay, days (range)</b>	3 (2-6)

PCI= peritoneal cancer index; TAH= total abdominal hysterectomy;  
BSO= bilateral salpingo-oophorectomy; ICU= intensive care unit.

Table 3. Pathological and biological features

Variable	Categories	n.
<b>Pathological features</b> (patients n=12)		
Histology	multicystic	11
	mixed multicystic and papillary	1
	well-differentiated	
Lymph-nodes	pathologically positive	-
	pathologically negative	6
	clinically neg./not sampled	6
Mitotic count/50HPF	median, (range)	1 (0-5)
<b>Immunohistochemical studies</b> (patients n=8)		
Cytocheratin5-6	Pos	8
Calretinin	Pos	5
WT-1	Pos	8
Mib-1	% of positive cells, median (range)	5 (1-10)
CEA	Pos	-
Ber-Ep4	Pos	-
<b>Circulating tumour markers</b>		
Serum CA125 (patients n= 8)	Pos	1
Serum CA15.3 (patients n= 5)	Pos	1

HPF= high power field; WT-1= Wilms Tumour-1; CEA= carcino-embryonic antigen.

Table 4. Literature data on cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) for multicystic mesothelioma

Center	Pts n.	Complete cytoreduction	Intraperitoneal chemotherapy	Disease status (months)
Washington, DC <sup>14</sup>	5	4	HIPEC (cis + dx)	4 NED (6-69) 1 AWD (25)*
Lyon, Fr <sup>16</sup>	3	3	HIPEC (cis + mit)	3 NED (4-56)
Basingstoke, UK <sup>17</sup>	3	3	HIPEC (cis + dx) + EPIC(cis + dx)	3 NED (NA)
Turin, It <sup>25</sup>	3	3	HIPEC (various)	3 NED (20-81)
Milan, It <sup>15</sup>	4	4	HIPEC (cis + dx)	4 NED (17-94)

Cis= cisplatin; dx= doxorubicin; mit= mitomycin-C; HIPEC= hyperthermic intraperitoneal chemotherapy; EPIC= early postoperative intraperitoneal chemotherapy; NED= no evidence of disease; AWD= alive with disease; NA= not available; \*= the patient died following this report.

## FIGURE LEGEND

Progression-free survival after 12 procedures of cytoreduction with hyperthermic intraperitoneal chemotherapy (HIPEC) (black line) and 14 debulking operations performed in 9 patients before combined treatment (red line).

Survival difference was statistical significant (two-tailed P-value <0.0001).

