

## **An Italian Multicentric Phase II Study on Peritonectomy and Intra Peritoneal Hyperthermic Perfusion (IPHP) to treat patients with Pseudomyxoma Peritonei**

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Pseudomyxoma peritonei (PMP) is a rare disease with a poor prognosis when not adequately treated. It is characterized by a complete redistribution of mucin within the peritoneal cavity. The aim of this multicentric study was to evaluate the survival, morbidity, toxicity and mortality of patients with PMP treated by cytoreductive surgery (CRS) with intraperitoneal hyperthermic perfusion (IPHP).

Seventy patients with PMP (31 males and 39 females) were enrolled onto a Phase II clinical trial. One patient was operated on twice because of disease recurrence. CRS was performed with peritonectomy procedures. The closed, opened and semi-closed abdomen techniques were employed for IPHP using cisplatin plus mitomycin-C for 60 minutes under hyperthermic conditions (42.5°C).

Sixty two (87%) patients were optimally cytoreduced. Five-year overall survival, progression-free survival and locoregional progression-free survival were 91%, 54% and 69%, respectively. Thirteen Grade III complications occurred in 10 (14%) patients and the most frequent one was gastrointestinal fistula/perforation (11%). There was one case (1.4%) of treatment-related mortality 21 days after treatment.

CRS associated with IPHP permitted complete tumour removal with an acceptable morbidity and mortality in patients with PMP. This study confirms the efficacy of the combined treatment on long-term survival and local disease control.

**Key Words:** Pseudomyxoma peritonei, Peritonectomy, Intraperitoneal hyperthermic perfusion

The current understanding of pseudomyxoma peritonei (PMP) is based on relatively small clinical case series. PMP is frequently a benign condition associated with appendiceal or ovarian mucinous tumours that have a protracted clinical course. The characteristic PMP dissemination within the peritoneal cavity was defined by Sugarbaker (1) as a complete redistribution phenomenon, indicating a complete and sequential invasion of the peritoneal cavity with large tumour volume localization at predetermined anatomical sites and minimal invasion at other sites. The modalities of

dissemination are strongly influenced by the histopathology of the primary tumour (2-4). Progression will eventually compromise gastrointestinal function due to bowel compression that may result in obstructive syndrome.

The traditional approach to PMP was based on repeated surgical debulking procedures often associated with intraperitoneal or systemic chemotherapy. The natural history of this disease has since been drastically modified by the introduction of a new surgical approach, proposed by Sugarbaker, defined as cytore-

ductive surgery (CRS) or peritonectomy procedure, which consists of the complete removal of the tumour. Surgery is followed by locoregional drug administration aimed at eliminating microscopic and/or minimal residual disease left in the abdominal cavity following surgical manipulations (3,4). This technique has been defined as intraperitoneal hyperthermic perfusion (IPHP). The rationale and the feasibility of this multidisciplinary approach have been described elsewhere (5,6). In the present paper we focused on the impact of CRS+IPHP on survival, morbidity, toxicity and mortality of patients with PMP.

## Patients and Methods

In accordance with study design, patients were considered suitable for recruitment after a complete evaluation including clinical examination, chest-abdominal-pelvic CT scan, ultrasonography and tumour markers (CEA, Ca125, CA19.9).

Eligibility criteria included: confirmed histological diagnosis of pseudomyxoma peritonei; age < 75 years; PS (WHO)  $\leq 2$ ; good cardiac, renal, hepatic and bone marrow functions; informed written consent to participate in the study.

The studied group included patients with PMP referred to 4 Italian Oncological centres: Istituto Nazionale per lo studio e la cura dei tumori (Milan), Polo Oncologico Istituto Regina Elena (Rome), Clinica Chirurgica Università di Padova (Padua), Ospedale S. Giovanni Battista, University of Turin, from September 1994 to September 2003. Seventy (31 males and 39 females) patients were enrolled onto the study. The mean age was 56 years (range 24-76). One patient was operated on twice because of disease recurrence. Seventeen (24%) patients had received systemic chemotherapy before the procedure.

**Cytoreductive surgery.** The techniques of cytoreductive surgery have been described previously (7). Briefly, the surgical procedure was carried out with one or more of the following steps, depending on disease extension: 1) greater omentectomy, right parietal peritonectomy  $\pm$  right colon resection; 2) pelvic peritonectomy  $\pm$  sigmoid colon resection  $\pm$  hysterectomy; 3) lesser omentectomy and dissection of the duodenal-hepatic ligament  $\pm$  antrectomy  $\pm$  colecystectomy; 4) right upper quadrant peritonectomy with Glissonian's capsule; 5) left upper quadrant peritonectomy  $\pm$  splenectomy; 6) other intestinal resection and/or abdominal mass resection. A ball-tip electro-surgical handpiece was used to dissect the tumour on peri-

toneal surfaces from normal tissue. The electro-surgery was used on pure cut at high voltage. The 2 mm ball-tip electrode was used for dissecting on visceral surfaces, including stomach, small bowel, and colon. The timing of intestinal anastomoses (after or before the cytoreduction) for patients who underwent bowel resections as well as the performance of diverting ostomies were decided at the each surgical staff discretion. Cytoreduction was classified into 3 levels according to the number of procedures performed: level I - 1- 2 procedures; level II - 3 or 4 procedures; level III - more than 5 procedures.

Peritoneal carcinomatosis was quantified according to Peritoneal Cancer Index (PCI) (8). Accordingly, the mean PCI was 24 (range: 2 to 36). Residual disease after surgery was classified according to Sugarbaker criteria (8): optimal cytoreduction=residual disease  $\leq 2.5$  mm; suboptimal cytoreduction=residual disease  $> 2.5$  mm.

**Intraperitoneal hyperthermic perfusion.** After CRS, the IPHP was performed according to the opened (9), semi-closed (10) and closed abdominal techniques (11). In order to perform continuous peritoneal temperature monitoring during IPHP, thermocouples were placed in the abdominal cavity. The pre-heated poly-saline perfusate containing cisplatin (CDDP: 25 mg/m<sup>2</sup>/l) plus mitomycin-C (MMC: 3.3 mg/m<sup>2</sup>/l) was instilled into the peritoneal cavity using a heart-lung pump at a mean flow of 600 ml/min for 60 minutes starting from the true hyperthermic phase (42.5°C). At the end of perfusion, the perfusate was rapidly drained and the abdomen closed after careful intra-cavitary inspection.

**Follow-up and statistical analysis.** In the postoperative period, patients were assisted in an Intensive Care Unit (ICU) for at least 5 days and assessed daily with laboratory and imaging exams. Long-term follow-up was carried out by physical examination, tumour marker monitoring, thoracic and abdominal CT scan every 6 months in the first 2 years and every 12 months, thereafter. Overall survival was calculated from the date of surgery to date of death or time of last follow-up; progression free survival was calculated from the date of surgery to date of disease progression, or date of death whichever occurred first; and local progression free survival was calculated from the date of surgery to date of local progression. Estimated survival curve distribution was calculated by the Kaplan-Meier method.

Evaluation of morbidity, toxicity and mortality.

Grading of complications was performed according to the following criteria: GI: no complications, GII:

minor complications, GIII: major complications (requiring reoperation or Intensive care unit admission or interventional radiology and GIV: in hospital mortality. Grading of toxicity was performed according to the WHO criteria. We considered only those unfavourable events occurring within the 28th day after the procedure.

## Results

Sixty two (87%), six (9%) and three (4%) cases were submitted to level III, II and I procedures respectively. Sixty two (87%) patients were optimally cytoreduced. Twenty six (37%), 24 (34%), 8 (11%) and 6 (8%) patients were submitted to 1, 2, 3 and 4 bowel anastomoses, respectively.

Thirteen Grade III complications were observed in 10 (14%) cases. They were as follow: 7 digestive fistula, 3 abdominal bleeding, 1 respiratory failure due to postoperative pneumonia, 1 sepsis and 1 abdominal incision breakdown. One (1.4%) patient presented an association of anastomotic fistula and abdominal bleeding evolving fatally in the 21st day post-intervention. Eight IPHP-related grade II toxicity occurred in 5 (7%) of the patients. They were as follow: 2 haematological, 2 renal 1 gastrointestinal and 3 fevers. No high-grade toxicity was observed.

Five-year overall survival (OS) was 91%. Five-year progression-free survival (PFS) was 54%, while 5-year local progression-free survival (LPFS) was 69% (Figures 1, 2 and 3). After a mean follow-up of 24 months (range: 0.3–72.1), 59 (83%) and 9 (13%) patients were disease-free (NED) and alive with disease (AWD), respectively. From the group which presented recurrent disease, 7/15 (47%) and 3/15 (20%) patients evolved with local and pleural progression, respectively.

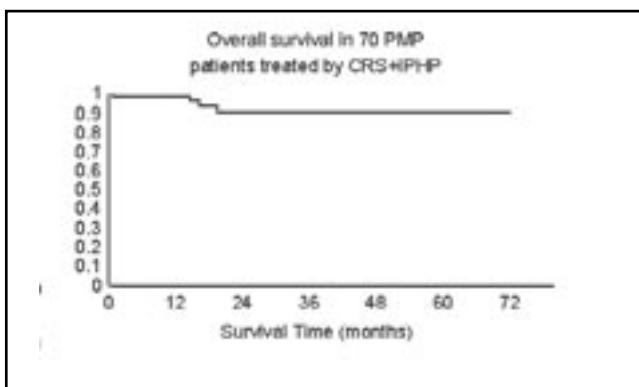


Figure 1

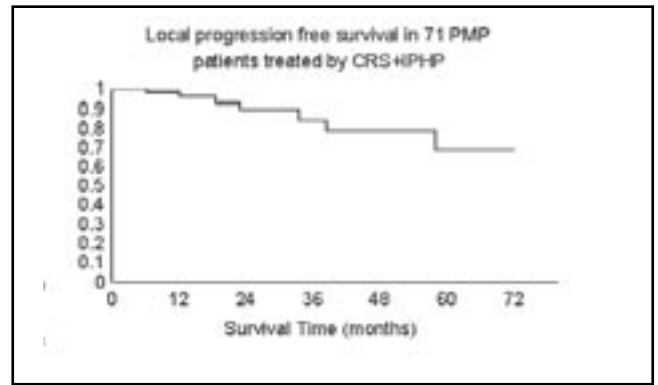


Figure 2

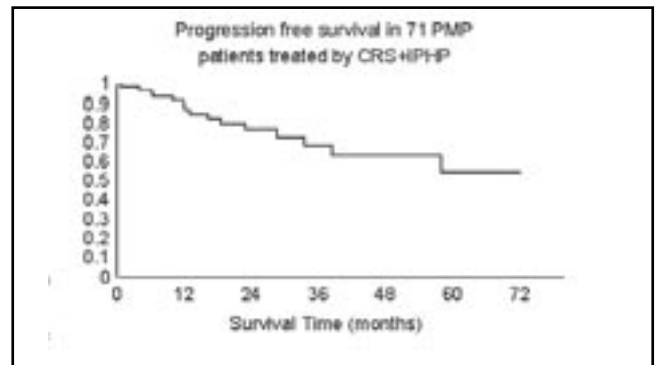


Figure 3

## Discussion

Although PMP is an indolent neoplastic disease, patients who do not receive definitive treatment have virtually no chance of survival. The primary tumour is usually localized in the appendix but occasionally originates in the ovary, gastrointestinal tract, gallbladder or pancreas. No controlled clinical studies have been conducted on PMP because of its rarity (1 case/million/year), and up until recently, treatment was directed at palliation and delaying the lethal outcome that seemed inevitable for these patients. Gough et al. conducted a study on 56 PMP patients treated with various modalities including repetitive debulking, intraperitoneal radioisotopes and/or chemotherapy and systemic chemotherapy, reported 1-, 5-, and 10-year survival rates of 98%, 53%, and 32%, respectively, with tumour progression in 76% of cases (12).

The advent of CRS followed by intraperitoneal chemotherapy seems to have impacted positively the prognosis of these patients. Similar promising results have been reported in other tumour types which evolve

with peritoneal carcinomatosis, according to prospective phase II (13,14) and phase III trials (15). This fact could result not only in an increased attraction by the scientific community to the locoregional therapy, but also in a widespread adoption of CRS+IPHP by insufficiently prepared centres. CRS+IPHP is a complex, time and labour consuming approach. It requires an intense effort by a highly skilled human resource, to guarantee its performance in a safely fashion, so that an initiation of a peritoneal surface program should be reserved only for a few a referral centres, specialized in oncology.

Our results in terms of morbimortality (grade III/IV complication rate = 14%, a grade III toxicity rate =1% and a mortality rate=1.4%), demonstrated the safety of the procedure, confirming the data emerged in our previous experiences (5,6). Moreover, these data are in alignment with those reported by other authors. In fact, Witkamp et al. published results on 46 patients treated with aggressive surgical cytoreduction and hyperthermic intraperitoneal chemotherapy with MMC followed by adjuvant 5-fluorouracil and leucovorin therapy on the basis of histological grading (16). They observed that 18 (39%) patients presented postoperative surgical complications, 4 patients evolved with treatment-related death and 22 patients presented bone marrow suppression due to MMC toxicity.

Equally promising results were observed in terms of survival rates in our study. The 5-year OS of 91% and local progression free survival of 69% accords with the literature data (16) and suggests that this new therapeutic approach is a potentially effective treatment for selected patients with PMP.

One of the limitations of the procedure is the non-local disease control. Pleural relapse, occurred in 3 cases, and could be resulted from an iatrogenic or contiguous dissemination rather than from distant hematogenous metastasis. The pleural spread of PMP is thought to be of negative prognostic value and is reported in up to 5.4% of cases (17).

Our findings suggest that PMP patients could benefit from CRS+IPHP in terms of survival and locoregional disease control. Although no randomized data are available to confirm its real efficacy, we believe the CRS+IPHP therapeutic approach should be considered the best option for patients with PMP.

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