

Peritonectomy and Intraperitoneal Hyperthermic Perfusion (IPHP): A Strategy That Has Confirmed its Efficacy in Patients with Pseudomyxoma Peritonei

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Background: Pseudomyxoma peritonei (PMP) is a rare disease with a poor prognosis 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).

Methods: Thirty-three patients with PMP (21 males and 12 females) were enrolled in a phase II clinical trial. One patient underwent surgery twice because of disease recurrence. CRS was performed with peritonectomy procedures. The closed abdomen technique was employed for IPHP with use of cisplatin (25 mg/m²/L) plus mitomycin-C (3.3 mg/m²/L) for 60 minutes under hyperthermic conditions (42.5°C).

Results: Thirty-one patients (92%) were optimally cytoreduced. Five-year overall survival, progression-free survival, and locoregional progression-free survival rates were 97%, 43%, and 59%, respectively. Grade II and grade III morbidity was observed in 5 patient (15%) and 6 patients (18%), respectively. There was one treatment-related death (3%), 21 days after treatment.

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

Key Words: Intraperitoneal hyperthermic perfusion—Peritonectomy—Pseudomyxoma peritonei.

The current understanding of pseudomyxoma peritonei (PMP) is based on relatively small clinical case series. Because of the rarity of this disease, its biological and clinical behavior, pathogenesis, and differential diagnosis have yet to be fully understood. PMP is frequently a benign condition associated with appendiceal or ovarian mucinous tumors that have a protracted clinical course. The characteristic PMP dissemination within

the peritoneal cavity was defined by Sugarbaker¹ as a complete redistribution phenomenon, indicating a complete and sequential invasion of the peritoneal cavity with large tumor 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 tumor.²

PMP has recently been classified into three diagnostic categories: disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and intermediate group (IG). Sugarbaker analyzed long-term follow-up data for a series of 109 patients with PMP to examine the prognostic utility of this pathological classification. Patients with DPAM had a 10-year survival of 68%, while patients with IG and PMCA had a significantly worse prognosis, with 10-year survival rates of 21% and 3%, respectively ($P = .0001$).³ It is important to highlight the low biological aggressiveness of the

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DPAM and IG forms in which mucinous tumor cells fail to implant and grow within vascular or lymphatic channels, resulting in an absence of lymph node or liver metastases. This indicates that benign PMP is an example of a metastatically inefficient tumor, unlike the very aggressive PMCA form, which results in peritoneal and/or visceral invasion and the presence of serous ascites.⁴

The first step of dissemination of PMP is the accumulation of tumor cells at the site of fluid reabsorption after exfoliation from the primary tumor. Large pores are present on the peritoneal surface of the omentum, and lymphatic lacunae are open at the underface of the diaphragm.^{1,2} Consequently, a large volume of tumor rapidly localizes at these anatomical sites within the abdominal cavity. Cells then settle by gravity within the independent portion of the abdomen, with large volume accumulation in the pelvis, in the right retrohepatic space, in the left abdominal gutter, and at the ligament of Treitz. However, irrespective of intra-abdominal disease distribution, the ileum remains tumor-free. Progression will eventually compromise gastrointestinal function because of 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 cytoreductive surgery (CRS) or a peritonectomy procedure, which consists of the complete removal of the tumor. Surgery is followed by locoregional drug administration aimed at eliminating microscopic and/or minimal residual disease left in the abdominal cavity following surgical manipulations.⁵ The added effects of hyperthermia, through the use of a special pump, increase local tissue drug concentration and consequently antitumor drug activity.⁶ This technique has been defined as intraperitoneal hyperthermic perfusion (IPHP).

The rationale of this multidisciplinary approach is based on several studies that have demonstrated an important impact of chemohyperthermia, when locally administered, in patients with peritoneal carcinomatosis treated by extensive CRS with minimal or no residual disease. The feasibility of this combined treatment according to histological subtype of PMP has been described elsewhere.⁷ Herein we focus on the impact of this combined approach on survival, morbidity, toxicity, and mortality among 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 computed tomography, ultrasonography, and tumor markers (with CEA, Ca125, CA19.9).

Eligibility criteria included the following: confirmed histological diagnosis of pseudomyxoma peritonei; age <75 years; World Health Organization (WHO) performance status ≤ 2 ; good cardiac, renal, hepatic, and bone marrow functions; and informed written consent to participate in the study.

From December 1996 to March 2003, 38 patients with PMP were referred to our institution. From this group, five patients (four with PMCA, one with DPAM) were not considered eligible for the study because of extremely aggressive disease involving extensive abdominal structure infiltration that precluded optimal cytoreduction. Thirty-three patients with PMP (21 males and 12 females) were enrolled in the phase II clinical trial. The mean age of patients was 53 years (range, 24–76 years); 18 (53%), 14 (41%), and 2 (6%) had a performance status (WHO) of 0, 1, and 2, respectively. All patients had mucinous ascites. One patient underwent surgery twice because of disease recurrence. Twenty-eight (85%) and 5 (15%) had DPAM and IG histological subtypes, respectively. Eighteen patients (53%) had previously undergone surgical debulking elsewhere. Ten patients (29%) had received systemic chemotherapy before the procedure.

Cytoreductive Surgery

Patients were put in a supine position, with gluteal folds advanced to the break in the operating table to allow full access to the perineum during the surgical procedure.

A three-way bladder catheter was inserted for cold lavage during hyperthermia in order to avoid mucosal damage. A large-bore silastic nasogastric tube was inserted. The abdomen was opened from xyphoid to pubis, and generous abdominal exposure was achieved through the use of a Thompson self-retaining retractor. A ball-tip electro-surgical handpiece was used on pure cut at high voltage as the standard tool to dissect tumor on peritoneal surfaces. CRS was carried out according to the peritonectomy procedures applied by Sugarbaker.⁸

The surgical procedure started with dissection from parietal peritoneum and abdominal wall, during which time the peritoneum remained closed. The peritoneum was then opened so that full access to the peritoneal cavity was possible.

CRS was carried out on the basis of disease extension by the following steps: (1) greater omentectomy, right parietal peritonectomy, right colon resection; (2) pelvic peritonectomy with sigmoid colon resection \pm hysterectomy; (3) antrectomy, colecystectomy, lesser omentectomy, and dissection of the duodenal-hepatic ligament; (4) right-upper-quadrant peritonectomy and Glissonian capsule resection; (5) left-upper-quadrant peritonectomy-splenectomy and left parietal peritonectomy; and (6) other intestinal resection and/or abdominal mass resection.

Intraperitoneal Hyperthermic Perfusion

After CRS, according to the closed abdomen technique, two inflow catheters were inserted, one in the right subphrenic cavity and one at deep pelvic level, and two outflow catheters were inserted, one in the left subphrenic cavity and one at superficial pelvic level. In order to perform continuous peritoneal temperature monitoring during IPHP, six thermocouples were placed in the abdominal cavity. After abdominal skin closure, the four catheters were connected to the extracorporeal circuit. The preheated polysaline perfusate (4–6 L) containing cisplatin (CDDP: 25 mg/m²/L) plus mitomycin-C (MMC: 3.3 mg/m²/L) was instilled into the peritoneal cavity with 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 was closed after careful intracavitary inspection.

Evaluation of Morbidity and Mortality

Treatment-related morbidity was evaluated according to the criteria outlined in Table 1.⁹ Analysis of IPHP-related systemic toxicity was performed according to WHO criteria.

Follow-Up and Statistical Considerations

In the postoperative period, patients were in an intensive care unit (ICU) for at least 5 days and were assessed daily with laboratory and imaging examinations. Long-term follow-up was carried out with physical examina-

tion, tumor-marker (CEA, Ca125, Ca 19–9) monitoring, and thoracic and abdominal computed tomography 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 (local relapse or distant metastasis) or date of death, whichever occurred first. Estimated survival curve distribution was calculated by the Kaplan-Meier method.

RESULTS

All the patients had mucinous ascites at laparotomy. After CRS, 31 cases (91%) were completely cytoreduced, while macroscopic residual disease (>2.5 mm) was present in three cases (9%). All but one patient underwent complete parietal peritonectomy, which included great and lesser omentectomy and Glissonian capsule removal. Surgical procedures associated with complete parietal peritonectomy are summarized in Table 2. Eight (24%), 11 (32%), 8 (24%), and 6 (18%) patients, respectively, were submitted to 1, 2, 3, and 4 bowel anastomoses. The mean duration of the surgical procedure, including IPHP, was 12.6 hours (range, 5–21).

Grade II and grade III morbidity was observed in 5 patients (15%) and 6 patients (18%), respectively. With regard to grade III treatment-related complications, 2 (6%) manifested anastomotic fistula (requiring relaparotomy), 1 (3%) had abdominal bleeding, and 1 (3%) had intestinal perforation. Concerning grade II complications, 2 patients had postoperative fistula (spontaneously resolved), 1 (3%) had biliary fistula, 1 (3%) had prolonged ileus, and 1 (3%) had pleural effusion. Finally, in one patient (3%), the association of anastomotic fistula and abdominal bleeding proved fatal at 21 days postintervention. IPHP (chemotherapy)-related systemic grade II toxicity was observed in three (9%) of the patients. No high-grade toxicity was observed.

TABLE 2. Surgical procedures associated with complete parietal peritonectomy

Surgical procedures	No.	%
Right colectomy	30	88
Sigmoidectomy	22	65
Gastrectomy	16	47
Total colectomy	2	6
Splenectomy	27	79
Cholecystectomy	26	76
Hysterectomy and bilateral salpingo-oophorectomy	6	50 (female group)

TABLE 1. Criteria for morbidity and mortality grading (9)

	Complications
Grade I	No complications
Grade II	Minor complications
Grade III	Major complications (requiring re-operation or ICU admission or interventional radiology)
Grade IV	In-hospital mortality

ICU, intensive care unit.

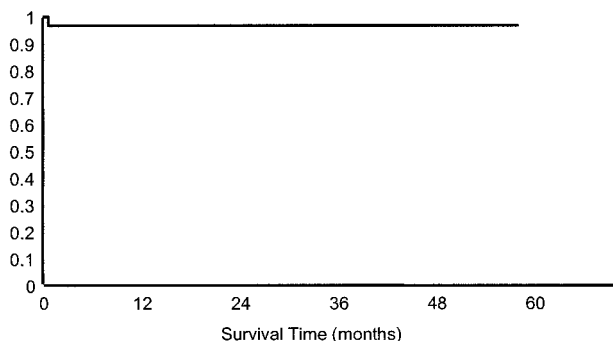


FIG. 1. Overall survival in 33 PMP patients treated with CRS+IPHP.

Five-year overall survival (OS) was 96% (Fig. 1). Five-year progression-free survival (PFS) was 43% (median, 57.9 months) (Fig. 2), while 5-year local progression-free survival was 59% (Fig. 3). After a mean follow-up of 28.6 months (range, 0.4–72 months), 25 (74%) and 8 (23%) were disease-free (NED) and alive with disease (AWD), respectively. In the group with recurrent disease, 6 (18%) and 2 (6%) manifested local and pleural progression, respectively.

DISCUSSION

PMP is an important example of low-grade tumor distribution associated with excess peritoneal fluid. Although PMP is an indolent neoplastic disease, patients who do not receive definitive treatment have virtually no chance of survival. The primary tumor 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 delay-

ing the lethal outcome that seemed inevitable for these patients.

The introduction of CRS, followed by intraperitoneal chemotherapy, has resulted in a favorable impact on the survival of these patients. CRS is a complex approach requiring peritonectomy procedures and is not free of postoperative complications. This technique is also employed in the treatment of other malignancies, such as gastric, ovarian, and colon cancer and peritoneal mesothelioma, in which peritoneal dissemination remains an important cause of surgical treatment failure.^{10,11}

The rationale for tumor volume reduction is the enhancement of neoplastic chemosensitivity due to the recruitment of tumor cells in the growth phase¹² and the possibility of clones of phenotypically resistant cells being removed by surgical resection. The main parameter used to establish the surgical extension of the procedure in the present study was the level of intra-abdominal disease dissemination. The aim of surgery was complete disease removal, with maximum preservation of organ function. As can be seen from the data presented in Table 2, all patients received extensive surgical treatment, which confirmed the advanced disease stage at the time of study enrollment. It is important to underline that the role of CRS is to radically remove the PMP implants, while that of IPHP is to sterilize microscopic residual disease.

As with any locoregional antineoplastic therapy, the objective of intraperitoneal drug administration is to expose the tumor to a high drug concentration, simultaneously reducing the systemic side effects. This requires a drug with a high molecular weight (with slow peritoneal absorption rate) and rapid systemic clearance. Pharmacokinetic studies have demonstrated an optimal ratio between the areas under the curve of mitomycin C, adriamycin, and cisplatin administered intraperitoneally, in comparison with those obtained with systemic admin-

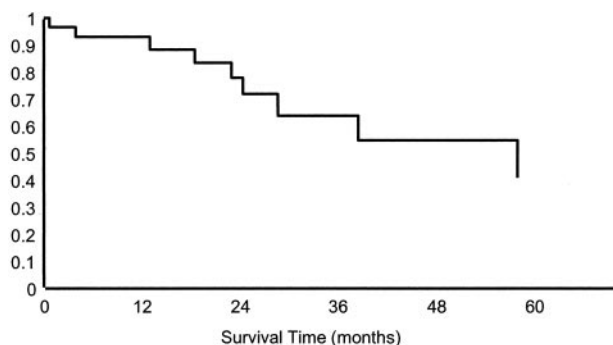


FIG. 2. Progression free survival in 34 PMP cases treated with CRS+IPHP.

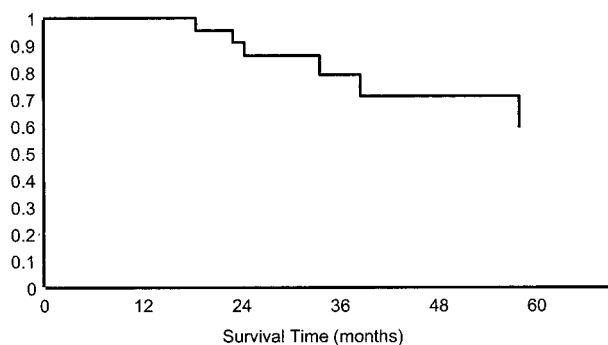


FIG. 3. Local progression free survival in 34 PMP cases treated with CRS+IPHP.

istration.¹³ Moreover, intraperitoneal drug instillation with a large amount of perfusate (at least 4000 mL) permits a kind of mechanical clearance that potentially removes small tumor residue left in the abdominal cavity.

The major limiting factor concerning the intraperitoneal approach is the possibility of drug resistance and the accessibility of the drug to the neoplastic cells. It has been demonstrated that at a depth of more than 3 mm, drug concentration decreases rapidly within the tumor,¹⁴ and one way of overcoming these problems is the association of hyperthermia after an accurate surgical cytoreduction.

The employment of heat, as a fundamental component of this new therapeutic methodology, is justified by its own cancericidal property and chemosensitivity-modulating capacity. The biophysical effects of hyperthermia are not completely understood but probably include membrane protein denaturation,¹⁵ increased vascular permeability,^{16,17} alterations in multimolecular complexes such as the insulin receptor¹⁸ and in the cytoskeleton,¹⁶ and changes in enzyme complexes for DNA synthesis and repair.¹⁹ Moreover, the architecture of the vasculature in solid tumors is chaotic, resulting in regions with low pH, hypoxia, and low glucose level.²⁰

This susceptible microenvironment renders solid tumors more sensitive to hyperthermia. In addition, at 40°C to 42°C, the neoplastic cell becomes more chemosensitive because of an increased intracellular drug concentration, an increase in its activation process, especially for alkylating agents, and an alteration in the DNA repair process.^{21,22} Heating cells to 43°C during CDDP exposure has been found to increase drug accumulation in CDDP-resistant cell lines, with little effect on CDDP-sensitive cell lines. Furthermore, DNA adduct formation has been found to be significantly increased in CDDP-resistant and -sensitive lines. Ongoing platinum-DNA adduct formation after the end of CDDP exposure is also enhanced and/or adduct removal is decreased in heated cells, resulting in considerably more DNA damage.²³

Of the 34 patients with PMP included in this study, 31 (91%) underwent complete CRS. There were no cases of

PMCA, whose histological subtype is characterized by peritoneal lesions composed of more abundant mucinous epithelium with the architectural and cytological features of carcinoma, with or without associated primary mucinous adenocarcinoma. Its histological architecture is a factor that indicates tumor aggressivity and features of dissemination, often resulting in abdominal structures infiltration.

All patients included in this phase II clinical study had either DPAM or IG subtype, which are characterized by peritoneal lesions composed of abundant extracellular mucin containing scant simple to focally proliferative mucinous epithelium with little cytological atypia or mitotic activity, with or without an associated appendiceal mucinous adenoma.⁴ The treatment strategy applied in this study demonstrated its efficacy on locoregional disease control and long-term survival, with acceptable morbidity and mortality.

Pleural relapse, observed in two cases, 23 and 30 months after the procedure, represents disease progression due to a possible iatrogenic or contiguous dissemination rather than a distant hematogenic metastasis. The pleural spread of PMP is thought to be of negative prognostic value and is reported in up to 5.4% of cases.²⁴

The 97% 5-year overall survival we observed suggests that this new therapeutic approach is a potentially effective treatment for selected patients with PMP. Conversely, Gough et al., who conducted a study on 56 PMP patients treated with various modalities such as 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 tumor progression in 76% of cases.²⁵

Our findings are in agreement with literature data regarding the impact of CRS + IPHP on survival and treatment-related morbidity and mortality among PMP patients (Table 3). Recently, Witkamp et al.²⁶ published results for 46 patients treated with aggressive surgical cytoreduction and hyperthermic intraperitoneal chemotherapy with mitomycin C. Surgical cytoreduction was optimal in 40 patients. Patients also received adjuvant 5-fluorouracil and leucovorin therapy on the basis of

TABLE 3. Literature data concerning results of locoregional treatment of PMP patients

Author/year	No.	Drug schedule	Morbidity (%)	Mortality (%)	Toxicity (%)	Survival (%)
Witkamp, 2001 [26]	46	IPHP MMC Postoperative 5FU + leucovorin	39	9	48	3-yr (81)
Sugarbaker, 2001 [27]	385	IPHP MMC Postoperative 5FU + leucovorin	27	2.7		5-yr (86)

PMP, Pseudomyxoma peritonei; IPHP, intraperitoneal hyperthermic perfusion; MMC, mitomycin-C.

histological grading. Eighteen patients (39%) had postoperative surgical complications, and there were four treatment-related deaths. Twenty-two patients had bone marrow suppression due to mitomycin C toxicity. Three-year actuarial survival was 81%.

Sugarbaker²⁷ reported on 385 patients with PMP treated with CRS + IPHP and/or perioperative intraperitoneal chemotherapy with mitomycin C. Patients with PMCA or IG histological subtype also received intraperitoneal 5-fluorouracil for 5 consecutive days. Completely cytoreduced DPAM patients had a 5-year survival of 86%, while that of IG patients was 50%. Five- and 10-year survival of patients who underwent incomplete CRS was 20% and 0%, respectively.

CONCLUSIONS

Our findings suggest that PMP patients could benefit from CRS + IPHP in terms of survival and locoregional disease control. Serial debulking is no longer indicated for these patients. Although conducting a randomized trial to confirm its real efficacy is virtually impossible because of the low prevalence of the disease, we believe the CRS + IPHP therapeutic approach should be considered the best option for patients with PMP.

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