

Management of Pseudomyxoma Peritonei by Cytoreduction+HIPEC (Hyperthermic Intraperitoneal Chemotherapy): Results Analysis of a Twelve-year Experience

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Abstract. *Background:* Pseudomyxoma peritonei (PMP) is a rare peritoneal carcinomatosis, characterized by a slowly progressive disease process with a large amount of mucus containing occasional epithelial cells. PMP is histologically classified into disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA) and an intermediate or discordant feature group (ID). Recent studies have shown that most cases of PMP originate from ruptured appendiceal tumors with progressive dissemination in the peritoneal cavity of mucin-producing epithelial cells. Encouraging results in the treatment of PMP have been reported by surgical cytoreduction of the primitive cancer, peritonectomy (stripping of implants on the peritoneal surface) and intraperitoneal hyperthermic chemoperfusion (HIPEC). In recent trials, this combined approach has been proposed as the standard treatment for PMP. *Patients and Methods:* In this study, the results of twelve years single-institution experience on 60 consecutive patients affected by PMP, treated by cytoreductive surgery and the original semi-closed HIPEC technique are reported with special reference to overall survival (OS) and progression-free survival (PFS). *Results:* The postoperative morbidity rate was 45% (27 patients); surgical morbidity was observed in 19 patients and medical complications in 9 cases. No postoperative deaths were observed. The survival data, 53 patients were analyzed (the last 7 were considered only for the complications rate, postoperative mortality and cancer features, not for OS or PFS because they were too recent for evaluation).

At the final follow-up of the 53 patients, five and ten years OS were respectively 94% and 84.6%. DFS was 80% and 70% at five and ten years respectively. The follow-up data indicated that the survival probability may be good in patients with histological type appendicular adenoma optimally cytoreduced (CCR-0). Interestingly if preoperative chemotherapy was performed represented a negative prognostic factor with statistically significant impact both on OS and DFS. Conclusion: As in other similar studies, cytoreductive surgery plus HIPEC, even when combined with an aggressive surgical procedure, is associated with an acceptable risk of postoperative complications and mortality. This combined treatment results in DFS and OS rates that are not described in the literature for surgery associated with systemic chemotherapy and, in our opinion, may be considered the gold standard treatment for this rare tumor.

Pseudomyxoma peritonei (PMP) is a rare peritoneal carcinomatosis, characterized by a slowly progressive disease process with a large amount of mucus containing occasional epithelial cells. According to Ronnet (1), PMP was histologically classified into disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA) and an intermediate or discordant feature group (ID). Recent studies have shown that most cases of PMP originate from ruptured appendiceal tumors with progressive dissemination in the peritoneal cavity of mucin-producing epithelial cells. Lymph-nodal or hematogenous metastases are rare in PMP and such evidence is also related to a poor prognosis (1-5).

PMP is generally considered a lethal disease, with progressive accumulation of mucus that usually leads the patient to bowel obstruction (6-12). While systemic chemotherapy has little impact on peritoneal mucus, some centres have reported encouraging results by surgical cytoreduction of the primitive cancer, peritonectomy

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(stripping of implants on the peritoneal surface) and intraperitoneal hyperthermic chemoperfusion (HIPEC) (11-12). The rationale of HIPEC is based on an elevated and persistent drug concentration in the peritoneal cavity associated with limited leakage of drugs to the systemic circulation due to the presence of plasma-peritoneal barrier. At least, hyperthermia increases drug penetration into tumoral tissues. Many studies have reported an impact on overall survival (OS) and disease-free survival (DFS) in patients affected by carcinomatosis, this is particularly true for PMP and, in recent trials, this combined approach has been proposed as the standard treatment for PMP (1-16) and is becoming a widely accepted procedure for the treatment of this rare condition.

In this study, the twelve-year single-institution experience of this treatment on 60 consecutive patients affected by PMP, treated with cytoreductive surgery and the semi-closed HIPEC technique, is reported, with special reference to OS and PFS.

Patients and Methods

In our Institution, 411 operations for peritoneal carcinomatosis (from ovarian and colonic cancer, peritoneal mesothelioma and PMP) were performed; in 232 cases, surgical cytoreduction+HIPEC had been possible. Ninety two patients affected by PMP were operated on: in 60 cases cytoreduction+HIPEC, in 29 cases diagnostic laparotomies/laparoscopies and/or cytoreduction, in 3 cases cytoreduction+EPIC (early postoperative intraperitoneal chemotherapy) were performed. For the present study, the 60 patients affected by PMP (25 male and 35 female, mean age 58 years, range 32-72) who had undergone cytoreduction+HIPEC between October 1996 and October 2008, were considered.

The preoperative evaluation always included thoracic and abdominal CT scan to stage the peritoneal disease and exclude distant metastases; upper digestive endoscopy and colonoscopy generally completed the tumor staging. A careful preoperative evaluation of the patient's general condition was always performed and included complete blood tests, electrocardiogram, cardiac ultrasound and spirometry. The presence of hepatic or extra-abdominal metastases, massive ileum involvement and age over 72 years were generally considered contraindications to the treatment (13-16). Informed consent was obtained from all the patients (15).

Just after laparotomy, complete intraoperative staging of the peritoneal disease was performed using the peritoneal cancer index (PCI), a score that varies from 0 to 39, where 0 means absence of disease (16): the mean PCI was 22.

Surgical technique. the peritonectomy procedure was classified and performed according to the Sugarbaker criteria (16): 1) central peritonectomy; 2) left upper quadrant peritonectomy; 3) right upper quadrant peritonectomy; 4) lesser omentum peritonectomy; 5) pelvic peritonectomy with *en bloc* removal of pelvic peritoneum, sigmoid colon, rectum, uterus and salpingo-oophorectomy; 6) peritonectomy of lateral abdominal wall. Implants on visceral serosa were removed by electrosurgical local dissection, the peritonectomies were variously combined with resections of the tumor-involved viscera (*e.g.* gastrectomy or colectomy).

The completeness of cytoreduction (CCR) (16) was also classified according to the Sugarbaker criteria as: CCR-0 (no residual tumor) in 42 cases; CCR-1 (no residual nodule greater than 2.5 mm in diameter) in 18 cases; CCR-2 (no residual nodules greater than 25 mm) and CCR-3 (residual nodules greater than 25 mm) in no cases.

HIPEC was performed according to the original "semi-closed" abdomen technique (17): 5 drain tubes were placed into the abdominal cavity, the two inflow ones are Y-shaped and present multiple openings. Backhaus forceps are used to close the cranial and caudal portion of the abdominal wound. The skin is then suspended on a self-retaining retractor, placed approximately at 15 cm from the abdomen, by plastic self-blocking strings. This kind of placement creates the virtual cavity needed to perform HIPEC. The central portion of the wound is also suspended on the retractor and covered with a laparoscopic device with sterildrape, with a hole in the middle. The drain tubes are connected to a perfusion system formed by two pumps and a heat exchanger to heat the perfusion liquid. The pumps (inflow and outflow), are connected through a reservoir, so a continuous circulation of the perfusate at a speed of approximately 1 l/min is achieved. The pumps are controlled by a computed system that allows checking of the flow rate and the temperature of the heat exchanger. Three intraperitoneal temperatures, the inflow, outflow, and the patient oesophageal temperature are checked by probes. The volume of the circulating perfusate (solution for peritoneal dialysis) is calculated according to the patient's body surface. During perfusion, the surgeon mixes the perfusate by hand through the hole in the sterildrape. When the ideal intraperitoneal temperature is reached, the drugs are added to the circuit and HIPEC is performed for 60 min.

Fifty-eight patients were treated with a protocol based on the administration of cisplatin 100 mg/sm plus C-mitomycin 16 mg/sm, at a temperature of 41.5°C. Two patients were treated with C-mitomycin 35 mg/sm for 60 minutes at a temperature of 40.5°C, according to the Netherlands protocol (12), because of serious side effects from preoperative systemic chemotherapy with platinum. Anastomoses were always performed at the end of HIPEC. The mean duration of surgery (including HIPEC) was 12 hours (range 8-16). At the end of the operation, the patients were admitted to the intensive care unit and then returned to the surgical department when cardiovascular and pulmonary functions became stable. The primitive neoplasia was an appendicular adenocarcinoma in 43 patients (71.6%) and an appendicular adenoma in 17 patients (28.3%). Twenty-two patients (51.1%) with histological diagnosis of appendicular adenocarcinoma had been treated with systemic chemotherapy before the HIPEC operation. Because of the massive involvement of viscera and peritoneum, in some selected patients the treatment was performed in steps. In fact three patients were treated in 2 steps, and one patient in 3 steps. In these cases, the upper abdomen cytoreduction was performed in the first step, then the patient was submitted to systemic chemotherapy for 2 or 3 months. The second step consisted of lower abdomen cytoreduction and peritoneal perfusion of the entire peritoneal cavity.

Statistics. OS was dated from the day of surgery to the time of death due to any cause and PFS was dated from the day of the surgery to the time of postoperative disease progression. The survival curves for both OS and PFS were calculated according to the Kaplan-Meier method. The log-rank test was used to assess the significance of the comparison between the survival curves. The Statistical Package for the Social Sciences software (version 11.0) (SPSS, Chicago, IL, USA) was used for the statistical analyses: *p*-value<0.05 was considered significant.

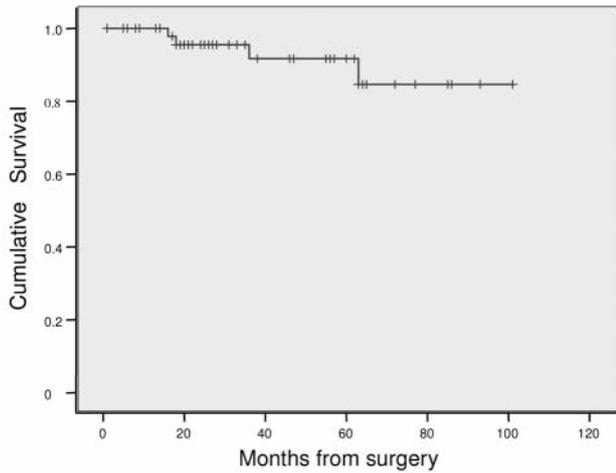


Figure 1. Overall survival, 53 cases of PMP (Kaplan-Meyer).

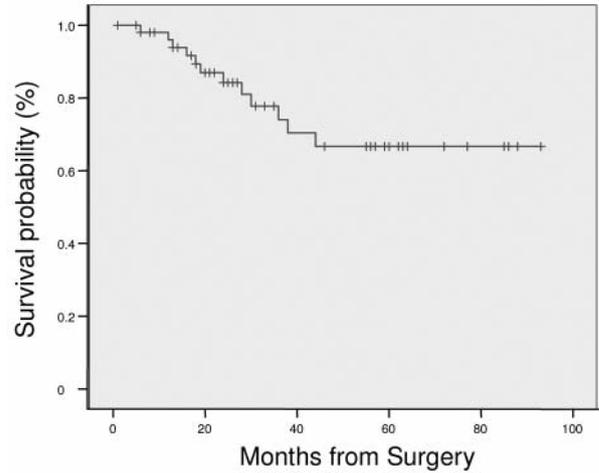


Figure 2. Disease-free survival (DFS), 53 cases of PMP.

Results

Postoperative complications occurring during the hospital stay or within 30 days of surgery were considered for morbidity rate. In 27 patients (45%) postoperative complications were observed: including associated complications, surgical morbidity was observed in 19 patients (6 intestinal or gastric fistulas, 2 urinary tract perforation, 2 abdominal abscesses, 4 wound infections, 1 prolonged ileus, 2 postoperative hemorrhage, 1 case of abdominal wall dehiscence, 1 bleeding from gastric ulcer) and medical complications in 9 cases (1 arrhythmia, 3 grade-2 hematological toxicities, 1 acute renal failure, 1 cutaneous rash, 2 cases of sepsis, 1 deep intravenous thrombosis). Nine patients were re-operated on, 2 patients had stentig of the urinary tract. One patient with an abdominal abscess was submitted to ultrasound-guided drainage and 1 bleeding from gastric ulcer was treated by endoscopic hemostasis; all the other complications were successfully treated by medical therapy. No postoperative deaths were observed.

Survival data. The survival data of 53 patients were analyzed (the last 7 were considered only for the complications rate, postoperative mortality and cancer features, not for OS or PFS because they were too recent for evaluation). At the final follow-up of the 53 patients, five and ten years OS were respectively 94% and 84.6% (Figure 1). DFS was 80% and 70% at five and ten years respectively (Figure 2).

OS according to the PCI, completeness of cytoreduction (CCR-score), histological type and preoperative chemotherapy (done *versus* not done) are shown in Figures 3-6. At the time of the analysis 48 patients were alive without disease. Two patients had died of systemic disease

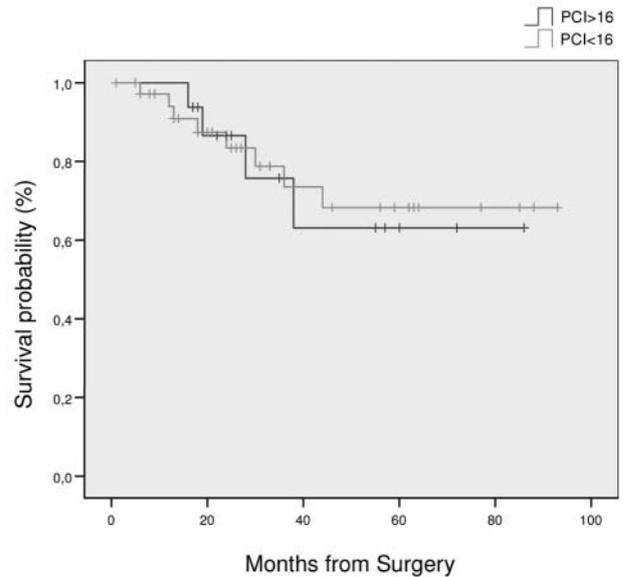


Figure 3. Overall survival (OS) according to PCI status, 53 cases of PMP (*p.n.s.*). PCI: peritoneal carcinomatosis index, *n.s.*: non significant.

progression respectively at 16 and 63 months after the operation; 5 patients were alive with disease with intraperitoneal relapse and not undergoing further surgery, with follow-up respectively of 57, 28, 24, 19 and 10 months. Three patients had intraperitoneal relapse and were treated again with cytoreduction: one of those who also received again HIPEC is alive without disease 17 months after the second surgical procedure, the other two patients were treated only with local tumor resection and they are alive without disease after 24 months of follow-up.

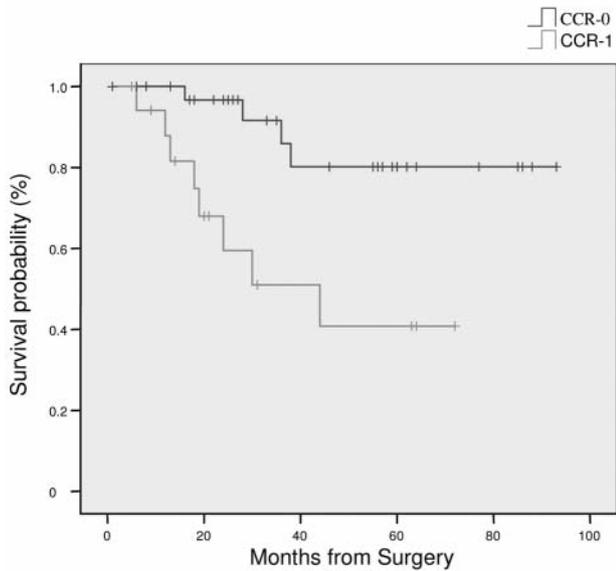


Figure 4. Overall survival (OS) according to the completeness of the surgical cytoreduction (CCR-score), 53 cases of PMP ($p < 0.003$).

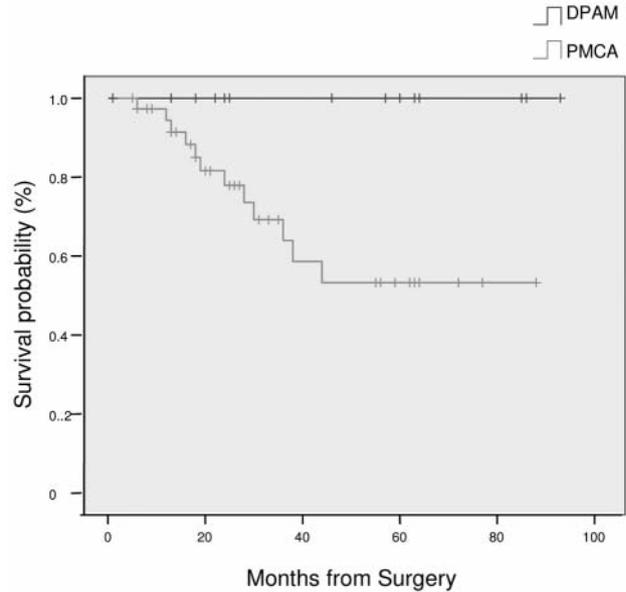


Figure 5. Overall survival (OS) according to the histological tumor type, 53 cases of PMP ($p < 0.014$). DPAM: disseminated peritoneal adenomucinosis. PMCA: peritoneal mucinous carcinomatosis.

Follow-up data from our experience on PMP indicate that survival probability may be good in patients with histological type appendicular adenoma and optimally citoreduced (CC0), while the extension of disease (PCI index) has no influence on patient's outcome.

An interesting relief is related to the preoperative chemotherapy: if performed represents a negative prognostic factor with statistically significant impact both on OS and DFI.

Discussion

In agreement with several studies, the present results with HIPEC indicated that, even when combined with an aggressive surgical procedure, this technique was associated with an acceptable risk of postoperative complications and mortality (18-24). The incidence of postoperative complications was similar to that of other reports (25-29). Major morbidity occurred in 45% of patients similar to other recent experiences (27-29-30) but no postoperative deaths were observed.

Neoplastic disease in an advanced stage, immunodeficiency in patients previously subjected to chemotherapy and the extended surgical procedure associated with HIPEC were all factors that probably contributed to the occurrence of septic complications. Intestinal fistulas have been reported to be an important cause of morbidity and mortality in patients subjected to HIPEC (31-34). We always performed anastomosis following HIPEC, but the three cases of intestinal fistula were due to intestinal perforation not involving the

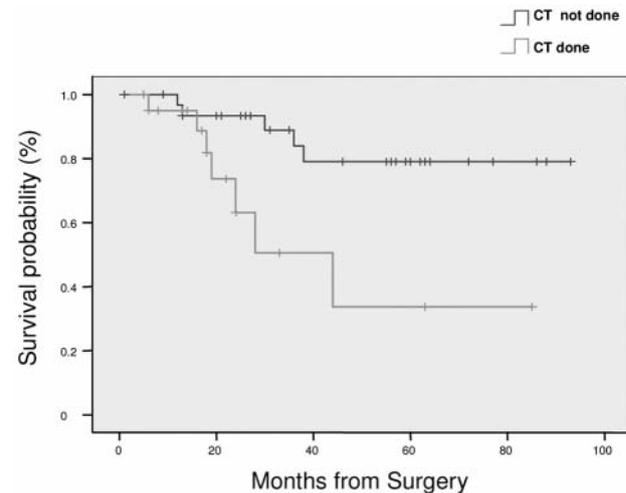


Figure 6. Overall survival (OS) according to the previous systemic chemotherapy (CT), 53 cases of PMP ($p < 0.034$).

anastomosis. All these patients recovered favorably, and there was no mortality.

The largest series of PMP undergoing combined treatment was reported by Sugarbaker (34) and CCR and Ronnet's criteria were the most important factors correlated with survival and morbidity (35).

The CCR-score, in the present study, was strictly correlated to the DFS with an evident result between CCR-0 and CCR-1 patients ($p < 0.003$) (Figure 4).

The follow-up data indicated that the long-term survival may be good in patients with the histological appendicular adenoma type optimally cytoreduced CCR-0 (DPAM *versus* PMCA $p < 0.014$, Figure 5), while the extension of disease (PCI index) had no influence on the patient's outcome. Furthermore in the present series the adverse prognostic value of preoperative systemic chemotherapy with a statistically significant impact both on OS and DFS, was a unexpected finding that may not be easy to explain: the patients that received such chemotherapy had a poor prognosis in relation to those that did not ($p < 0.034$) (Figure 6). Similar evidence was observed in other studies (12) leading to the hypothesis that mucinous appendiceal tumors, after chemotherapy, change to a more invasive type. It is quite possible that differences in chemotherapy penetration of mucinous and solid tumors may result in the persistence and progression of the more solid components of a non-uniform tumor tissue. It is possible that this process selects resistant and more aggressive tumor cell clones, but the explanation for the poor results of the treatment of these patients requires further investigation.

Conclusion

An aggressive approach can improve survival in patients with PMP: even if HIPEC combined with cytoreductive surgery involves a high risk of morbidity, postoperative complications can be resolved favorably in most cases with appropriate surgical technique and adequate postoperative care, to minimize mortality. CCR, preoperative chemotherapy and histological type PCMA significantly influence the prognosis of these patients.

The need for an integrated approach with this rare neoplasm, to identify the biological aspect of the PMP that may be influencing the prognosis and the evolution of the disease is suggested. The correlation between expression of EGFR, MUC 7, MUC 20 and disease prognosis is currently under investigation.

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