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ORIGINAL ARTICLE

# Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in pseudomyxoma peritonei of appendiceal origin: result of a single centre study

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**Abstract**
Pseudomyxoma peritonei (PMP) is a rare condition characterized by the intraperitoneal accumulation of mucus derived mostly by appendiceal mucinous neoplasm. Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) can offer a favourable overall survival. In this study, we report a single-institute outcomes following CRS and HIPEC in patients with this condition. This is a review of prospectively collected data from 32 patients (11 men and 21 women) affected by PMP of appendiceal origin who underwent CRS and HIPEC from 2008 to 2016 in our Surgical Unit of General and Esophagogastric Surgery. The median age of the patients was 53 years (range 25—77 years). After CRS, all patients underwent HIPEC (mytomicin C 3.3 mg/m$^2$/L and cisplatin 25 mg/m$^2$/L at 41 °C for 60 min) with closed abdomen technique. The median (range) follow-up time for surviving patients was 43 (18–119) months. The median peritoneal cancer index (PCI) was 17. Complete cytoreductive surgery (CC0) was achieved in in 22 patients (69%). The majority of patients (88%) had grade I–II complications, 3 (9%) had grade III complications, and 1 (3%) patient had a grade IV complication. There were no perioperative mortalities. The median hospital stay was 9.5 (range 9–24) days. One year and 5-year overall survival (OS) were 90% and 58%, respectively. Regardless of histotype, disease-free survival was 95% at 1 year and 46% at 5 years. CRS in combination with HIPEC is a feasible treatment strategy and can achieve a satisfactory outcome in patients with PMP of appendiceal origin.

**Keywords** Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy · HIPEC · Appendiceal neoplasms · Pseudomyxoma peritonei · PMP

## Introduction

Pseudomyxoma peritonei (PMP) is a rare condition characterized by progressive accumulation of mucinous ascites and mucinous implants throughout the peritoneum, derived mostly by appendiceal mucinous neoplasm. The incidence of this neoplasia is about 1–2 cases per million of inhabitants, more frequently in women over 40 years old [1]. Evidences support the theory that most of this condition originates from an appendiceal neoplasm that spreads through the abdominal cavity to the peritoneal surface of the organs filling the abdomen with mucinous ascitis. In 10% of cases it can arise from an intra-abdominal extra-appendicular neoplasm of the ovary, colon, small bowel, and urachus. Usually, the disease is casually discovered after appendectomy for misdiagnosed acute appendicitis, due to rupture of mucocele and inflammation; in more advanced disease the most common sign in both men and women is a gradually increasing abdominal girth; in women it can be discovered during a gynaecological examination and mistaken for an ovarian mass [2]. Appendiceal neoplasms frequently lack malignant behaviour such as lymphatic spreading, hematogenous metastases or infiltrative invasion. One of the classifications of PMP was proposed by Ronnett et al. in the early 90′s. It divided the pathology into two diagnostic categories: disseminated peritoneal adenomucinosis (DPAM) and peritoneal mucinous carcinomatosis (PMCA). DPAM is characterized by peritoneal lesions composed by abundant

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extracellular mucin and few cells with little cytologic atypia or mythosis with associated appendiceal adenoma. PMCA has more malignant behaviour and has more abundant mucinous epithelium with architectural and cytologic features of carcinoma [3].

The treatment of PMP has been described in the 1990s by Sugarbaker et al. and consists in macroscopic removal of the peritoneal disease (cytoreductive surgery—CRS) and intraperitoneal perfusion of chaemotherapic drugs at high temperatures (hyperthermic intraperitoneal chemotherapy—HIPEC). Nowadays, CRS plus HIPEC have been widely accepted as the standard treatment of PMP. In fact, the aim of the cytoreduction is to leave no visible disease (completeness of cytoreduction CC-0) or at least implants not greater than 2.5 mm in size (CC-1) because intraperitoneal chemotherapy is not effective in eradicating tumour implants larger than 2.5 mm [4]. This may require also visceral resection, to remove all tumour nodules. Once a complete cytoreduction is achieved, chaemoperfusion can start: the infusion of the chaemotherapic drugs may differ according to the histology of the primitive tumour, but is also based on decisions made by single institutions: there is in fact still no consensus as to which drugs are the most effective when used for HIPEC. The chaemotherapics are usually diluted in saline solution and infused at around 40 °C. The perfusion time usually lasts from one hour to 90 min. There are two different approaches for the delivery of the chemotherapeutic agent: the open- and closed-abdomen technique, each of which has different pros and cons; the choice between them usually depends on the surgeon [5].

Our endpoints were to determine the overall and disease-free survival after CRS and HIPEC in patients with pseudomyxoma peritonei of appendiceal origin. We also wanted to assess post-operative morbidity and mortality.

## Materials and methods

### Patients

We collected prospective data from 32 patients from 2008 to 2016 in the Unit of General and Esophagogastric Surgery of the Borgo Trento Hospital in Verona, Italy. All patients underwent CT and/or PET scan for preoperative staging and were evaluated by a multi-disciplinary team composed by our Surgeons, Oncologists, Radiologists and Radiotherapists. Before surgery, the patients were also evaluated by Nephrologists and underwent proper hydration and changes in the usual personal therapies, to prevent kidney injuries due to chemohyperthermia. All patients had a diagnosis of PMP and had been selected based on good general health conditions and peritoneal implant localization limited to the abdominal cavity, without evidence of liver metastases. Some patients underwent surgery as first treatment after diagnosis (front line), others had already undergone diagnostic or non-radical surgery (second look). The median age of the patients was 53 years (range between 25 and 77 years); we enrolled 11 men (34%) and 21 women (66%) (Table 1).

Institutional ethical approval was received for the study, and all patients were subject to informed consent.

### Surgery and HIPEC

At the time of xifo-pubic laparotomy, the extent of peritoneal seeding was calculated using the peritoneal carcinomatosis index (PCI). All patients underwent cytoreduction of visible lesions; the target was reaching a complete cytoreduction as described by Jacquet and Sugarbaker [6]. After the demolitive time and the reconstitution of eventual intestinal anastomoses and ostomy, we administered Mytomicin C 3.3 mg/m$^2$/L and Cisplatin 25 mg/m$^2$/L at 41 °C for 60 min with closed abdomen technique. We applied four drainages, two for the input and two for the output of chemotherapic agents diluted in saline solution.

### Follow up

After treatment, patients underwent CT scans and measurement of CEA, CA19.9 and CA 125 at 3–6–12 months and then every year after surgery. The median (range) follow-up time for surviving patients was 43 (18–119) months. Three patients were lost to follow-up.

### Statistical analysis

The statistical analysis was carried out with software STATA 13; statistical significance was defined as $p < 0.05$. The survival curves were obtained using Kaplan–Meier method and compared with log-rank test to evaluate the significance. The differences between the two groups (DPAM and PMCA) were then calculated with the Wilcoxon–Mann–Whitney test.

**Table 1** Characteristics of patients

| Variable | No. of patients (%) |
|---|---|
| Male | 11 (34) |
| Female | 21 (66) |
| Median age (range) | 53 (25–77) years |
| Median BMI (range) | 23 (17–30) kg/m$^2$ |
| NACHT | 7 (22) |

**Table 2** Characteristics of surgery

| Variable | No. of patients (%) |
|---|---|
| HIPEC | |
| Front line | 21 (65) |
| Second look | 6 (19) |
| Loco-regional relapse | 5 (16) |
| CRS + HIPEC median duration (range) | 540 (240–900) min |
| Median in-hospital stay | 9.5 (9–24) days |

**Table 3** PCI and cytoreduction in our patients [6]

| PCI index (number of patients) | CC-0 No. of patients (%) | CC-1 No. of patients (%) | CC ≥ 2 No. of patients (%) |
|---|---|---|---|
| ≤ 19 (19) | 18 (95) | 1 (5) | – |
| ≥ 20 (13) | 4 (31) | 6 (46) | 3 (23) |

**Table 4** Complications according to Clavien–Dindo classification

| Grade of complication | Number of patients (%) |
|---|---|
| I | 16 (50) |
| II | 12 (38) |
| III | 3 (9) |
| IV | 1 (3) |
| V | 0 |

## Results

Twenty-one patients (65%) underwent a first look surgery, 6 (19%) a second look, and 5 (16%) cytoreduction after locoregional relapse. The median time of surgery + HIPEC was 540 min (range 240–900 min) (Table 2) and the median PCI index was 17. We obtained a complete cytoreduction (CC-0) in 22 patients (69%) and CC-1 in 7 patients (23%); cytoreduction was incomplete in 3 patients, with 2 CC-2 (residual implants between 2.5 mm and 2.5 cm) (6%) and one CC-3 (residual nodules larger than 2.5 cm) (2%). Twenty-three patients (72%) had ascitis at the time of the surgery, and 9 patients (28%) had also mucin and peritoneal implants of neoplastic cells (Table 3).

Histology demonstrated that 13 patients had DPAM (40.6%) and 19 had PMCA (59.4%).

The majority of patients had grade I–II complications according to Clavien–Dindo classification (Table 4); three patients had grade III complications (one patient had a port-a-cath infection by *S. aureus* that required its removal in local anaesthesia, two patients underwent evacuative thoracentesis for pleural effusion); one patient had a grade IV complication with the formation of a cerebral haematoma due to hypertension that required neurosurgical evacuation. We did not have any grade V complications. The median hospital stay was 9.5 days with a range between 9 and 24 days.

One-year overall survival (OS) was 90% and 5-year OS was 58% (Fig. 1a). Disease-free survival (DFS), regardless of histotype, was 95% at 1 year and 46% at 5 years (Fig. 2a).

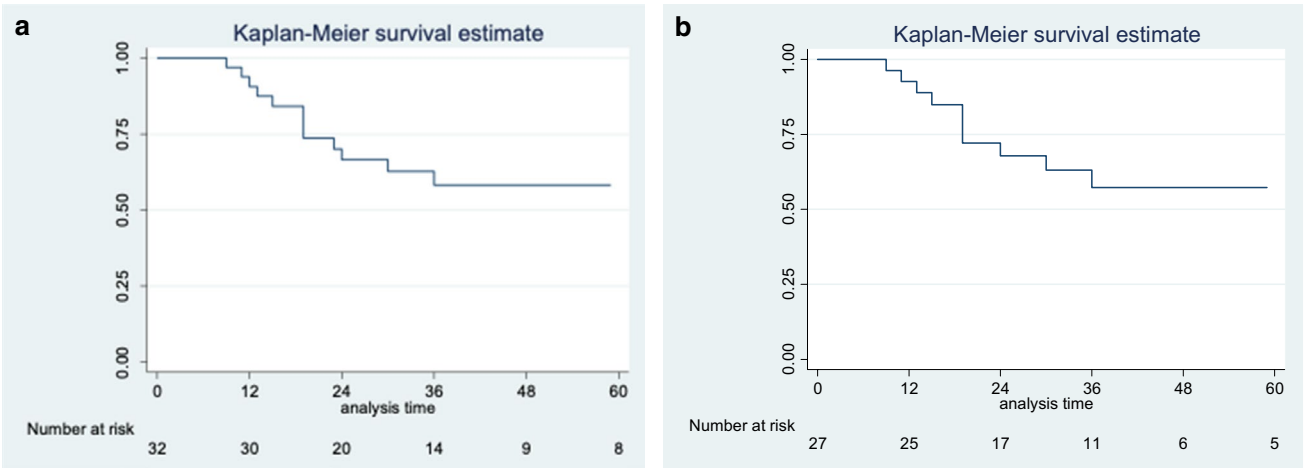


**Fig. 1** **a** Overall survival (OS) in our patients; **b** excluding loco-regional relapse

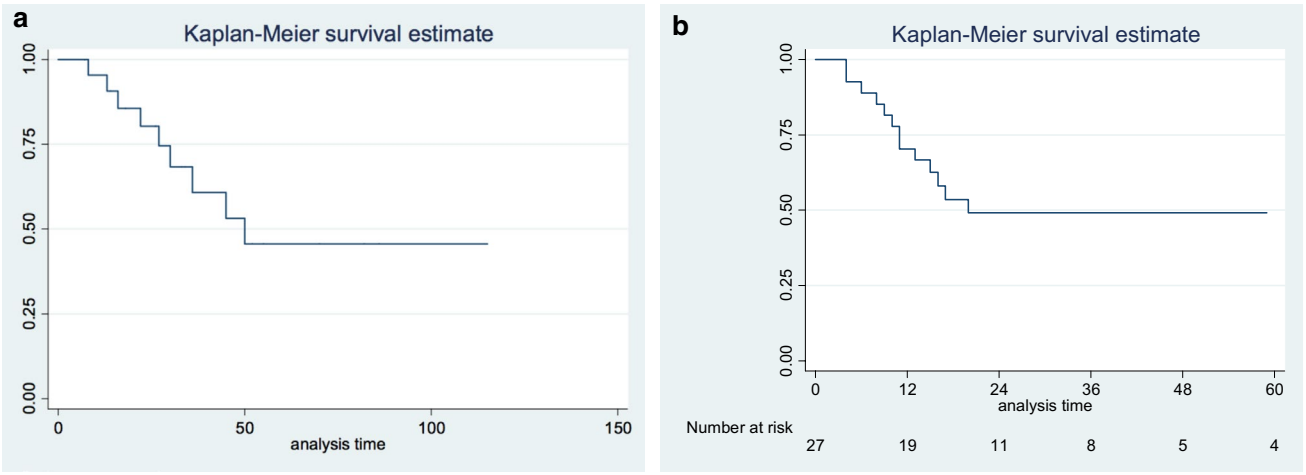


**Fig. 2** **a** Disease-free survival (DFS) in our patients; **b** excluding loco-regional relapse

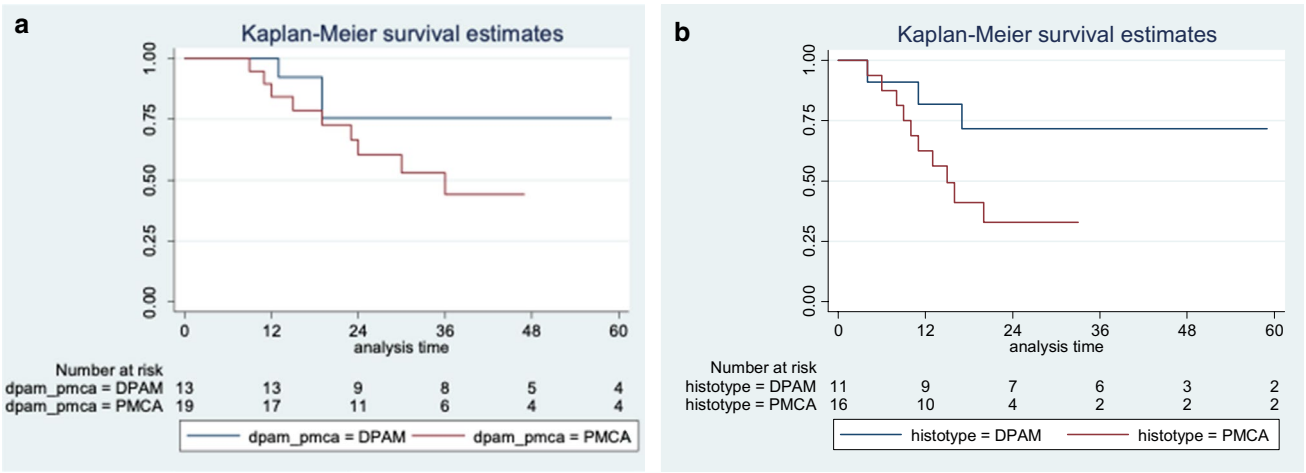


**Fig. 3** **a** OS in DPAM (in blue) and PMCA (in red) patients who underwent CRS + HIPEC; **b** DFS after excluding loco-regional relapse (color figure online)

Analyzing survival based on the histological type according to Ronnett's system (Fig. 3a), we found that the OS was better in the DPAM group, with a 1-year OS of 100% and a 5-year OS of 75%; in the PMCA group 1-year OS was 84% and 5-year OS was 44% ($p = 0.11$).

After excluding 5 patients (2 PMCA and 3 DPAM) who underwent CCR + HIPEC for loco-regional relapse, estimated 1-year and 5-year OS was 92% and 57%, respectively (Fig. 1b). Disease-free survival was 70% at 1 year and 49% at 5 years (Fig. 2b). In patients with DPAM, 1-year OS was 100% and 5-year OS was 70%, whereas in those with PMCA 1-year OS was 87% and 5-years OS was 45% ($p = 0.33$). We registered a borderline significant improved disease-free survival in the DPAM group; indeed, 1-year DFS was 81% and 5-year DFS was 71% for the DPAM group, whereas 1-year DFS and 5-year DFS was 62% and 32% ($p = 0.06$) for the PMCA group, respectively (Fig. 3b).

The higher the initial PCI index, the shorter was the 5-year OS: with a PCI index $\leq 19$ it was 67%, reaching 36% with a PCI $\geq 20$ ($p = 0.0164$). In the 13 patients with PCI index $\geq 20$ a complete cytoreduction was more difficult to achieve, and, in fact, was possible in only 4 patients; in the remaining patients we obtained CC $\geq 1$.

## Discussion

Since the 1980s, peritonectomy and HIPEC have appeared to be an effective approach to reduce the aggressiveness of peritoneal spreading in different malignant neoplasms. Its use in a condition as rare as PMP seems to be the most

effective one. The results available in literature indicate a good long-term control and better overall results if compared to debulking surgery alone, with 5-year survival ranging between 60 and 97% and 15-year survival up to 59%. However, the prognosis seems to be strictly related to PMP histology and cytoreduction achieved during surgery [7–13].

In our monocentric, prospective study we analysed the effect of cytoreduction and HIPEC in 32 patients with Pseudomyxoma peritonei. Although our patient volume was small, we obtained satisfactory surgical expertise and interesting results. In fact, we achieved a high percentage of complete cytoreduction. Indeed, comparing to Chua et al., who analysed 2298 patients with PMP in a multi-institutional registry, we achieved 69% of CC-0 compared to their 51%, and 23% of CC-1, compared to their 32%. Nonetheless, their 5-year OS was 74, compared to our 58% [12].

In our analysis, we obtained a 5-year OS which is below average if compared to other studies [1]. We interpreted these results considering pathological findings, according to the Ronnett's classification [3]. In fact, we had more patients with PMCA (59%) than with DPAM histology (41%), and stratifying our results by histology we achieved a 5-year OS of 75% in patients with DPAM, and of 44% in patients with PMCA. Similarly, the large multi-institutional registry study reported 5-year survival of 81% for DPAM (62% of patients) and 59% for PMCA (30% of patients) [12]. Although this binary pathological classification system is simple, many authors think that it is not a true reflection of the biology or outcomes of the disease [14]. Indeed, among the PMCA group, the presence of signet ring cells (SRC) is generally associated with aggressive disease and a poor outcome. Therefore, the authors argue that lesions with SRC involvement should be classified separately [15, 16].

The adverse events suffered by our patients were mostly of low-grade morbidity according to the Clavien–Dindo scale, and only 12% of patients had grade III complications or more. Our results were more or less in line with the available literature but our in-hospital stay was significantly lower (9.5 days) compared to the 20 days reported by Delhorme et al. or the 16 days reported by Schneider and his group [1, 8, 9, 13].

Notably, we had no grade V complications, which is a remarkable achievement considering mortality rates reported in the literature: in fact, in the Delhorme[1] study mortality was 2.5% [1]. Moreover, Piso et al., in their recent retrospective analysis of the StuDoQ-HIPEC Registry involving 2149 consecutive patients from 52 hospitals that perform cytoreduction and HIPEC for different tumours, demonstrated that mortality was 3.4% in centres with < 100 procedures, and reached 1.5% in high volume centres with more than 100 procedures [17].

During HIPEC procedure, we administered mytomicin C 3.3 mg/m$^2$/L and Cisplatin 25 mg/m$^2$/L at 41 °C for 60 min with closed abdomen technique. Different kind of chemotherapic drugs are used depending on the Centre, with different impacts in post-operative morbidity and mortality. Usually, the choice of one or a combination of drugs is based on histology, compatibility with hyperthermia and lowest possible post-operative complications [7]. Nevertheless, there is still a lack of standardization in the literature regarding this procedure, as there are no randomized trials including a high volume of patients. Little we know about the right duration of the treatment, the drugs that should be administered, the timing of HIPEC related to neo-/adjuvant treatment and the best operative technique (open/closed abdomen) [18].

Recently, pressurized intraperitoneal aerosol chemotherapy (PIPAC) was proposed as a new and potential additional treatment modality also in patients with PMP. Although this therapeutic tool seems promising, further investigations are needed to understand if PIPAC may become a complementary or alternative treatment to repeated surgery and intraperitoneal chemotherapy in patients with PMP [19].

Our study had several limitations. A major limitation was the small amount of patients. This is due to the fact that our Department is mainly dedicated to upper GI treatment. It is also important to consider the rarity of this kind of neoplasia, especially in Italy. Notably, since we started cytoreduction and chemiohyperthermia almost 15 years ago, we reached a significant volume of peritonectomy and HIPEC procedures for different primary diseases, thus obtaining a proficient surgical expertise even for a low volume center.

## Conclusions

In conclusion, the results of our study seem to increase the knowledge about PMP and show that CRS + HIPEC is an effective treatment for this tumour and can be managed by skilled surgeons.

### Compliance with ethical standards

**Conflict of interest** None of the authors have any conflicts of interest.

**Research involving human participants and/or animals** The study was in accordance with the ethical standards of the institutional research committee.

**Informed consent** Informed consent was obtained from all individual participants involved.

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