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ORIGINAL ARTICLE

Hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal malignancies using new hybrid CO_2 system: preliminary experience in referral center

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Abstract

The most frequent peritoneal surface malignancies originate principally by gastric cancer, colorectal cancer and ovarian cancer. Apart from the origin, peritoneal carcinosis (PC) is considered a negative prognostic factor. The hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) in the treatment of peritoneal malignancies is considered an attractive method to deliver chemotherapy with enhanced effect directly at the tumor site. The use of such loco-regional approach has proved to improve prognosis of peritoneal carcinomatosis from different origins. Recently, new devices are suitable for loco-regional intraperitoneal chemotherapy as Peritoneal Recirculation System (PRS-1.0 Combat) with CO_2 technology. This is a retrospective study with the aim to assess the perioperative outcomes using PRS. Seventeen patients were enrolled affected by colorectal or ovarian cancer. Complete cytoreduction (RT = 0) was achieved for all cases. Median operative time was 420 min (range: 335–665) and median drugs dose used for HIPEC was 137 mg/m2 (115–756). Median EBL was 200 ml (range 50–1000). Median post-operative hospital stay was 9 days (range: 4–24). Treatment-related early complications were recorded in 8 (47.0%) cases and were G1–G2 Major complications occurred in two (11.7%) cases. Considering our aim to test the PRS in different cases and in different pathologies, the results confirmed that the technique is feasible with good perioperative outcomes.

Keywords HIPEC · CO_2 · Ovarian cancer · Colorectal cancer · Gastric cancer · New technology

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Introduction

Surgical treatment represents the cornerstone for the management of several benign [1–8] as well as malignant [9–15] gynaecological diseases, even using minimally invasive approach.

The most frequent peritoneal surface malignancies originate principally by gastric cancer, colorectal cancer and ovarian cancer. Regardless of the origin, peritoneal carcinosis (PC) is considered a negative prognostic factor. The surgical approach, when feasible, for this type of disease is considered a fundamental step of treatment [16–18].

Debulking techniques involve the surgical removal of all macroscopically visible tumor volume by visceral resections and peritonectomy. More often, the preferred approach is open surgery; however, as for benign pathology [19–31], even in oncologic field, laparoscopy can be performed in selected cases [32–37].

One of the most debated arguments in the last years is the role of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) in the treatment of peritoneal malignancies. This is considered an attractive method to deliver chemotherapy with enhanced effect directly at the tumor site.

The use of such loco-regional approach has proved to improve prognosis of peritoneal carcinomatosis from different origins (colo-rectal, appendix, pseudomyxoma peritonei and peritoneal mesothelioma) [38].

Regarding ovarian cancer, some studies have demonstrated it is able to prolong post-recurrence survival [39, 40], and even in a recent randomized trial, the role of HIPEC seems to be effective even at first diagnosis [41].

New techniques and devices are available for intraperitoneal delivery of chemotherapy, such as PIPAC (Pressurized IntraPeritoneal Aerosol Chemotherapy) [42, 43] and Peritoneal Recirculation System (PRS-1.0 Combat) with CO_2 technology [44].

The PRS hybrid technique was previously investigated by Spanish group [44–46] demonstrating the feasibility of this technique. The present study is aimed to report preliminary Italian experience in a referral center with PRS in gastrointestinal and ovarian cancer malignancies treatment.

Methods

This is a retrospective single-arm study conducted at Policlinico Agostino Gemelli Foundation, IRCCS, University Hospital, Rome, from July 2017 to May 2018, and was approved by our IRB. Informed consent was obtained from all subjects.

All enrolled patients underwent pre-operative evaluation by chest/abdomen CT scan, pelvic and or abdominal ultrasound and tumor markers (CA125, Ca19.9,CEA, CA 15.3). Major criteria to abort surgical procedure were the Poorest Eastern Cooperative Oncology Group performance status (i.e., ECOG-PS > 2) and/or higher American Society of Anesthesiology score (i.e., ASA > 2). All patients were submitted to staging laparoscopy to evaluate and quantify peritoneal dissemination using two different scores [47, 48].

The inclusion criteria were as follows: age between 18 years and < 75 years; ECOG-PS ≤ 2; life expectancy of at least 3 months; normal cardiac, hepatic, respiratory and bone marrow functions (creatinine clearance > 60 ml/min according to Cockroft formula, absolute neutrophil count > 1500/ll, a platelet count > 150,000/ll, bilirubin levels and creatinine < 1.5 times upper the range); optimal primary cytoreduction achieved (CC-0, CC-1) [49]; and signed informed consent form.

The exclusion criteria were as follows: peritoneal carcinosis spread considered not suitable for cytoreduction; coexistence of other oncologic disease; body mass index (BMI) > 35 kg/m^2; active infection or general conditions that could interfere with treatment (vasculopathy, autoimmune disorders, diabetes); refusal to sign the informed consent form; previous recipient of chemotherapy treatment; distant (extra-abdominal) unresectable metastases and bowel obstruction.

The patients who met inclusion criteria, and that were considered suitable for surgical treatment at staging laparoscopy, underwent surgical multivisceral cytoreduction. The completeness of cytoreduction (CC) was assessed using a score ranging from 0 to 3 (CC-0 indicates no residual tumor; CC-1 indicates nodules < 0.25 mm; CC-2 indicates nodules between 0.25 and 2.5 cm in diameter; and CC-3 indicates nodules > 2.5 cm). After completion of cytoreduction, four drains were positioned in the four abdominal quadrants, the reservoir of PRS system was installed and fixed in the abdomen, the CO_2 tube was positioned. HIPEC perfusion was performed with closed technique and the abdomen was carefully re-explored after HIPEC completion. All patients received intraperitoneal cisplatin 75 mg/m^2 or oxaliplatin 360 mg/m^2 at the temperature of 41.5 °C for 30 or 60 min depending on different protocols used, in one case, one patient affected by ovarian cancer received even taxol (175 mg/m^2) associated with cisplatin.

Patients affected by ovarian cancer received HIPEC treatment in the context of ongoing registered trials (HORSE NCT01539785, CHORINE NCT01628380).

Results

Seventeen patients were enrolled for the present study. All patients' records were reviewed for the purposes of the study. Patients' characteristics are shown in Table 1. The detailed surgical procedures performed are reported Table 2. Peri-operative outcomes are reported in Table 3. Complete cytoreduction (RT = 0) was achieved for all cases. Median operative time was 420 min (range: 335–665) and median drugs dose used for HIPEC was 137 mg/m2 (115–756). Median EBL was 200 ml (range 50–1000). Median post-operative hospital stay was 9 days (range: 4–24). Treatment-related early complications (within 30 days from surgery), according with Dindo classification [50], were recorded in 8 (47.0%) cases and were G1–G2 consisting in urinary infection treated with antibiotics, pleural effusion and increased creatinine levels spontaneously solved (Table 3). Major complications occurred in 2 (11.7%) cases, bowel anastomosis dehiscence and pelvic abscess required readmission in operative room for colostomy and abscess drainage, respectively. Late complications (after 30 days from surgery) were related to one case of bowel obstruction required ileostomy. No post-operative death was recorded. Subsequent systemic chemotherapy was administered in 100% of cases.

Table 1 Patients' characteristics

Cases *N*. 17	Median
Age	54 (range 38–74)
BMI	24 (range 18–34)
ECOG	0 (range 0–1)
Ovarian cancer (first diagnose)	1 (5.8%)
Ovarian cancer recurrence	8 (47.0%)
Appendiceal cancer	6 (35.2%)
Colorectal cancer	1(5.8%)
Gastric cancer	1(5.8%)
Stage	
III	11 (64.7%)
IV	6 (35.2%)
PCI	7 (range 0–20)
Histotype	
Serous	9 (52.9%)
LAMN	4 (23.5%)
Adenocarcinoma	4 (23.5%)
Grade	3 (1–3)

Table 2 Surgical procedures

	N (%)
Hysterectomy	7 (41.1)
BSO	8 (47.0)
PE/LA lymphadenectomy	3 (17.6)
Omentectomy	11 (64.7)
Appendectomy	4 (23.5)
Bowel resection	9 (52.9)
Diaphragm peritonectomy	7 (41.1)
Splenectomy	9 (52.9)
Peritonectomy	6 (35.2)
Cholecystectomy	4 (23.5)
Others	5 (29.4)

Discussion

The rational to perform HIPEC in ovarian cancer, peritoneal cancer and gastric/colorectal cancer is particularly convincing, based on the prevalent intra-abdominal diffusion of the disease, which is also the main driver of survival in these subsets of patients. Indeed, this approach combines the advantage of the intraperitoneal chemotherapy administration with the complete diffusion of the drug in the whole abdomen, all enhanced by hyperthermia [32, 38]. However, although several data in the literature show an improvement in survival rates of patients undergoing HIPEC procedure, especially for ovarian cancer treatment the results are still conflicting [51].

Table 3 Peri-operative outcomes

	Median—*N*
RT 0	17 (100%)
EBL (ml)	200 (range 50–1000)
Operative time (min)	420 (range 335–665)
HIPEC drugs	8 (47.0%) cisplatin (60 min)
	1 (5.8%) cisplatin + taxol (90 min)
	8 (47.0%) oxaliplatin (30 min)
HIPEC drug dosage (mg/m2)	137 (range 115–756)
Post-operative complications	
Grade 1–2	8 (47.0%)[a]
Grade 3–4	2 (11.7%)[b]
Hospital stay (days)	9 (4–24)

[a]Urinary infection, pleural effusion, creatinine enhanced, rectal bleeding

[b]Bowel anastomotic leak, pelvic abscess

For colorectal cancer, the peritoneal metastases' resection followed by HIPEC is considered a valid therapeutic option both in prophylactic and in adjuvant settings. Recently, three different studies found that the use of HIPEC during the resection of primary tumor is a valid strategy to prevent local peritoneal recurrences and to prolong survival [52–55].

Peritoneal carcinosis for gastric cancer has the worst prognosis compared with other etiologies but HIPEC combined with CRS increases OS and DFS in high selective patients with limited and resectable metastases [56].

A recent randomized trial by van Driel et al. [41] reported important data in favor of HIPEC treatment for ovarian cancer patients underwent interval debulking surgery after neoadjuvant systemic chemotherapy.

Considering the innovation in loco-regional treatment field we tested a new technology, Peritoneal Recirculation System (PRS-1.0 Combat).

This system consists of a hybrid technique in which chemotherapy infusion is in a liquid status with the addition of CO_2 that amplifies the intra-abdominal fluid circulation. This new technology consisted of two roller pumps and a warm external reservoir for heating the perfusate solution, two inflow tubes, two outflow tubes and another tube used for CO_2 infusion [44].

The advantage of this technique is the presence of a reservoir (Fig. 1) that allows to verify the level of intraperitoneal solution and consequently to confirm that the abdomen is completely filled. Moreover, the presence of CO_2 could allow creating a sort of intraperitoneal circulation with the aim to create a more homogeneous drug distribution.

The distribution of a tracer during HIPEC using PRS was recently tested in a porcine model [57].

Another important factor is the thermal distribution; in fact, it is demonstrated that hyperthermia works by amplifying the cytotoxic mechanism of platinum compounds

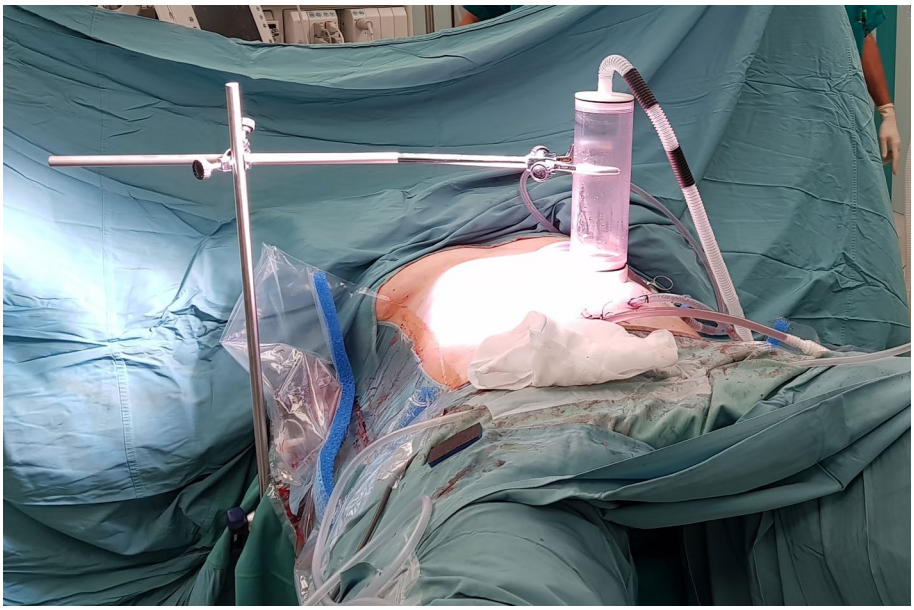

Fig. 1 HIPEC with PRS system

[58]. In this context, the presence of recirculating mechanism could amplify even the thermal distribution.

In another study by Padilla-Valverde et al. [45], a thermographic camera was used during an HIPEC procedure in a porcine model to value the thermal distribution inside the abdomen. They divided the abdomen in four quadrants, demonstrating a homogeneous thermal distribution inside the abdomen.

Sànchez Garcìa et al. conducted different studies about this new technology reporting good perioperative outcomes [44–46]. In fact, in a series of 21 patients, the complication rate was 57.1% (grade 1–2) and 38.1% (grade 3–4) that compared with our results and literature results are in an acceptable range.

In our series, grade 1–2 complication was principally related to pleural effusion in a patient who underwent total right diaphragmatic peritonectomy and was not symptomatic and did not required pleural drainage. The patient was discharged with indication to repeat chest X-ray that after 7 days from discharge was negative. The increased creatinine level in other two patients was recorded in third post-operative day and in both cases was < 3 mg/dl. The level was normalized before discharged only with hydration. The patients with rectal bleeding had bowel resection; the symptoms were spontaneously solved during recovery. In patients with early grade 3 complications, it occurred during recovery after 3 and 4 days from surgery, respectively, for anastomotic leak and pelvic abscess. The late complication, consisting of bowel obstruction, occurred after 62 days from surgery in a patient affected by ovarian cancer recurrence submitted to large bowel resection during systemic chemotherapy treatment. The readmission to operative room to perform ileostomy was required without post-operative complications.

Considering our aim to test the PRS in different cases and in different pathologies the results confirmed that the technique in feasible with good perioperative outcomes. However, considering the nature of the study as preliminary experience, the sample is not sufficient to give definitive conclusions. Moreover, other studies are needed to confirm even the oncologic outcomes; in fact, pharmacokinetic studies and more other specific studies aimed to test PRS are actually ongoing.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals All procedures performed in studies involving animals were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Not applicable for this type of study.

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