Iterative Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Recurrent Peritoneal Metastases

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Abstract. *Background:* Our aim was to analyze the safety and efficacy of iterative cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (iCRS–HIPEC) in patients with peritoneal recurrence from different tumor types. *Patients and Methods:* Data on indications, intraoperative findings and postoperative outcome of all patients treated with iCRS–HIPEC at our Institution were reviewed. *Results:* Between 2010-2018, 10 iCRS–HIPEC procedures for peritoneal recurrence in eight patients were performed. The median peritoneal cancer index was 14.5 (range=2-33). Completeness of cytoreduction was CC0-1 in most cases (9/10). Three grade III-IV complications (two intestinal fistulas, one bleeding) were recorded and there was no operative mortality. After a median follow-up of 19.5 months, six patients experienced recurrence after a median of 12.5 months. *Conclusion:* iCRS–HIPEC is a safe procedure in selected patients with recurrent peritoneal surface malignancies. Selection criteria still remain questionable and need to be further evaluated in large cooperative multi-institution studies.

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) represents an established therapeutic approach for several peritoneal surface malignancies (PSM). It provides remarkable locoregional disease control and a survival benefit in selected patients (1). The rationale of this locoregional treatment is to surgically remove all visible peritoneal nodules, allowing the heated chemotherapy to treat eventual microscopic residual tumor directly in the abdominal cavity.

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Key Words: Peritoneal carcinomatosis, iterative surgery, HIPEC.

Over the years, innovations and refinements in surgical technique, technology, anesthesiological care and more defined selection criteria have produced continuous improvement in the oncological outcome of patients treated with CRS–HIPEC. For malignant mesothelioma and peritoneal pseudomyxoma (PMP) (2, 3), CRS–HIPEC has led to substantially improved survival compared to historical data and is considered a primary option at experienced referral centers. Moreover, in colorectal, gastric and ovarian peritoneal carcinomatosis, randomized prospective trials have confirmed the added value of CRS–HIPEC in a multimodality and multistep approach of systemic chemotherapy (4-7).

Peritoneal recurrence after CRS–HIPEC remains a common event. In colorectal peritoneal metastases, 26% of patients treated with CRS–HIPEC develop isolated peritoneal recurrence (8). The recurrence rate after CRS–HIPEC for PMP and mesothelioma is expected to be up to 40% (9, 10). The peritoneum often remains the only site of disease, characterizing the whole natural history of disease until death. In these cases, the option of potentially curative iterative CRS–HIPEC (iCRS–HIPEC) becomes a possible consideration. However, repeated surgery after previous CRS–HIPEC represents a major challenge as the effect of scarring and adhesion induced by HIPEC is largely unknown. Moreover, limited data on recurrent PSM treated with iCRS–HIPEC are available and indications still remain unclear (11).

The aim of this study was to evaluate the safety and efficacy of iCRS–HIPEC in patients with peritoneal recurrence. Data on indication, postoperative outcome and prognosis of recurrent PSM treated with iCRS and HIPEC from a single institution were analyzed.

Patients and Methods

Retrospective data were obtained from a prospectively maintained database of the Department of Surgical Oncology of the Veneto Institute of Oncology. Clinical and pathological pre-operative data,

intraoperative details and postoperative outcome were retrieved from the database. All patients were selected and treated after multidisciplinary team discussion. Patients signed a detailed, written-informed consent form and were uniformly treated according to an Institutionally approved internal protocol (Qualy-HIPEC protocol July 2018, IOV-CESC 2018/85). Tumor spread was scored at the time of laparotomy using the peritoneal cancer index, PCI (range=1-39) (12).

The objective of CRS was directed to eradicate all visible tumor nodules, performing en-bloc resection of the involved organ(s) and stripping of the parietal peritoneum. Residual disease after CRS was classified according to the completeness of cytoreduction (CC0: no residual disease, CC1: less than 2.5 mm, CC2: between 2.5 mm and 2.5 cm, CC3: more than 2.5 cm) (13). A CC score of 2 more represented a contraindication for HIPEC and the procedure was then considered palliative. HIPEC was performed with the open- or closed-abdomen technique according to surgeon preference. Peritoneal perfusion was achieved by an open circuit consisting of two inflow and two outflow catheters connected to a pump, supplied with a heater and a heat exchanger. A temperature monitoring system consisting of four thermal probes placed on different sites of the circuit and in the peritoneal cavity was used. Once the target temperature (41.5°C) was reached, cisplatin at 25 ml/m²/l plus 3.3 mg/m²/l mitomycin-C in patients with gastrointestinal histology, and cisplatin at 45 mg/l plus 15 mg/l doxorubicin for those with ovarian carcinomatosis, mesothelioma or peritoneal sarcomatosis, were bolus-injected into the circuit and the perfusion maintained for 60 minutes.

Postoperative complications were classified using the Clavien–Dindo classification (14). Patient outcome was evaluated in terms of peritoneal and systemic disease progression by abdominal/thoracic computed tomographic scan performed every 6 months for the first 2 years after treatment, then annually.

Statistical analysis. Survival was calculated as the interval between iCRS–HIPEC and recurrence or death due to PSM. Statistical analyses were conducted with SPSS 17.0 (SPSS Statistics, Release 17.0.0; SPSS, Chicago, IL, USA).

Results

From January 2010 to April 2018, 77 CRS–HIPEC procedures in 67 patients were performed at the Veneto Institute of Oncology. Ten iCRS–HIPEC procedures performed in eight patients (six females) with peritoneal recurrence were analysed (six patients underwent two procedures, two underwent three procedures). The median age at the time of iCRS–HIPEC was 48 (range=24-75) years. The most frequent indication was PMP with seven cases. Patient and PSM features are summarized in Table I.

The median time between previous CRS–HIPEC and iCRS–HIPEC was 20 (range=8-68) months. The median PCI at the time of surgery was 14.5 (range=2-33). Completeness of cytoreduction was CC0-1 in most cases (9/10). In one patient, residual tumor >2.5 mm (CC2) was obtained. The median operative time was 512 (range=405-630) minutes. The median length of stay was 10.5 (range=8-60) days. No intra- or postoperative mortality was recorded. Incidence of grade III-IV adverse events was 30% (two small bowel fistulas, and one intra-abdominal bleeding). In one of the two

patients who experienced small bowel fistula, the postoperative course was complicated by a double perforation of the small bowel during the third HIPEC.

After a median follow-up of 19.5 (range=3-74) months, one patient had died of causes unrelated to PSM. The median time to recurrence was 12.5 months. Isolated peritoneal disease progression occurred in five patients, two of them treated with a third CRS–HIPEC, two with systemic chemotherapy, and one with close observation. One patient experienced simultaneous local and distant progression and is still undergoing systemic chemotherapy.

Discussion

CRS–HIPEC has become a valuable treatment option in patients affected by primary or secondary PSM. Over 20 years of experience at several specialized centers worldwide have perfected this procedure, achieving an acceptable morbidity profile and a mortality rate comparable to those of other major surgical operations (15). Cancer outcomes are continuously improving, mainly due to a better knowledge of prognostic factors, which leads to more appropriate patient selection (16). However, peritoneal recurrence after CRS–HIPEC still represents a major challenge for several reasons. Peritoneal recurrence is often characterized by a short life expectancy and poor quality of life. Frequently, the peritoneal cavity remains the only site of relapse and any disease progression implies complications difficult to palliate (*i.e.* intestinal obstruction, fistulas and pain). Moreover, any surgical approach to peritoneal recurrence, especially after CRS–HIPEC, is feared by surgeons, as the abdomen contains scars and adhesions from previous extensive surgeries. In addition, when considering surgical exploration in patients previously treated with CRS–HIPEC, the effects of hyperthermia and intraperitoneal drugs are largely unknown and, at the same time, the benefit of an iterative procedure in terms of oncological outcome is difficult to balance against the potential risk of complications and death.

In our study, we confirmed that iCRS–HIPEC is safe and that the number of complications is very similar to that reported in our series after primary treatment (data not shown). Previous experience showed that iCRS–HIPEC is associated with an acceptable morbidity profile. The grade III-IV morbidity rate after iCRS–HIPEC ranged between 20-40%, which is in line with the complication rate reported after primary CRS–HIPEC. Mortality is around 3%, similar to that reported after first CRS–HIPEC (15). The morbidity and mortality profile similar to that reported after primary CRS–HIPEC is in part the result of a more accurate selection process, which includes age, performance status and tumor extension. The relationship between tumor extension and postoperative morbidity after CRS–HIPEC is well known (17). In our experience, the median PCI is relatively low

Table I. Clinical pathway of patients who underwent iterative cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (iCRS–HIPEC).

Patient	Age (years)	Gender	Histotype	Grading	Site of primary	Third iCRS–HIPEC	CHT	Current status	Survival (months)*
1	75	F	Low-grade mucinous tumor	1	Appendix	No	No	DOC	68
2	45	F	Low-grade mucinous tumor	1	Appendix	No	No	NED	20
3	33	F	Low-grade mucinous tumor	1	Appendix	Yes	No	AWD	36
4	52	F	Low-grade mucinous tumor	1	Appendix	Yes	No	NED	37
5	57	F	Leiomyosarcoma	1	Uterus	No	Yes	AWD	18
6	42	F	Mixed PMP, low- and high-grade	3	Appendix	No	Yes	AWD	24
7	51	M	Epithelial mesothelioma	1	Peritoneum	No	Yes	AWD	16
8	24	M	Mucinous adenocarcinoma	3	Colon	No	Yes	NED	3

AWD, Alive with disease; CHT, chemotherapy; DOC, died of other causes; F: female; M: male; NED, no evidence of disease; PMP: peritoneal pseudomyxoma. *Calculated from time of first iCRS–HIPEC.

(14.5) and, in other studies, it rarely exceeded 16 (11). This means that iCRS–HIPEC can generally be proposed for younger patients with a good performance status and a relatively lower tumor load.

The long-term effects of intraperitoneal drugs after HIPEC on normal tissues and the peritoneum are unknown. The hypothesis is that HIPEC might have a potential detrimental effect on the peritoneal layers and small bowel wall, through a direct cytotoxic effect of the drugs. The subsequent long-term damage and weakness of bowel layers and the presence of more scar tissue make surgery after HIPEC even more dangerous. Clinical data on the onset of abdominal adhesions after HIPEC show that intraperitoneal mitomycin C, cisplatin, and doxorubicin induce local toxicity through an irritator effect on the peritoneal layer (18). The final effect is a higher incidence of postoperative adhesions whose severity is dependent on the type of drug infused. Adhesion after intraoperative intraperitoneal cisplatin can produce intestinal obstruction requiring surgery in 6% of cases (19). Doxorubicin, which is an alkylating agent exerting its antineoplastic activity through DNA intercalation, inhibition of topoisomerase II, and formation of oxygen free radicals (oxidative stress), causes a severe inflammatory reaction in the peritoneum and significant fibrosis when used for intraperitoneal therapy. A dose-escalation study demonstrated that intraperitoneal administration of doxorubicin at total dose of 15 mg/m² resulted in a thin layering of fibrosis on peritoneal layers (20). This sclerosing effect of doxorubicin is useful for the treatment of debilitating malignant ascites and is considered the best drug for palliative laparoscopic HIPEC (21). Similarly, the effect of heat in the intraperitoneal area during HIPEC on normal tissues is poorly understood. In *in vitro* studies, the thermal dose (derived from exposure time and given temperature) required to induce hyperthermic cell death varies according to cell type. Hyperthermia can induce irreversible changes to tissue microcirculation, with a breakdown of circulation even after

termination of heat exposure (22). Further studies are needed for clarify if regional hyperthermia can induce more intraperitoneal scar adhesion and small bowel weakness. In our study, two out of the three reported III/IV complications were related to small bowel fistulas (all unrelated to anastomosis). In one case, we observed perforation in two different loops, interestingly after the third CRS–HIPEC. This finding support the hypothesis that previous HIPEC could have weakened intestinal layers, leaving them at a higher risk for perforation. This hypothesis should be further explored.

From the oncological point of view, histological type should probably be the main selection criterion for iCRS–HIPEC. We selected, in most cases, only patients with PMP with low-grade features (5/8) and the two patients who underwent a third iCRS–HIPEC both had low-grade mucinous tumor. Of the remaining three patients, two had low-grade histology (uterine sarcomatosis and epithelial mesothelioma) and one had a high-grade colorectal peritoneal recurrence. It is well known that some PSM tumors are characterized by intraperitoneal spread throughout the entire disease history and systemic chemotherapy is rarely effective and not routinely used. The lack of valuable therapeutic alternatives and low-grade histology were the most determinant selection factors for iCRS–HIPEC in our series. This ‘selection effect’ has been confirmed in several studies, where PMP and mesothelioma represent the most frequent indications for iCRS–HIPEC (11).

The cancer outcome after iCRS–HIPEC is satisfactory, with most patients being alive, and about half without evidence of disease at study end. However, even considering previous experience with iCRS–HIPEC, data are scarce and difficult to compare as indications vary and HIPEC protocols differ among centers. Although some benefit is expected in patients treated for PMP and mesothelioma, the long-term results of iCRS–HIPEC remain uncertain and should be further evaluated.

Conclusion

Our study confirmed that iCRS–HIPEC is a safe procedure in selected patients with recurrent PSM when performed at experienced centers. Indication for iCRS–HIPEC should be better defined, preferably within prospective multi-institutional studies.

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Received July 5, 2018

Revised July 26, 2018

Accepted July 27, 2018