Iterative procedures combining cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for isolated peritoneal recurrence

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Abstract

Purpose: The aim of this study was to analyse feasibility, morbidity and outcome of repeat complete cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC). CRS combined with HIPEC is becoming the gold standard treatment for resectable peritoneal carcinomatosis in highly selected patients. As yet treatment of isolated peritoneal recurrence with iterative CRS and HIPEC has not been thoroughly explored.

Materials and methods: We selected 16 patients presenting isolated peritoneal recurrence who had undergone iterative CRS and HIPEC from a dataset of 322 CRS associated with HIPEC performed between 1996 and 2012.

Results: Peritoneal carcinomatosis (PC) was due to colorectal and ovarian cancer, peritoneal mesothelioma and pseudomyxoma peritonei (PMP). Disease-free survival (DFS) was 13 months after the first procedure and 13.7 months after the second one. Overall morbidity rate was 43.7% (7/16) for all patients, with grade III–IV complications in three patients (18.7%).

Conclusions: Iterative procedures combining cytoreductive surgery and HIPEC are feasible with acceptable morbidity and mortality rates in strictly selected patients. DFS following repeated CRS and HIPEC is comparable to that registered after the first procedure.

Keywords
Carcinomatosis, chemotherapy, cytoreduction, HIPEC, hyperthermia

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Introduction

Peritoneal carcinomatosis (PC) treatment is traditionally palliative and has poor prognosis whatever its origin [1–2]. Over recent decades, prognosis of tumour types such as colorectal and ovarian cancer, pseudomyxoma peritonei (PMP) and peritoneal mesothelioma has considerably improved with the introduction of an aggressive approach combining cytoreductive surgery (CRS) with peritoneectomy procedures and hyperthermic intraperitoneal chemotherapy (HIPEC) in selected patients.

The overall 5-year survival rate following this new treatment ranges from 22–51% for patients with colorectal PC, from 29–63% for peritoneal mesotheliomas, from 12–54% for ovarian cancer and rises to 80% in patients with PMP [3–11]. However, 80% of patients treated for PC from CRC relapse after CRS and HIPEC, as do 40% of those with peritoneal mesothelioma, 60–70% in ovarian carcinoma and 25–44% of patients treated for PMP [12–16].

In some cases, recurrences may be confined to the peritoneal cavity and are completely resectable. It is thus supposed that patients presenting with a good general status could benefit from repeat CRS and HIPEC. Many centres have already published their experience with iterative procedures, reporting a 5-year survival rate of 72.5% [17–18] and a median overall survival (OS) from diagnosis of 140 months [18], but indications and outcomes remain unclear.

The aim of this study was to analyse feasibility, indications, post-operative and long-term outcomes of these iterative procedures.

Materials and methods

Patients

From 1996 to 2012, 322 procedures combining CRS and HIPEC were performed in one referral centre involved in the management of peritoneal surface malignancies. All iterative procedures were selected for this study.

The selection criteria for a second CRS associated with HIPEC were first time CRS with HIPEC performed in our institution, limited co-morbidity and good general status as per ECOG score rating, physiological age <65 years, histological evidence (biopsy) recurrence, or strongly suspected PC from elevated tumour marker and abnormal abdominopelvic imaging. Nevertheless, fundamental characteristics of the patient selection process were Peritoneal Cancer Index (PCI) [19] at ≤ 16 and a progression-free interval of at least 12 months between first HIPEC and the recurrence diagnosis. Informed consent was obtained from all
patients. Exclusion criteria were extra-abdominal cancer dissemination, no likelihood of achieving complete cytoreduction according to preoperative computed tomography (CT) scan, and severe liver, renal, pulmonary or cardiac disease.

All patients had a preoperative abdominal CT and positron emission tomography scan in order to exclude extraperitoneal disease. The decision to perform an iterative procedure was confirmed during a multidisciplinary meeting.

Data were retrospectively collected from a prospective database including clinical records, biological parameters, modalities of procedure, extent of resection and post-operative follow-up.

Cytoreductive surgery

A midline incision from the xiphoid process to the symphysis pubis was routinely performed. Adhesiolysis was performed to assess disease distribution and identify factors precluding a complete cytoreduction (massive bladder or gastric involvement and especially small bowel status). The extent of recurrent peritoneal disease was evaluated using the PCI, which ranges from 1 to 39 [19]. Peritonectomy procedures and organ resections, if indicated, were then performed. Peritonectomy extension was recorded as the sum of PCI and organ resections, if indicated, were then performed. Peritonectomy procedures was calculated as the sum of peritonectomy sites classified in six areas [20]. Cytoreduction completeness (CC) was classified according to the CC score [21]. HIPEC was only performed if all macroscopically detectable disease was completely resected or after optimal cytoreduction (CC = 0/1); otherwise patients underwent only a debulking procedure. Anastomoses were created after perfusion.

HIPEC

All the HIPEC procedures were carried out intra-operatively with an original ‘semi-closed’ technique [22], as previously reported. HIPEC was performed for 60 min at 40–41°C throughout the abdominopelvic cavity. Circulating perfusate volume was calculated according to patient body surface. Different drugs were used depending on carcinomatosis origin, dissolved in peritoneal dialysis solution. Pseudoxyoma peritonei and colonic tumours perfused using cis-diaminedichloroplatinum (CDDP) 100 mg/m² and mitomycin C (MMC) 16 mg/m² [23] at first intervention, were perfused at the second with MMC 35 mg/m² following the Netherlands protocol [3]. Cisplatin 100 mg/m² and Adriamycin 15 mg/L were used for ovarian carcinoma and peritoneal mesothelioma both for the first and the second procedure [24].

After the operation, patients were admitted to the intensive care unit and then returned to the surgical ward when cardiovascular and pulmonary functions became stable.

Follow-up

Morbidity and mortality were investigated up to 30 days or until hospital discharge. Complications were recorded by Clavien-Dindo classification [25]. On the basis of histopathology results, each case was discussed at a multidisciplinary meeting to decide the best adjuvant treatment according to accepted guidelines and current protocols. Patients were followed up every 3 months with a clinical examination, imaging investigation and blood marker determination except for patients with low-grade PMP who were followed up every 6 months. No patient was lost to follow-up and no patient was excluded from the analysis.

Statistical analysis

Data were obtained retrospectively from a prospective database containing clinical records, surgical reports and regular systematic follow-up information on patients treated by our team. Categorical variables were compared with the Mann-Whitney U test, a two-tailed chi-square test, or Fisher’s exact test, as appropriate. Continuous variables were compared with the Student t-test. Survival curves were calculated using the Kaplan–Meier method and compared with the log-rank test. Two recurrence-free survival (RFS) times were computed:

- time from initial CRS with HIPEC to first recurrence,
- time from second-time CRS with HIPEC to second recurrence.

Patients without recurrence or who had died without recurrence were censored.

Results

A total of 16 patients underwent iterative CRS and HIPEC for isolated peritoneal tumour recurrence. Candidates comprised seven men and nine women, and median age at diagnosis was 51.2 years (range 65–30 years). The primary tumour locations were ovarian (n = 4), colorectal (n = 3), peritoneal mesothelioma (n = 2) and pseudomyxoma peritonei (n = 7). Median interval between initial and second CRS with HIPEC was 19 months (range 12–111 months). Eight patients received adjuvant chemotherapy after the first procedure; these patients had PC from ovarian cancer (n = 3), colorectal cancer (n = 3) and peritoneal mesothelioma (n = 2). Systemic chemotherapy was administered before repeat CRS plus HIPEC in 10 patients (three PMP, four ovarian cancer and three colorectal cancer). The neoadjuvant systemic therapy was specific for patients with known chemo-response in order to down-stage and limit disease progression (i.e. patients with colorectal or ovarian carcinomatosis). Given that effects of systemic chemotherapy in PMP show limited success, it was administered only to patients with peritoneal malignant carcinomatosis (PMCA).

Second CRS + HIPEC

Intra-operative characteristics of these patients are reported in Table 1. At second CRS with HIPEC mean PCI was 8 (median PCI = 11; range 1–16). The mean number of resections was 1.0. The mean number of peritonectomy procedures was 1.1. No bowel anastomoses were performed in 11 patients (68.7%), one bowel anastomosis was performed in three patients (18.7%), and two bowel anastomoses in two patients (12.5%). The mean operating time was 8.9 h (range 6–11 h) for all patients. At the completion of best surgical effort, 12 patients (75%) were classified as CC-0 resection, four patients (25%) were considered as CC-1.
Morbidity and mortality

No patient died post-operatively. Nine patients (56.2%) had an uneventful post-operative course. Overall morbidity was 43.7% (7/16) for all the patients, but with different grading distribution. In particular, grade I complications occurred in two patients (12.5%), grade II in two (12.5%) and grade III–IV in three (18.7%). The type of complications and their Clavien-Dindo classification in the two groups are reported in Table 2. Post-operative complications included pleural effusion (n = 1), haemoperitoneum (n = 1), stomal high flow (n = 1), biliary or pancreatic fistula (n = 2), others (n = 2). The mean duration of hospitalisation was 22 days (range 12–41 days) for all patients.

Survival and recurrences

Median follow-up after second CRS and HIPEC was 20 months (range 6–100 months). Second recurrence occurred in nine patients (56.2%). After the first CRS with HIPEC mean disease-free survival (DFS) was 13 months and after the second procedure DFS was 13.7 months with no statistical significance between the two groups (P = 0.41). DFS curves after the first and second procedures are similar (Figure 1). Median overall survival was 54 months.

At the end of the study, seven patients had no evidence of disease recurrence (43.7%, including two unrelated deaths), two patients were alive with recurrence and seven patients had died with recurrence.

Table 1. Intra-operative characteristics of 16 patients who underwent repeat CRS and HIPEC for recurrent peritoneal carcinomatosis.

<table>
<thead>
<tr>
<th></th>
<th>I CRS + HIPEC</th>
<th>II CRS + HIPEC</th>
<th>P</th>
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<tbody>
<tr>
<td>PCI (mean)</td>
<td>16.2</td>
<td>7.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of resected organs</td>
<td>3.1</td>
<td>1.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of peritonectomies</td>
<td>3.4</td>
<td>1.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of anastomoses</td>
<td>5</td>
<td>11</td>
<td>0.076</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completeness of cytoreduction</td>
<td></td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>CC0</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>CC1/2</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Mean operating time (h)</td>
<td>11.9</td>
<td>8.9</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Table 2. Post-operative course of 16 patients who underwent repeat CRS + HIPEC for recurrent peritoneal carcinomatosis.

<table>
<thead>
<tr>
<th></th>
<th>I CRS + HIPEC</th>
<th>II CRS + HIPEC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative mortality at 90 days</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Post-operative complications</td>
<td>44% (7/16)</td>
<td>44% (7/16)</td>
<td></td>
</tr>
<tr>
<td>Abdominal complications</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Extra-abdominal complications</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Reoperations</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>Clavien-Dindo grade I–II</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Clavien-Dindo grade ≥ III</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Median hospital stay (days)</td>
<td>27.9</td>
<td>22.0</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Figure 1. DFS curves after the first and the second CRS + HIPEC.
Discussion

Management of patients with recurrence following initial CRS with HIPEC is challenging. With no established protocol, experienced peritoneal tumour centres approach recurrent disease in a variety of heterogeneous ways [8,13]. Repeat CRS with HIPEC is an option under investigation. The most relevant issues are the morbidity of a new procedure in an abdomen already treated with intra-operative chemotherapy, and the expected survival after a repeat procedure. Our data, although a limited series, show that repeat procedures are feasible with an operative risk which is no higher than that of the initial operation. Moreover, the DFS after the second procedure does not appear to be inferior to that of the first HIPEC.

Morbidity and mortality following initial CRS and HIPEC has been extensively reported in the literature. In our institution overall morbidity rate was 36.3% (117/322) with a major morbidity rate of 16.1% (52/322) out of a total of 322 procedures performed between 1996 and 2012. These data are in accordance with those reported in the literature, where mortality and morbidity rates range from 0–12% and from 12–55%, respectively [26,27].

However, there is little published literature on iterative CRS and HIPEC [12,13,17,18,28]. In our study, immediate post-operative morbidity and mortality from second CRS + HIPEC are comparable with that derived from the first intervention (p = 0.76). This result can be partially explained by the limited peritoneal disease extension (mean PCI 7.9 versus 16.2 of the first procedure) presented by most patients as a consequence of the strict selection policy for repeat HIPEC, requiring fewer peritoneal and visceral resections. Our results in terms of morbidity and mortality are in line with those obtained from other published series of iterative CRS and HIPEC [17,18]. Golse et al. reported a mortality rate of 3.3% and a grade III–IV morbidity of 40% [18].

Iterative surgery for recurrent disease has been shown to be effective for liver and lung metastases. The results after repeat HIPEC are less known. Our data, using each patient as its own control, suggest that the DFS after the second procedure is not significantly lower than that obtained with the first operation and that repeat CRS and HIPEC may be a valid option in a selected group of patients with isolated peritoneal recurrence.

Unlike other studies [17,29], our treatment strategy was uniform for all patients and included a semi-closed abdomen HIPEC with no early post-operative intraperitoneal chemotherapy. We did not routinely change the chemotherapy used during HIPEC, although it has been suggested that lack of response to a chosen intraperitoneal drug might be responsible for recurrence [17]. In the case of impaired renal function (creatinine clearances <70 ml/min), a 30% reduction of CDDP dose was made or only MMC was used.

As described by Golse et al. [18], an incomplete first cytoreduction did not preclude a complete second cytoreduction. Even if better outcomes have been reported when complete cytoreduction can be obtained at initial surgery [13], we do not consider a CC > 1 following the first intervention as a valid contraindication to iterative surgery.

Conclusions

Iterative CRS with HIPEC can be performed with acceptable morbidity and mortality rates similar to those reported following the first operation in highly selected patients with limited and isolated peritoneal recurrence. The DFS following a repeated CRS + HIPEC is comparable to that registered after the first procedure. Selection of good candidates should take into consideration the general status of the patient, co-morbidities, the extent of peritoneal recurrence, the interval between the first procedure and recurrence, and the likelihood of achieving an optimal cytoreduction.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References


