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ORIGINAL ARTICLE

Reoperation combining re-cytoreductive surgery and re-HIPEC for recurrent peritoneal carcinomatosis

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Summary

Purpose: *Cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is the proper treatment for resectable peritoneal carcinomatosis (PC). The aim of this study was to evaluate the postoperative course and long-term outcome of repeat CS (reCS) plus repeat HIPEC (reHIPEC) in patients with recurrent disease, after primary CS plus primary HIPEC.*

Methods: *From 2004 to 2012 85 patients were subjected to primary CS + HIPEC. Fourteen of those patients developed recurrent PC and were subjected to reCS+reHIPEC during the same time period. Eligibility criteria included limited extent of the peritoneal disease, and interval of more than 12 months from the primary CS+HIPEC. The origins of the tumors were ovarian cancer (n=7) colorectal cancer (n=3), pseudomyxoma peritonei (n=3), and uterine sarcoma (n=1).*

Results: *At second laparotomy, mean peritoneal cancer index (PCI) was 5.3 ± 2.8. Among the 14 procedures, HIPEC was used in all patients. The postoperative mortality was 0% and grade 3-4 postoperative complications occurred in 4 patients. The overall 1-, 2- and 3- year overall survival rate was 90, 40 and 30%, respectively.*

Conclusion: *ReCS+reHIPEC is feasible and yields an accepted survival in highly selected patients.*

Key words: cytoreductive surgery, HIPEC, peritoneal carcinomatosis

Introduction

PC is associated with poor prognosis, whichever its origin [1-3]. The treatment of PC presents unique and challenging problems to the clinical oncologist. Patients with PC, more than many other cancer patients, often suffer from severe and disabling symptoms as a direct result of total tumor burden and the disease site. The surgeon often is confronted with the challenge of controlling or palliating the locoregional abdominal progression in the absence of extra abdominal disease [4,5] In the last 15 years treatment with CS plus HIPEC, as described by Sugarbaker in carefully selected patients, offers an overall 5-year survival rate of 20-70% in patients with colorectal PC or with peritoneal pseudomyxomas, mesotheliomas or PC from ovarian cancer [6,7]. One of the most important factors in the prognosis of this patient population is the peritoneal recurrence after this aggressive treatment [8,9].

In some cases these recurrences are located only in few areas of the peritoneal cavity and in this condition a benefit from repeat CS+HIPEC is questionable.

The aim of this study was to examine the postoperative course and the long-term outcome of reCR plus reHIPEC in cases of peritoneal recurrence following primary CS and HIPEC.

Methods

During the last 8 years a new program of treatment of peritoneal surface malignancy was established in southwestern Greece in Messolongi General Hospital and from June 2009 this program was transferred to "Metaxa" Cancer Hospital in Piraeus, Greece. During this period, 85 patients with PC had been included in the program of CS and HIPEC [10,11] with excellent results. From this group of patients, 14 (16.4%) developed recurrence in the peritoneal cavity (Table 1) and were subjected to reCS plus reHIPEC. These patients were retrospectively analysed.

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Table 1. Patient and tumor characteristics in 14 cases

Characteristics	*Patients, N*	*Median*	*Range*
Age (years)	55±6	58.1	36-74
Gender (m/f)	2/14		
Primary tumor			
Colorectal cancer	3		
Ovarian cancer	7		
Pseudomyxoma peritonei	3		
Sarcoma	1		
Interval between CS+HIPEC and diagnosis of recurrence (months)	16±7.1	14	6-23
Preoperative systemic chemotherapy	14		

CR: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy, m: male, f: female

Eligibility criteria

Eligibility criteria for reCS+reHIPEC included the following:

- Good performance status.
- Peritoneal recurrence without distant spread.
- Interval >12 months between the first HIPEC and the diagnosis of recurrence.
- Limited extend of peritoneal recurrence.
- Patient signed informed consent for the repeat procedure.

All patients had a chest and abdominal CT scan. In order to rule out extra-peritoneal disease spread a PET/CT scan was carried out to confirm that the disease was restricted into the peritoneal cavity. At laparotomy, the peritoneal cavity was thoroughly explored. The extent of peritoneal recurrence was evaluated using the PCI as described by Sugarbaker [12]. The operation included complete resection of tumor recurrences in order to achieve complete cytoreduction according to the Completeness of Cytoreduction Score (CCS) as described in the literature, resulting in CCC_0 status [13]. HIPEC was performed after the end of cytoreduction and before the phase of anastomoses. Clinical parameters, intraoperative and postoperative measurements of temperature, arterial pressure, central venous pressure, biological measurements, extent of resection, duration of surgery and blood loss were recorded.

For reHIPEC we used drugs different from the primary HIPEC.

ReHIPEC regimens were:

- Intraperitoneal (i.p.) oxaliplatin (360 mg/m^2) + irinotecan (360 mg/m^2) in 2 L/m^2 dextrose 5% for colorectal recurrences (n= 3).
- Mitomycin C i.p. (10 mg/m^2) in 3.5 L/m^2 Ringers lactate for ovarian cancer recurrences (n=1).
- Mitomycin C i.p. (20 mg/m^2) + cisplatin (200 mg/m^2) in 3.5 L/m^2 Ringers lactate for ovarian cancer recurrences (n=6).
- Oxaliplatin i.p. (460 mg/m^2) in 2 L/m^2 dextrose 5% for pseudomyxoma peritonei and sarcoma patients (n= 4).

ReHIPEC was performed with the open coliseum technique as described previously [12,13], for 60 min, achieving a mean i.p. temperature of 42.5° C. Morbidity and mortality were recorded until discharge from hospital. Complications were classified according to our system described previously [14]. Patients were followed up every 3 months with serum biochemistry plus tumor markers and abdominal CT.

Table 2. Operation characteristics in 14 cases

Characteristics	*Mean*	*Median*	*Range*
Previous PCI	18.3 ± 10.4	16	4-32
Recurrent PCI	5.3 ±2.8	4	1-9
Blood loss (ml)	610 ±210	400	100-1200
Intrapreoperative blood transfusion (units)	3		
Fresh frozen plasma (units)	4		
Type of intraoperative treatment	HIPEC		
Mean operative time (min)	410 ±110	390	180-600

PCI: peritoneal carcinomatosis index, HIPEC: hyperthermic intraperitoneal chemotherapy

Results

The mean age of the 14 patients was 55 ±6 years (median 58.1, range 36-74).

The origins of the primary tumors were ovarian cancer in 7 cases, colorectal cancer in 3 cases, pseudomyxoma peritonei in 3 cases and uterine sarcoma in 1 case.

Patient and tumor characteristics are summarized in Table 1.

Systemic chemotherapy before reCR and reHIPEC had been administered to 10 patients (ovarian and colorectal cancer). The mean interval between the primary CS+HIPEC and the diagnosis of peritoneal recurrence was 16±7.1 months (median 14, range 6-23).

Operation characteristics

The results are summarized in Table 2. Ten patients underwent only peritonectomy without intestinal resections. In the remaining 4 patients 3 rectal resections, 5 small intestine resections and one partial gastrectomy were performed (Figure 1).

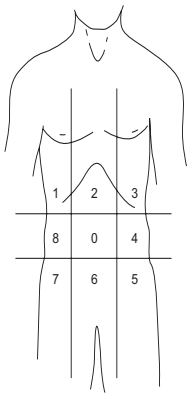
Morbidity - mortality

No patient died because of treatment. The postoperative morbidity rate was 28.5% (4 patients). Three were 3 grade IV complications (one anastomotic leakage, one pancreatic fistula and one acute respiratory distress syndrome). The patient with the anastomotic leakage required re-operation (Table 3). Median hospital stay was 13 days (range 8-64).

Survival

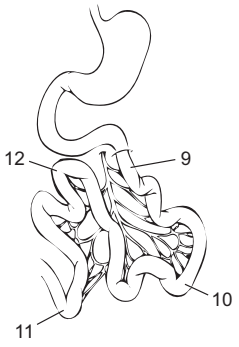
The median follow-up was 40 months (range 12-65). One-year overall survival was 90%, 2-year overall survival 40% and 3-year overall survival 30%. Three patients developed distant metastases in the liver and lungs together with re-recurrences in the abdominal cavity.

Figure 1. Intraoperative invaded areas in 14 patients, among the 13 areas defined by Sugarbaker et al [12].



Regions

	No. of patients involved	*Lesion size (LS) score (CM)*
0 Central	_4_	LS 0 No tumor seen
1 Right Upper	___	LS 1 Tumor up to 0.5
2 Epigastrium	_1_	LS 2 Tumor up to 0.5
3 Left Upper	___	LS 3 Tumor >5.0 or confluence
4 Left Flank	___	
5 Left Lower	___	
6 Pelvis	_9_	
7 Right Lower	_2_	
8 Right Flank	_2_	
9 Upper Jejunum	___	
10 Lower Jejunum	___	
11 Upper Ileum	___	
12 Lower Ileum	_6_	



	N = 10	*Median*	*Range*
Number of invaded areas	4.1±3.2	3.5	2-12
Number of resected areas	3.5±1.1	2.9	0-8
Number of anastomoses	0.6±0.9	1	0-3

Four patients developed new isolated peritoneal recurrences (2 with pseudomyxoma, 1 with ovarian and 1 with colorectal cancer). Two of them underwent a third CS+HIPEC.

Table 3. Morbidity/mortality/complications in 14 cases

	Patients, N	*%*
Postoperative mortality (in 30 days)	0	0
Postoperative mortality (in 90 days)	0	0
Morbidity	4/14	28.5
Reoperation	1/14	7.1
Abdominal complications	4/14	28.5
Respiratory complications	1/14	7.1
Hospitalization (days)	13	8-64

Discussion

Evidence that supports a combined treatment in PC has grown significantly in the last decades.

The pattern of failure after an initial optimal treatment with complete cytoreduction and perioperative intraperitoneal chemotherapy is multifactorial. Diffuse intra abdominal recurrence probably indicates failure of HIPEC to eradicate tumor cells after initial cytoreduction, and is associated with worse outcomes. The localized form of recurrence within the abdomen is the result of surgical failure to completely eliminate disease due to tumor cells entrapped in the scar tissue which is less likely to be eradicated by HIPEC. The tumor cells also are entrapped on the small bowel during initial cytoreduction since the electroevaporative surgery cannot be used in the same manner as in other anatomic locations such as parietal peritoneum, and finally decreases the possibility for complete adhesiolysis before the administration of i.p. chemotherapy during the initial CS [15,16].

In half of colon cancer patients the first recurrence is in the liver, but the tendency for intraabdominal spread, especially in rectal cancer, can be attributed to either a factor which makes tumor cells to adhere to the peritoneum favoring local seeding or that local recurrence occurs long before systemic metastasis develops [17].

In this small series of patients with peritoneal recurrence who had already undergone CS + HIPEC for peritoneal dissemination, reCS+reHIPEC resulted in a 3-year overall survival rate of 30% with acceptable morbidity and no mortality. Only few studies have been published on this topic [7-9,18].

Completeness of cytoreduction appears to be a prognostic factor for long-term survival in patients who underwent reCS+reHIPEC. After this procedure recurrence in the peritoneal cavity remained elevated, ranging between 22.6-35% in different studies [8,18]. In our study the recurrence rate was 18.1%.

Another important issue is what regimen to use during reHIPEC. It appears logical to use a different HIPEC regimen during the second procedure, but the benefit of this approach is controversial. The hypothesis that the peritoneal recurrence could be due to failure of intraperitoneal chemotherapy is only a possible factor which has to be demonstrated. This hypothesis is also supported by other authors [18].

Peritoneal recurrence occurring in patients who underwent CS+HIPEC could also be attributed to the extent of disease spread at the time of primary diagnosis. In our study the PCI was 18.3±10.4 at the time of the first procedure. The interval between the first procedure and the recurrence is an important prognostic factor and may play a role in patient selection for a second

attempt. In our study the mean interval between the first operation and the diagnosis of peritoneal recurrence was 16±7.1 months. In another study the majority of recurrences developed in a period of less than 24 months, but due to the small number of cases it is not possible to reach a clear conclusion. On the other hand, it is controversial to propose a more or less arbitrary time limit to define the meaning of early or late peritoneal recurrence following the first procedure. However, it seems that survival depends on the interval between initial treatment and the appearance of recurrent disease. For example, in PC from colon cancer the treatment of recurrence within the first year after the initial CS+HIPEC resulted in a low 5-year survival rate (<15%), in contrast to recurrences treated after 3 years (≤35%) [9]. In our study morbidity and mortality of reCS+reHIPEC were 40 and 0%, respectively. In a recent study morbidity varied from 48 to 67.6% and mortality from 4 to 9% [18]. The low complication rate observed in our study can be explained by the fact that most re-operated patients had isolated peritoneal seedings (mean PCI = 5.3 ± 2.8).

In summary, reCS+reHIPEC with drugs different from the primary HIPEC in well selected patients is a feasible procedure which prolongs overall survival.

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