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ORIGINAL ARTICLE

Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy in the treatment of rare tumors with peritoneal metastases

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Summary

Purpose: *Cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal intraoperative chemotherapy (HIPEC) is the standard treatment for tumors presented with peritoneal metastases (PM). Data in the literature about the treatment of rare tumors with PM are limited and of low-quality. The aim of the study was to assess the outcome and safety of CRS and HIPEC for these tumors.*

Methods: *Patients with rare tumors with PM that underwent CRS and HIPEC between 2005-2018, were retrospectively analyzed. Clinical and histopathological variables were correlated to survival.*

Results: *43 patients, mean age 55.7 ± 12.9 years, underwent 48 cytoreductions. The most frequent histopathologic type was sarcomatosis (31.3%). The majority of the patients (70.8%) had limited extent of peritoneal disease. Complete or near-complete cytoreduction was achieved in 83.3% of the cases. Severe morbidity was recorded in 12.6%. The median disease-free survival and overall survival were 11 and 63 months, respectively. Although the completeness of cytoreduction was found to be significantly related to survival, the extent of peritoneal carcinomatosis was the single prognostic factor.*

Conclusions: *CRS followed by HIPEC is an effective and safe method in the treatment of rare tumors with PM. Further large, well-designed prospective studies are needed to validate these results.*

Key words: *HIPEC, morbidity, rare tumors, survival*

Introduction

In 1980 John Spratt performed the first cytoreduction combined with HIPEC [1]. Over the next few years, a number of clinical variables were identified that made possible the prediction of the prognosis of patients with peritoneal malignancy of gastrointestinal tumors. Researches in Washington Hospital Center in USA and in a few centers in Europe made important contributions in the identification of the basic criteria for proper patient selection, which could undergo major cytoreduction in combination with HIPEC with significant survival benefit and acceptable morbidity and hospital mortality [2-4]. During the following years CRS and HIPEC were considered the standard treatment for colorectal cancer with peritoneal carcinomatosis, pseudomyxoma peritonei, and peritoneal mesothelioma [5-7]. Moreover, CRS plus HIPEC were also used in gastric and ovarian cancer with promising results [8]. In 2018, one prospective randomized study showed that CRS+HIPEC offered significant survival benefit in women with advanced epithelial ovarian cancer [9].

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However, there is little evidence about the efficacy of CRS and HIPEC in the treatment of rare tumors with PM, that may arise from the pancreas or the corpus uteri, etc. The aim of the study was to identify the efficacy and safety of CRS and HIPEC in the treatment of rare tumors with PM, by analyzing the survival, morbidity and mortality rates.

Methods

The records of the patients with rare tumors and PM that underwent CRS and HIPEC from 2005 until 2018 by one surgical team were retrospectively reviewed. The diagnosis was established by biopsies from the tumors or was based on previous histopathological report. The inclusion criteria for patients undergoing CRS+HIPEC were; age>16 and <80 years, no distant metastatic disease, normal hematological profile, blood urea level <50 mg/dl, creatinine level <1.5mg/dl, and normal hepatic examinations (except for biliary obstruction). Pregnant women, patients with psychiatric disease or addiction, with poor performance status (<50% according to Karnofsky performance scale), with previous history of neoplastic disease at risk for recurrence (except for basal cell carcinoma, or *in situ* cervix carcinoma properly treated) and with obvious distant unresectable metastatic lesions were excluded from this study.

The performance status was assessed by the Karnofsky performance scale. The extent of previous surgery was assessed using the Prior Surgical Score (PSS) [10] and the extent of tumor dissemination by the Peritoneal Cancer Index (PCI) [11]. The completeness of cytoreduction was assessed after the completion of the operation with the use of CC-score. CC-0 indicated no macroscopic residual disease, CC-1 residual disease <2.5mm, CC-2 residual disease 2.5mm and 25mm and CC-3 residual disease >25mm. Complete cytoreduction was defined as CC-0, and near-complete cytoreduction as CC-1 surgery [11]. The Ethical Committees of the Hospitals approved the protocol and all patients signed an informed consent form.

A vertical mid-line incision extending from the xiphoid process to the symphysis pubis was always used for maximal abdominal exploration. After lysis of the adhesions the PCI score was calculated. Standard peritonectomy procedures [12] and all the required visceral resections were performed in order to achieve complete or near complete cytoreduction. After the resection of the tumor burden and before the reconstruction of the gastrointestinal tract HIPEC was performed. The Coliseum technique [12] was possible at 42.5-43°C for 90 min when Cisplatin, Mitomycin-C and Doxorubicin were used and for 60 min when Gemcitabine or Melphalan were used. HIPEC was performed via a circuit of 4 drains (2 inflow and 2 outflow) that were connected to an extracorporeal sterile circuit in which a 3-liter perfusate was circulated by two peristaltic pumps (one inflow and one outflow) at a flow rate of 2 lit/min. The sterile circuit was heated by a thermal exchanger connected to the heating circuit.

Postoperative complications (30 days from surgery) were documented using Clavien-Dindo classification system and all grades 2b complications were considered as severe. The patients were followed up every 4 months during the first year from surgery and then every 6 months. Each appointment included physical examination, hematological-biochemical lab tests, tumor markers (CEA, CA-125) and abdominal CT scans. The recurrences and the sites of recurrence were recorded. The data in this study were reported according the PROCESS criteria for case series [13].

Statistics

Statistical analyses were made using the SPSS package. The proportions of patients with a given characteristic were compared by chi-square test or by Pearson's test. Differences in the means of continuous measurements were tested by the Student's *t*-test. The survival curves were obtained using the Kaplan-Meier method, and the comparison of curves was calculated using the log-rank test. Cox regression analysis made possible multiple analyses of survival. A two-tailed p value <0.05 was considered statistically significant.

Table 1. Patient characteristics

Patient characteristics	*n (%)*
Age (years)	
Mean	55.7 ± 12.9
Range	27 – 80
Gender	
Female	32 (74.4)
Male	11 (25.6)
Histology	
Sarcomatosis	15 (31.3)
Endometrial	11 (22.9)
Pancreatic	7 (14.6)
Cholangiocarcinoma	6 (12.5)
Ovarian Carcinosarcoma	5 (10.4)
Yolk sac	2 (4.2)
Unknown primary	2 (4.2)
PSS	
0	5 (11)
1	5 (11)
2	26 (56.5)
3	10 (21.5)
PCI	
0 - 13	33 (71.7)
14 - 20	7 (15.2)
21 - 39	6 (13.7)
CC	
CC-0	35 (72.9)
CC-1	5 (10.4)
CC-2	2 (4.2)
CC-3	6

Results

From 2005 until 2018, 43 patients underwent 48 CRS followed by HIPEC for tumors that rarely are associated with PM. These consisted 5.7% out of 837 CRS+ HIPEC that were performed in the same period. One patient underwent three cytoreductions. The mean age of the patients was 55.7±12.9 (27-80) years old. There were 32 women (74.4%), and 11 (25.6%) men. Histopathologically, the majority of the cases were peritoneal sarcomatosis (31.3%), followed by peritoneal carcinomatosis from endometrial cancer (22.9%), pancreatic cancer (14.6%), cholangiocarcinoma (12.5%), ovarian carcinosarcomas (10.4%), yolk sac tumors (4.2%), and of an unknown primary site (4.2%). The clinical and histopathological details are listed in Table 1. The median hospital stay was 14 days. Severe morbidity was recorded in 6 cases (13.7%). There were 3 enterocutaneous fistulas, 1 anastomotic failure, 1 abdominal abscess, and 1 acute hepatic failure. One patient (2.2%) died within the first 30 days. The median follow-up was 63 months. During this time, 29 patients (60.4%) were recorded with recurrence. The sites of recurrence were distant in 11 cases (15.3%), and loco-regional in 18 cases (25%).

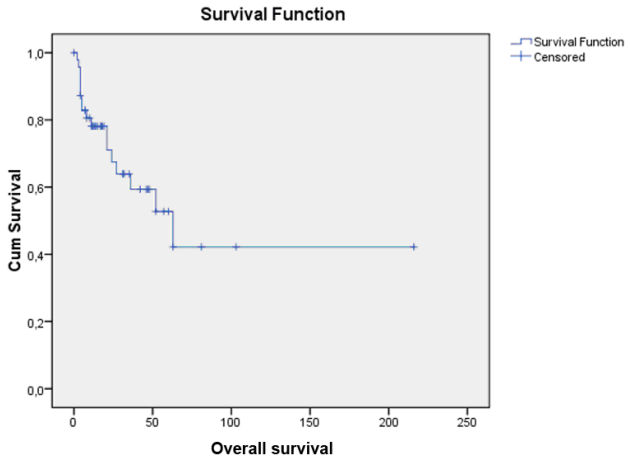

Figure 1. Survival analysis.

Table 2. Overall survival (Cox regression)

	Univariate model		*Multivariate model*	
	p value	*HR*	*95% CI*	*p value*
Age (years)	0.414			
Sex	0.245			
PSS	0.046			
PCI	< 0.001	10.251	1.399, 4.037	0.001
CC	0.06			
Morbidity	< 0.001			

The median disease-free survival (DFS) and overall survival (OS) was 11 and 63 months, respectively. The 5- and 10-year overall survival rate was 42% (Figure 1).

Univariate analysis revealed that the extent of peritoneal dissemination, the completeness of cytoreduction, the extent of previous surgery, and the morbidity were related to survival ($p<0.05$). The extent of peritoneal dissemination was the single prognostic variable of survival (Table 2).

Discussion

CRS in combination with HIPEC is the standard treatment of pseudomyxoma peritonei and peritoneal mesothelioma [5,6]. Recently, the role of HIPEC in colorectal cancer with PM has been debated by PRODIGE 7, a French multi-institutional prospective randomized trial [14]. The role of HIPEC in colorectal cancer is currently under re-investigation in a number of ongoing prospective randomized trials. One prospective randomized trial showed that HIPEC as upfront treatment offered significant survival benefit in women with locally advanced epithelial ovarian cancer [9]. Similar ongoing trials are expected to validate the role of HIPEC as upfront treatment in ovarian cancer.

There are a few insufficient data about the role of CRS and HIPEC for rare tumors with PM based on low quality retrospective studies or case reports. As a consequence, there is not sufficient evidence about the efficacy of CRS and HIPEC in rare tumors with PM [15]. A few studies have shown that advanced age should not be an exclusion criterion for patients capable to undergo CRS+HIPEC [15,16]. Patients over 70 years were included in the present study and underwent successfully CRS+HIPEC.

The extent of previous surgery is a significant variable of survival for ovarian cancer [17], or sarcomatosis, or even peritoneal mesothelioma [18]. Extensive previous surgery implies that a new surgical intervention is rather a difficult and long-acting procedure which means that these patients are at high-risk to develop severe complications. Although the majority of patients in our study were assessed as PSS-2, and PSS-3, only 13.7% of them were recorded with severe morbidity, probably because all underwent surgery by the same surgical team. Most studies in the international literature have shown that severe morbidity is usually around 20% [15-17] with a 30-day in-hospital mortality no more than 3% [2,4,15-17]. Severe morbidity has been identified to be significantly related to survival because it extends the hospitalization time and delays the use of systemic adjuvant chemotherapy [19].

The completeness of cytoreduction as well as the extent of peritoneal dissemination have been identified as the most significant variables of long-term survival [11,12,14]. Despite the aggressive biological behavior of the tumors included in the study, the limited extent of PM made possible the performance of complete or near complete cytoreduction in the majority of the cases with an overall 5- and 10-year survival rate of 42% which is comparable to the results of the largest multi-institutional world-wide study of PSOGI for PM of rare tumors [16]. The adequate data of previous surgery makes possible the precise assessment of PSS which is another significant variable of long-term survival [10]. In contrast to many studies which identify the completeness of cytoreduction as the most significant prognostic indicator of survival [3,5,6,8,10], the PCI was eventually identified as the single prognostic variable of survival in our study [17]. One multicentric study showed that the limited extent of PM was a prognostic indicator of survival for patients with hepatocellular carcinoma and peritoneal dissemination [20]. In contrast, the completeness of cytoreduction was a significant but not prognostic indicator of survival in another study [21]. Neo-adjuvant chemotherapy was found to be a prognostic indicator of survival in one recent multi-institutional study in patients with biliary carcinomas and PM. The same study revealed that extensive cytoreduction combined with HIPEC offered significantly better survival than systemic chemotherapy [22]. It appears that the prognostic indicators of survival have not been entirely identified in patients with rare tumors and PM. The origin of the tumor and its biological behavior are probably the factors that are related to survival [16].

The high incidence of recurrence (60.4%) was in agreement with the results of the international literature [16,17] and the sites of local-regional recurrences were more frequent than the distant. These results are comparable to those for colorectal cancer with PM [23,24]. Interestingly, the multivariate analysis of one study showed that the PCI and the CC-score were not prognostic indicators of survival either for DFS or for OS [16]. Our results are different probably because of the small number of the included patients. The difference could also be the result of the high heterogeneity of the largest study in the literature, such as different surgeons and HIPEC methods.

Last but not least, our study has the same weaknesses as the other studies in the literature, due to its retrospective nature. In the literature there is one large multicenter study [14] that was conducted retrospectively via a questionnaire, with highly selected patients, which is a significant bias in the selection of the population. Another strength of our study is the homogeneity in our data, because all patients had approximately the same intervention, meaning that they underwent CRS+HIPEC by the same experienced surgical team. The quality of our results is empowered by the fact that all patients had a long follow-up period, which led to important data about DFS and OS.

As shown above, CRS combined with HIPEC is a safe and effective method in the treatment of rare tumors with PM. Although the presented results are encouraging further large prospective and well-designed studies are needed to validate these findings.

Conflict of interests

The authors declare no conflict of interests.

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