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ORIGINAL ARTICLE

Cytoreductive Surgery in Combination with HIPEC in the Treatment of Peritoneal Sarcomatosis

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Abstract
Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is an effective treatment for peritoneal carcinomatosis, but it has been debated for peritoneal sarcomatosis. The purpose of the study is the presentation of perioperative and long-term results of CRS and hyperthermic intraoperative intraperitoneal chemotherapy in patients with peritoneal sarcomatosis. Retrospective study in a prospectively maintained database of 20 patients that underwent 29 CRS + HIPEC for peritoneal sarcomatosis. Clinical and histopathologic variables were correlated to survival. Complete cytoreduction was possible in 86.2% of the cases. The hospital mortality and morbidity rate were 0 and 20.7%, respectively. The median follow-up was 26 months, and recurrence was recorded in 20 cases (69%). The median and 5-year survival was 55 ± 13 (34–58) months and 43%, respectively. Prior surgical score (PSS) was the single variable related to survival ($p = 0.018$). The histologic subtype of the tumor was related to recurrence ($p < 0.001$). CRS and HIPEC in peritoneal sarcomatosis may offer a survival benefit in selected patients with low hospital mortality. The variety of histologic types of sarcomatosis has not made possible the identification of subgroups of patients that may be offered significant benefit by CRS and HIPEC. Further studies are required.

Keywords Peritoneal sarcomatosis · Cytoreductive surgery · HIPEC

Introduction

The most frequent sites of failure of abdominal and retroperitoneal sarcomas are the resection site, the adjacent organs, and the peritoneal surfaces, in contrast to hematogenous metastases to distant sites (liver, lungs) which are less frequent [1]. Peritoneal sarcomatosis is the result of tumor disruption or exfoliation of cancer cells from venous blood loss either preoperatively spontaneously or intraoperatively iatrogenically. Tumor emboli that disseminate at the peritoneal surfaces are entrapped in fibrin accumulation and during wound healing stimulated by growth factors give rise to tumor nodules within 2–3 years after initial surgery [2]. The prognosis of patients with primary or recurrent abdominal sarcomatosis is generally poor with a reported median survival of 6–15 months [3]. The results of debulking surgery followed by systemic chemotherapy are poor, and the recurrence rate even after complete resection is high reaching 40–60% [3–5].

CRS in combination with HIPEC has shown favorable results in patients with peritoneal carcinomatosis from appendiceal, ovarian, and colorectal carcinomas as well as from peritoneal mesothelioma [6–9]. The data about the treatment of peritoneal sarcomatosis are conflicting. There is no consensus about the benefit survival of patients with peritoneal sarcomatosis from CRS and HIPEC [10]. Treatment with tyrosine kinase inhibitors has shown that the survival of patients with gastrointestinal stromal tumors and peritoneal sarcomatosis is improved and since then, CRS with HIPEC has rarely been used [11].

The objectives of the study are the calculation of overall survival, the identification of the variables that are related to survival, and the assessment of recurrence in patients with peritoneal sarcomatosis treated by one surgical team.

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Patient Methods

The data of the patients with peritoneal sarcomatosis either at initial diagnosis or at recurrence who were treated between 2004 and 2016 were retrospectively reviewed in a prospectively maintained database.

All patients with peritoneal sarcomatosis, from 16 to 90 years of age, with acceptable performance status (Karnofsky performance scale > 50%), normal hepatic and renal function, white blood cell count > 4000, platelet count > 100,000, and absence of distant metastasis as assessed by thoracoabdominal computed tomography were included in the study. The protocol was approved by the ethical committee of the hospital, and an informed consent was obtained by all patients.

Treatments

A midline incision from the xiphoid process to symphysis pubis was always used for maximal abdominal exploration. The extent of peritoneal sarcomatosis was assessed after lysis of the adhesions using the peritoneal cancer index (PCI). Patients with nodules that had maximal diameter < 0.5 cm were indicated as low-volume, and those with nodules that had maximal diameter > 0.5 cm were indicated as large-volume. Tumor volume has been indicated to be significantly related to survival in colorectal and appendiceal cancer [12]. The extent of previous surgery was assessed using prior surgery score (PSS). Patients without any history of surgery for cancer were indicated as PSS-0. Patients who had previously undergone surgery in one abdominopelvic region or simple biopsy were indicated as PSS-1. Those patients that had undergone previous surgery in two to five regions were indicated as PSS-2 and as PSS-3 for those that had undergone surgery in more than five abdominopelvic regions [13].

Cytoreductive surgery included both visceral and parietal peritonectomies [14]. The purpose of surgery was the complete removal of the entire macroscopically visible tumor load. The quality of cytoreductive surgery was assessed using the completeness of cytoreduction score (CC score).

Hyperthermic intraperitoneal chemotherapy was possible with the open abdominal (Coliseum) technique [15]. Cisplatin (50 mg/m^2) with doxorubicin (15 mg/m^2) was used during HIPEC for 90 min at 42.5–43 °C. The reconstruction of the gastrointestinal tract was always performed after the completion of HIPEC. All patients remained in the intensive care unit for at least 24 h. A heater circulator with two roller pumps, one heat exchanger, one reservoir, an extracorporeal system of two inflow and two outflow tubes, and four thermal probes was used for HIPEC (Sun Chip, Gamida Tech, Villejuif, France). A prime solution of three lit normal saline was instilled prior to the administration of the cytostatic drug. As soon as the mean abdominal temperature exceeded 40 °C, the cytostatic drugs were administered in the abdominal cavity. During perfusion, adequate fluids were infused in addition to dopamine 3 μgr/k.b.w., in order to maintain diuresis at 500 ml/h. Dopamine was also used for 24 h after surgery at the same dose to maintain diuresis at the same levels.

All specimens were histopathologically examined in detail. Patients with GIST-induced sarcomatosis or uterine leiomyosarcomas were not included in the analysis.

The variables that were correlated to survival and recurrence were the performance status, the CC score, the extent of peritoneal sarcomatosis (PCI), the extent of previous surgery (PSS), the tumor volume, the tumor grade, and the histopathologic subtype.

Statistical Analysis

Statistical analysis was made using the SPSS (Statistical Package for Social Sciences, version 17.0). The proportions of patients with a given characteristic were compared by chi-square analysis 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. A two-tailed *p* value < 0.05 was considered statistically significant.

Results

From 2004 until 2016, 20 patients with peritoneal sarcomatosis underwent 29 cytoreductions in combination with HIPEC. There were nine males and 11 females, mean age 59.5 ± 14 years (32–87). The general characteristics of the patients are listed in Table 1.

The primary site of all leiomyosarcomas was the retroperitoneal area, except one that originated from the small bowel. In four cases, the primary site of rhabdomyosarcomas was the large bowel and in one case the pelvis after previously performed total abdominal hysterectomy for benign disease. The mean PCI was 6 (2–24). Complete cytoreduction was possible in 86.2% (25 cases). One patient underwent CC-1 surgery, another one underwent CC-2 surgery, and two patients who did not receive HIPEC underwent CC-3 surgery. The types of peritonectomy procedure and their number are listed in Table 2. The hospital mortality and morbidity rate were 0 and 20.7% (six patients), respectively. The complications were wound infection in two patients (33.3%), anastomotic failure in two patients (33.3%), central line septic condition in one patient (16.6%), and urinary tract infection in one patient (16.6%). All patients with anastomotic failure were readmitted in the operating theater and underwent surgery. Grade II, III, and IV complications according to NCI CTCAE ver4.0 were 6.9, 6.9, and 6.9%, respectively. The

Table 1 Patient characteristics

	No. of patients	%
Karnofsky performance status		
90–100%	27	93.1
70–80%	2	6.9
ASA score		
I	26	89.7
II	3	10.3
PSS score		
PSS-0	8	27.6
PSS-1	1	3.4
PSS-2	13	44.8
PSS-3	7	24.1
Tumor grade		
Low-grade tumor	3	10.3
High-grade tumor	26	89.7
Tumor volume		
Small	3	10.3
Large	26	89.7
CC score		
CC-0	25	86.2
CC-1	1	3.4
CC-2	1	3.4
CC-3	2	6.9
PCI		
PCI < 6	20	69
PCI > 6	9	31
Histopathology		
Leiomyosarcoma high-grade	4	20
Liposarcoma low-grade	2	10
Liposarcoma high-grade	5	25
Rhabdomyosarcoma	5	25
Mixed Mullerian ovarian	4	20

Table 2 Peritonectomy procedures

Peritonectomy procedure	No.
Epigastric peritonectomy	5
Right subdiaphragmatic	5
Left subdiaphragmatic	1
Greater omentectomy	11
splenectomy	3
Lesser omentectomy	6
cholecystectomy	6
Omental bursectomy	1
Right parietal	4
Left parietal	3
Pelvic peritonectomy	17
appendectomy	4
Right colectomy	5
Segmental intestinal resection	15

mean hospital stay was 13 days (6–25). During surgery, the mean blood loss was 100 ml (0–500 ml), the mean blood transfusion was 1 unit, and the mean fresh frozen plasma transfusion was 3 units.

The median follow-up time was 26 months. Recurrence was recorded in 20 cases (69%). The recurrence was locoregional in 19 cases and distant in one case. All patients with rhabdomyosarcoma were recorded with recurrence and two of them twice. Three patients with high-grade leiomyosarcoma and two patients with high-grade liposarcoma developed recurrence twice despite CC-0 surgery and one of them three times. By univariate analysis, it was found that recurrence was related to histopathology ($p < 0.001$). The low-grade liposarcoma patients have been alive disease-free for more than 5 years, in addition to mixed Mullerian ovarian patients that had the lowest rate of recurrence. All patients with high-grade disease were recommended to receive systemic chemotherapy but six of them refused it.

The median disease-free survival was 9 ± 2 (4–16) months. The median and 5-year survival were 55 ± 13 (34–58) months and 43%, respectively (Fig. 1). PSS was the single variable that was found to be related to survival ($p = 0.018$) (Table 3). The mean survival of PSS-0, PSS-1, PSS-2, and PSS-3 patients was 58 ± 9, 41 ± 8, 40 ± 9, and 8 months, respectively. Currently, seven patients are alive without evidence of disease, eight patients died because of disease progression, one patient died because of reasons unrelated to disease, and four patients are alive with disease.

Discussion

Although cytoreductive surgery in combination with HIPEC is currently considered the standard of care in patients with peritoneal carcinomatosis, its use in the treatment of peritoneal sarcomatosis has been strongly questioned [16]. Conventional treatment of peritoneal sarcomatosis with debulking surgery followed by systemic chemotherapy is associated with dismal prognosis, with an overall survival of 14–18 months [2]. Patients with peritoneal sarcomatosis have long been treated with conventional debulking surgery followed by systemic chemotherapy and/or radiotherapy. Karakousis [17] reported a median survival 23 and 9 months, respectively, for complete and incomplete resection in 72 patients. Billimoria [3] reported a median survival of 13 months in 39 patients treated with surgery only. There is no controlled randomized study with CRS and HIPEC for peritoneal sarcomatosis. In the single randomized controlled trial, Bonvalot [18] reported that the median survival of patients treated with surgery alone was 29 months, which was the same as that of patients that underwent surgery combined with early postoperative intraperitoneal chemotherapy (EPIC). However, EPIC does not seem to be equally effective to HIPEC, because heat is not

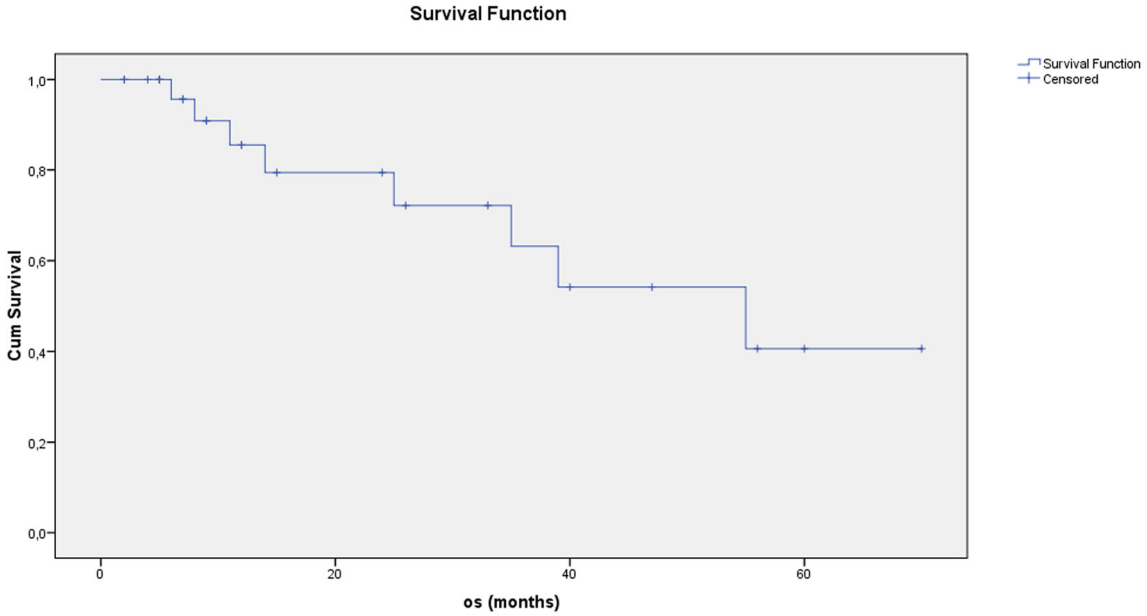

Fig. 1 Overall survival of 29 CRS+HIPEC for peritoneal sarcomatosis

included, and the cytostatic drugs are not uniformly distributed in the abdominal cavity [19].

In our study, the median and the 5-year survival were 55 months and 43%, respectively. The published data from other institutions report a median survival from 6 to 34 months and a 5-year survival rate from 5 to 45% [20, 21]. It is obvious that there is a wide range in survival that may be interpreted by the wide variety of different histologic types with different biologic behavior. PSS was the single variable that was found to be related to survival. Similar results have been reported by others [20, 22]. The explanation for this is not still possible. However, the message of this finding is that the first surgical intervention is crucial for survival.

The purpose of surgery in the treatment of peritoneal sarcomatosis is the removal of the entire macroscopically visible tumor in order to achieve complete or near complete cytoreduction. Standard peritonectomy procedures are in use for this reason [14]. The mean low PCI that was found in our study made possible CC-0 surgery in the majority of the cases, although 89.7% of the cases were high-grade. Although the extent of sarcomatosis has been reported to be a significant indicator of survival [22], it has not been reproduced in our study because in many cases with limited peritoneal extent, the recurrence rate was high despite complete cytoreduction. The completeness of cytoreduction is probably the most significant indicator for long-term survival, which also has not been reproduced in our study, because the number of patients that underwent other than CC-0 surgery was too small [11, 16, 20–22]. Despite the high incidence of complete cytoreduction, the recurrence rate has been high. The purpose of intraperitoneal chemotherapy is the eradication of the residual microscopic tumor. However, cytostatic drugs administered intraperitoneally may penetrate nodules less than 2.5–3 mm in their largest diameter. As a consequence, HIPEC is meaningless to be used after CC-2 or CC-3 operations. Therefore, we have not used HIPEC after incomplete cytoreductions. The cytostatic drugs and their dose for HIPEC differ from center to center. In our study, cisplatin combined with doxorubicin has been used always. Mitomycin-C, cis-platin, mitoxantrone, and doxorubicin have been used by others in various combinations during HIPEC without indicating which has been the most effective drug or combination of drugs [16, 23, 24]. Melphalan has been used in one prospective study and has shown considerable efficacy in a few cases of peritoneal sarcomatosis [25]. Even after complete cytoreduction and HIPEC, the incidence of recurrence has been reported to be as high as 67%, which is similar to our results [16]. In contrast, the incidence of recurrence at remote sites (lung or liver) has been reported to be significantly lower [16, 21]. The histopathologic subtype has been found to be related to recurrence in contrast to other reports [5, 22], although Baumgartner has included GIST in his report [5]. Gastrointestinal stromal tumors with peritoneal sarcomatosis

Table 3 Univariate analysis of survival

Variable	*p* value
CC score	0.859
Performance status	0.324
PSS	0.018
Tumor grade	0.182
Tumor volume	0.169
PCI	0.676
Histopathology	0.585

have been shown improved survival after tyrosine kinase inhibitor treatment. Since then, CRS with HIPEC is rarely used in these patients. In addition, patients negative to tyrosine kinase inhibitor do not show favorable response to CRS and HIPEC [11]. Probably patients with uterine leiomyosarcoma are offered the best survival benefit with CRS and HIPEC [20, 21, 26]. In our attempt to identify the subgroup of patients that shows a favorable response after CRS and HIPEC, we did not include patients with gastrointestinal tumors and uterine leiomyosarcomas. Rhabdomyosarcoma, high-grade leiomyosarcomas, and liposarcomas have been identified as the most aggressive types. The patients with low-grade liposarcoma have been disease-free for more than 5 years, and the patients with mixed Mullerian ovarian carcinosarcomas had the lowest rate of recurrence. As a consequence, it is likely that neither complete cytoreduction nor the combination of cytostatic drugs seems to influence the outcome of patients with peritoneal sarcomatosis, probably because the biologic behavior of the tumor plays a significant role in survival.

Postoperative morbidity was recorded in six patients (20.7%), and the hospital mortality was 0. The morbidity rate ranges between 9 and 50% and the mortality between 0 and 11% in recent reports [16, 20, 21]. Nevertheless, cytoreductive surgery and HIPEC for peritoneal sarcomatosis were associated with lower morbidity and mortality rates when compared with CRS and HIPEC for other malignancies in our institution [27].

Conclusions

These data show that cytoreductive surgery combined with HIPEC in peritoneal sarcomatosis may offer a survival benefit in properly selected patients with acceptable mortality rates. Because of the wide variety of different histologic subtypes, more studies are required to identify the subgroup of patients that may be offered a benefit and establish an effective and widely accepted treatment protocol.

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