SRYAHWA PUBLICATIONS

Archives of Oncology and Cancer Therapy
ISSN: 2638-5074 | Volume 4, Issue 1, 2024
https://doi.org/10.22259/2638-5074.0401003

RESEARCH ARTICLE

20-Year Experience with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Sarcomatosis

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Received: 13 February 2024 Accepted: 23 February 2024 Published: 01 March 2024

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Abstract

Background-Aims: About 80-90% of Soft Tissue Sarcomas (STS) patients develop peritoneal sarcomatosis. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been used in the treatment of peritoneal sarcomatosis but their role has not been clearly defined. The purpose of the study is the presentation of the experience in peritoneal sarcomatosis with CRS plus HIPEC and review of the literature.

Patients-Methods: All patients with peritoneal sarcomatosis treated from 2004-2024 were retrospectively reviewed. Clinical and histopathologic variables were correlated to survival, recurrence, and morbidity.

Results: Thirty-one patients, mean age 59.3±15 (24-93) years underwent 42 cytoreductive surgical operations. HIPEC was used in 33 cases. CC-0 surgery was possible in 90.6%. The 90 days hospital mortality was zero. The morbidity rate was 24.3% but severe complications were recorded in 7.3%. The 10-year survival and disease free survival rate was 78% and 76% respectively.The mean and median follow-up time was 26±27 (2-128) months, and 15 months respectively. The recurrence rate was 53.5%. The age > 65 years was identified as an independent variable of survival. No independent variable of recurrence and morbidity was identified.

Conclusion: A high proportion of patients with peritoneal sarcomatosis may undergo complete cytoreduction. It appears that some histopathologic subtypes may be offered significant benefit from CRS.The heterogeneity of histopathology, the rarity of the disease, and the high rate of recurrence do not allow us to draw definitive conclusions. Further studies are required to understand and define the proper treatment of peritoneal sarcomatosis.

Keywords: Cytoreductive Surgery, HIPEC, Peritoneal Sarcomatosis, Survival, Recurrence, Morbidity.

1. Introduction

Peritoneal sarcomatosis (PS) originates either from recurrent intra-abdominal sarcomas or may be metastatic from extremity sarcomas. The most common histopathologic subtypes that develop PS are the gastrointestinal stromal tumors (GIST), the liposarcomas, and the leiomyosarcomas [1]. The recurrence rate of soft tissue sarcomas (STS) varies from 35% to 82% after initial surgery [2]. The peritoneum is the most common site of STS recurrence in approximately 80-90% [3].

The standard treatment of PS has not yet been defined. The rarity of STSs and the large range of the histopathologic subtypes are not helpful in the performance of clinical trials that may define the most proper treatment for PS. In the contrary, the

Citation: Antonios-Apostolos Tentes, Dimitrios Kyziridis, Apostolos Kalakonas, et al. 20-Year Experience with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Sarcomatosis. Archives of Oncology and Cancer Therapy. 2024;4(1): 25-35.

classification of the subtypes of STS on the basis of molecular pathology may be proven to be helpful in standardizing the proper treatment [4, 5]. For the time being, the treatment options for PS are either the palliative debulking treatment or the aggressive and extensive cytoreduction combined with hyperthermic intraperitoneal chemotherapy (HIPEC) which appears to be potentially curative in many cases.

Cytoreductive surgery (CRS) followed by systemic chemotherapy has been used in the treatment of PS with poor results. The recurrence rate is estimated between 40-60% [6, 7, 8]. CRS with HIPEC has been used in the treatment of PS with contradictory results. The 5-year survival rate ranges from 7% to 65%, the morbidity rate from 9% to 44% and the in-hospital mortality from 0% to 11%. Therefore, CRS with HIPEC has not been recommended in the treatment of PS, unless the patients are treated in experienced centers, or have been properly selected and are included in experimental protocols [9]. The use of tyrosine kinase inhibitors (TKI) has been proved to be an effective treatment in PS from GIST and have practically eliminated the use of CRS and HIPEC in GIST originated PS [10].

The purpose of the study is the presentation of the 20-year experience of one surgical and anesthesiological team and review of the literature in order to understand whether CRS and HIPEC are beneficial as a treatment option in PS.

2. Patients - Methods

The data of patients with PS who were treated from 2004 until 2024 were retrospectively collected from a prospectively maintained data base.

Patients older than 16 years, and younger than 86, capable to undergo major surgery, with acceptable performance status (Karnofsky performance scale > 50%), without recent cardiopulmonary disease, with normal hepatic and renal function (blood urea level < 50mg/dl, creatinine level < 1.5mg/dl), with a white blood cell count > 4,000, platelets > 100,000, and absence of unresectable distant metastases were included in the study. Patients younger than 16 years and older than 86 years, with poor performance status (Karnofsky performance status < 50%), pregnant women, patients with recent history of acute cardiopulmonary disease, with abnormal hepatic and renal function (blood urea level >20mg/dl, creatinine level >1.5 mg/dl), with a white blood cell count < 4,000 and platelets <100,000, or those with unresectable distant metastases, or patients with addiction or severe psychiatric disease were excluded from the study.

The diagnosis was established by physical examination, hematologic-biochemical examinations, tumor markers (CEA, CA 19-9, CA-125), gastroscopy and colonoscopy, thoracic and abdominal CT-scan, MRI, or PET-scan and biopsy.

All patients signed an informed consent and the Ethical Committee of the Hospital approved the protocol.

3. Treatments

The extent of previous surgery was assessed according to previous official surgical report using the prior surgery score (PSS). The abdominal exploration was possible through a mid-line incision from the xiphoid process to the symphysis pubis. After lysis of the adhesions the extent of the peritoneal dissemination was calculated using the peritoneal cancer index (PCI). CRS included parietal and visceral peritonectomies. The quality of the surgical operation was assessed using the completeness of cytoreduction score (CC-score) after the completion of the resection of the macroscopically visible tumor [11]. Patients capable to tolerate chemotherapy were treated with HIPEC which was administered with the open abdominal technique (Coliseum technique). 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 (Sun Chip, Gamida Tech, Villejuif, Paris, France). A prime solution of 2-3 lit Normal Saline was instilled prior to the administration of the cytostatic drug. As soon as the mean abdominal temperature exceeded 40°C, cis-platin (50 mg/m^2) and doxorubicin (15 mg/m^2) were instilled via the device for 90 min at 42.5-43°C. Intravenous chemotherapy with Ifosfamide (1300mg/m^2) and mesna (260mg/m^2) was given in a few patients concurrently to perfusion. The reconstruction of the continuity of the gastrointestinal tract was made after the completion of HIPEC. The patients that underwent CRS and HIPEC remained in the ICU for at least 24 hours.

All resected specimens were histopathologically examined. The subtype of the primary tumor was identified and the number of the resected and positive lymph nodes was also recorded. The tumor grade and the degree of differentiation were also recorded.

The complications were recorded according to the Clavien-Dindo classification. The hospital mortality

was assessed as 90 days mortality. Re-admissions during the first 90 postoperative days were also recorded.

3.1 Follow-up

All patients were followed-up every 4 months for the first year, every 6 months until the completion of 5years, and once a year later. The follow-up included physical examination, hematologic-biochemical examinations, tumor markers (CEA, CA 19-9, CA-125), CT-scan or MRI or PET-scan, and endoscopy of the upper or lower gastrointestinal tract whenever it was needed. The recurrences and the sites of recurrence were recorded in detail.

The performance status, the ASA stage, the CC-score, the PCI, the PSS, the tumor volume, the tumor grade, the degree of differentiation, and the histopathologic subtype were correlated to overall survival, recurrence, and morbidity.

4. 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. The survival curves were obtained using the Kaplan-Meier method, and the comparison of curves was calculated using the log-rank test. The identification of the independent variables of survival was possible using Cox regression analysis. Logistic regression analysis was also used to identify the independent variables of recurrence and morbidity. A two-tailed p value < 0.05 was considered statistically significant.

5. Results

The files of 32 patients, with mean age 59.9±15 (24-93) years were retrieved. These patients underwent 43 cytoreductions. The cohort consisted of 13 men (40.6%) and 19 women (59.4%). The general characteristics of the patients are listed in Table 1.

The majority of them were in excellent performance status, had minor comorbities, large-volume and high-grade tumors, and in the past had undergone extensive surgery. All, except 4 patients underwent complete cytoreduction. Most of them underwent conventional lymph node resection. CRS plus HIPEC was undertaken in 33 cases, and 6 patients were treated with bi-directional chemotherapy (HIPEC and intravenous). The peritoneal dissemination was not largely extended for most of the patients. The mean PCI was 7±5 (2-24). Only one patient with malignant histiocytoma was identified with liver metastatic disease at the time of the initial diagnosis. The mean blood loss was 122±143 ml (100-500). The mean number of the transfused blood units and fresh frozen plasma (FFP) was 1±1 (0-2), and 2±2 (0-6) respectively.

The most frequent histopathologic subtype was leiomyosarcoma and in 2 women of them the tumor originated from the corpus uteri. One of the patients with liposarcoma was diagnosed with low-grade myxoid liposarcoma. The women with malignant mixed mullerian ovarian tumors (MMMOT), the patient with the desmoplastic small round cell tumor (DSRCT), the patients with rhabdomyosarcoma, and a few patients with leiomyosarcoma received neo-adjuvant chemotherapy. These patients were considered inoperable because of extensive peritoneal disease. Adjuvant chemotherapy was given to patients that underwent CC-1 and CC-2 surgery as well as to a few patients with CC-0 surgery and G_3 differentiation.

The morbidity rate was 24.3% (10 cases). Grade I and II complications were recorded in 17% (7 cases). Severe complications Grade IIIB were recorded in 3 cases (7.3%). All were anastomotic failures, successfully treated with re-operation under general anesthesia. One patient with sub-total pancreatoduodenectomy (Whipple procedure) was complicated with bile-leak which was successfully treated with T-tube placement proximal to the choledocho-jejunal anastomosis. The other 2 patients had anastomotic failure from colo-rectal anastomoses. Loop-ileostomy and suturing of the colo-rectal anastomoses was undertaken in both patients.

The 90-days hospital mortality was zero and no patient was re-admitted during the first 3 postoperative months. The mean number of hospitalization was 12±7 days (5-27).

Table 1. General Characteristics

	No of cases	%
Performance status		
90-100%	38	88.4
70-80%	5	11.6

ASA stage		
I	38	88.4
II	5	11.5
PSS		
PSS-0	11	25.6
PSS-1	2	4.7
PSS-2	22	51.1
PSS-3	8	18.6
Tumor volume		
Large-volume	37	86
Small-volume	6	14
CC-score		
CC-0	39	90.7
CC-1	1	2.3
CC-2	1	2.3
CC-3	2	4.7
Lymph node resection		
Extensive	7	16.3
Conventional	36	83.7
HIPEC	34	79.1
IV chemotherapy	6	14
PCI		
PCI 0-10	33	76.7
PCI 11-39	10	23.3
Tumor grade		
High-grade	41	95.3
Low-grade	2	4.7
Distant metastasis	1	2.3
Age		
<65	23	53.5
>65	20	46.5
Histology		
Leiomyosarcoma	16	37.2
Liposarcoma	9	20.9
Malignant histiocytoma	1	2.3
Rhabdomyosarcoma	3	7
Desmoplastic tumor	1	2.3
MMMOT	7	16.3
GIST	5	11.6
Degree of differentiation		
G1	3	7
G2	7	16.3
G3	33	76.7
Positive lymph nodes	3	7
Recurrence	23	53.5%
Pattern of recurrence		
Distant	6	14
Local-regional	21	48.8
Neo-adjuvant chemotherapy	16	37.2
Adjuvant chemotherapy	25	58.1
Morbidity	10	23.3
Grade I	6	14
Grade II	1	2.3
Grade IIIB	3	7
Grade IV	0	0
Grade V	0	0

Explanations: MMMOT=Mixed malignant mullerian ovarian tumors.

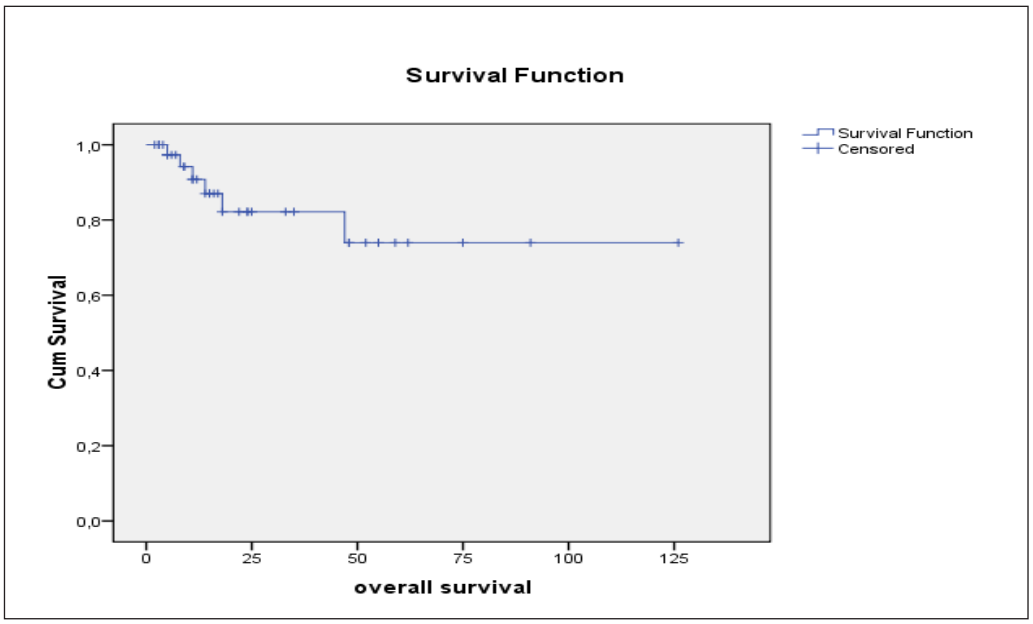

Figure 1. overall 5- and 10-year survival rate

6. Survival

The 5- and 10-year survival rate was 78% (Figure 1). The median survival was not reached. Female patients were found to have worse prognosis (p=0.041) compared to men. The histopathologic subtype (leiomyosarcomas, liposarcomas, malignant histiocytomas) (p=0.02) and the nodal involvement (p=0.048) were found to be related to survival (Table 2).Patients with rhabdomyosarcomas were recorded with the most unfavorable survival. The gender was an independent variable of survival (Table 2).No variable was found to be related to morbidity (Table 3).

Table 2. Survival Analysis

Univariate analysis		**Multivariate analysis**		
variable	P value	HR	P value	95% CI
Performance status	0.205			
ASA-stage	0.24			
PSS	0.001			
Tumor volume	0.442			
CC score	0.91			
Lymph node resection	0.605			
HIPEC	0.684			
IV chemotherapy	0.243			
gender	0.041	1.269	0.013	0.057-41161.356
Neo-adjuvant chemotherapy	0.946			
Adjuvant chemotherapy	0.338			
Histologic subtype	0.02			
Tumor grade	0.467			
Degree of differentiation	0.628			
Lymph node involvement	0.401			
Metastasis	0.707			
PCI	0.321			
Age	0.127			
Morbidity	0.336			
PSS	0.174			
Nodal status	0.048			

Table 3. Morbidity Analysis

Variable	P value
Performance status	0.19
ASA stage	0.19
PSS	0.573
Tumor volume	0.727
CC-score	0.72
Lymph node resection	0.206
HIPEC	0.063
IV chemotherapy	0.529
Distant metastases	0.066
PCI	0.183
Age	0.637
PSS	0.391
Neo-adjuvant chemotherapy	0.835
Gender	0.179
Histology	0.073
Tumor grade	0.425
Degree of differentiation	0.777
Lymph node involvement	0.315
ns	0.807

6.2 Follow-Up

The mean and median follow-up time was 26±27 (2-128) months, and 15 months respectively. During follow-up recurrence was recorded in 22 cases (52.4%). Distant metastases were recorded in 5 of them (11.9%), and local-regional in 17 (40.5%). In regard to histopathologic subtype, 7/14 leiomyosarcomas), 6/9 MMMOT, 3/3 rhabdomyosarcomas, 2/5 GIST, 1/1 DSRCT, and 3/9 liposarcomas developed recurrence. No variable was found to be related to recurrence. The extent of peritoneal disease (p=0.055) and the use of intravenous chemotherapy concurrently to perfusion (p=0.051) showed a trend to significance (Table 4). The disease free survival rate was 76% (Figure 2).The median disease free survival was not reached.

Currently, 14 (43.7%) patients are alive without evidence of disease, 10 (31.3%) are alive with recurrence, 6 patients (18.8%) died because of the disease, and 2 more patients (6.2%) died from causes unrelated to cancer. In regard to the histopathologic subtype 4 MMMOT patients, 3 GIST, 2 liposarcomas, 2 uterine leiomyosarcomas, 1 low-grade myxoid liposarcoma, 1 malignant histiocytoma, and 1 retroperitoneal leiomyosarcoma patients are alive without evidence of disease.

Table 4. Recurrence Analysis

Variable	P value
Performance status	0.52
ASA stage	0.756
Tumor volume	0.077
CC-score	0.566
Lymph node resection	0.517
HIPEC	0.541
IV chemotherapy	0.051
Morbidity	0.637
Gender	0.75
Neo-adjuvant chemotherapy	0.362

Adjuvant chemotherapy	0.697
Histology	0.6
Tumor grade	0.12
Lymph node involvement	0.667
PCI	0.055
Age	0.669
PSS	0.894
Degree of differentiation	0.109
ns	0.527

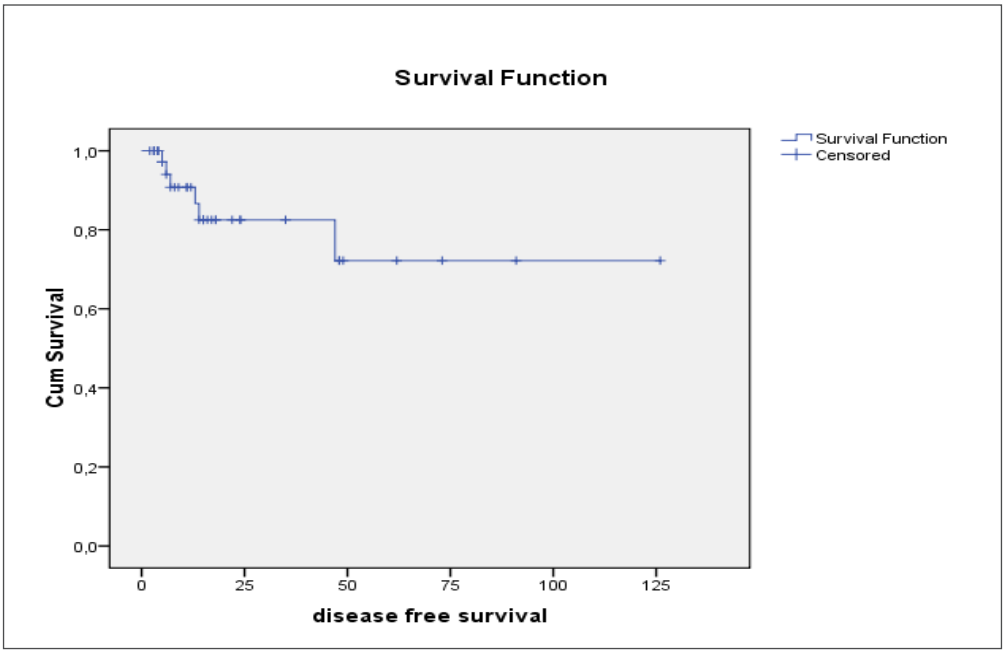

Figure 2. 5- and 10-year disease free survival rate

7. Discussion

PS has long been considered a lethal and terminal disease with poor prognosis. The most powerful tool in the treatment of localized and clinically resectable or advanced or even metastatic STSs is surgery with complete resection of all adjacent tissues and organs. So far, it has been shown to be the single potentially curative treatment option. Radiation therapy may follow surgical resection [12]. Bilimoria et al. reported that debulking surgery followed by systemic chemotherapy was associated with 13 month median survival [6]. Others reported 6-15 months median survival after palliative surgery [9, 13]. Karakousis et al. showed that complete cytoreduction is associated with 29 months median survival and incomplete cytoreduction(debulking surgery) with 6 months [14]. Similarly, Bonvalot et al. in a prospective randomized trial showed that the median survival was 29 months after complete cytoreduction combined with early postoperative intraperitoneal chemotherapy (EPIC) [15]. This was the single published randomized trial for PS treated with CRS and intraperitoneal chemotherapy. EPIC differs from HIPEC because the cytostatic drugs are not uniformly distributed at the peritoneal surfaces, and once it is performed under normal temperature (body temperature) the synergistic effect between heat and chemotherapy does not exist.

It seems that the biologic behavior of the peritoneally disseminated sarcoma is similar to the behavior of the primary tumor. The retroperitoneal sarcomas and the GIST are characterized by slow and indolent growth with a tendency to recur despite complete resection [16]. The desmoplastic small round cell tumor (DSRCT) is a chemosensitive but aggressive tumor that was described in 1989. The extra-abdominal disease, the extent of peritoneal dissemination, and the completeness of cytoreduction have been identified as possible prognostic indicators of survival for DSRCT but there is no clear evidence that HIPEC offers additional benefit [17] although Hayes-Jordan et al. found that CRS and HIPEC offered significant survival in patients with DSRCT compared to patients with other sarcomatous subtypes [18]. Lal et al. have shown that radical surgery followed by

systemic chemotherapy is the best treatment option for DSRCTS in pediatric patients. The authors believe that CRS and HIPEC are in investigation [19]. CRS and HIPEC appear to improve survival in PS from leiomyosarcoma or liposarcoma [20]. Baumgartner et al. have reported that CRS and HIPEC may improve the loco-regional disease control in PS [21]. Randle et al. have questioned the role of HIPEC, although in their study patients with GIST and uterine leiomyosarcomas have been included [22]. Bryan et al., have found that CRS and HIPEC is a favorable treatment option in sarcomatosis from GIST before these patients become unresponsive to tyrosine kinase inhibitors (TKI). Patients on TKI treatment have 7.89 years median survival while those without TKI have 1.04 years median survival [10]. Baratti et al. have reported that CRS with HIPEC is not favorable for patients with PS of GIST origin because the overall survival is similar to survival achieved by TKI therapy. In addition, they have reported that CRS and HIPEC should be further investigated for patients with uterine leiomyosarcoma [23]. All the above studies have included small numbers of patients. In general, the role of CRS appears to be beneficial but the role of HIPEC has been strongly questioned. Lim et al. have shown that HIPEC in PS is associated with significant toxicity and limited clinical benefit. The combination of cytostatic drugs does not show to offer any benefit compared to platin alone [24]. The majority of the publications include patients with various histologic subtypes. The extent of peritoneal dissemination and the completeness of cytoreduction appear to be the most consistent and significant prognostic indicators for long-term survival [2, 10, 22, 25]. In addition, Billimoria et al. [6] have identified the tumor volume as another prognostic indicator of survival, with the small-volume tumor patients having 82% 2-year survival while large-volume tumor patients only 24%. Multifocal retroperitoneal sarcomas have poor prognosis and are associated with a median survival of 13-18 months [26].

In the present study we have included all patients with PS in contrast to a previous publication [27] in which patients with GIST and uterine sarcomas were excluded. The morbidity rate was 23.3% but most of the complications were Grade I and II according to Clavien-Dindo classification. Severe morbidity (Grade IIIB) was 7%, and all these patients underwent re-operation under general anesthesia. Similar morbidity and mortality rate has been reported by others [2, 14, 25, 28] although Randle et al. have recorded 50% morbidity and zero mortality [21]. In one of the first publications with CRS and HIPEC the reported mortality was as high as 7% [25]. High morbidity with severe complications around 60% and in-hospital mortality around 20% has also been reported after palliative surgery [29]. Despite the use of bidirectional chemotherapy in 6 cases, hematologic toxicity was zero, in contrast to Lim et al. [23] who have recorded high toxicity in their study.

The rate of complete and incomplete cytoreduction was 90.1% and 7% respectively. PS may occur either preoperatively spontaneously or intraoperatively iatrogenically. Preoperative dissemination is the result of tumor penetration through the full-thickness of the bowel wall.As soon as the serosa is disrupted the cancer cells are exfoliated and seed the peritoneal cavity. The intraoperative dissemination is the result of a surgical procedure usually performed in narrow limits of resection. Cancer emboli arise from the traumatized interstitial tissues, from venous blood lost, or from the severed lymphatic network [30]. The sarcomatous implants are distinct from implants of epithelial cancer. The nodules of sarcomatosis are spherical and uniform in size. The nodules are supposed to be uniform because they grow rapidly but do not develop further spread [31].

The prognosis of PS depends upon the underlying histologic subtype [32]. The response to chemotherapy depends on histology and location of the primary tumor. The use of adjuvant or neo-adjuvant treatment is controversial [33]. Gynecologic leiomyosarcomas show different response to chemotherapy from leiomyosarcomas arising from other anatomic sites. The chemosensitivity of liposarcomas depend on the degree of differentiation [32]. Hassan et al. showed that the histologic type was the only variable predicting survival [34]. Well differentiated liposarcomas metastasize infrequently in contrast to dedifferentiated liposarcomas that are aggressive, metastasize frequently and carry dismal prognosis. In addition, myxoid liposarcomas accounting 20-30% of all the liposarcomas carry a genetic translocation that is responsible for a high rate of primary multifocal appearance and metastasize with significantly better prognosis than dedifferentiated liposarcomas [35]. In our study the 5-year overall, and the disease free survival rate have been found to be 78% and 76% respectively. Neither the extent of the peritoneal dissemination, nor the completeness of cytoreduction were identified as independent variables of survival, because probably the majority of patients had limited

extent of peritoneal disease, and only a small number of them underwent incomplete cytoreduction. The gender has been identified as a possible prognostic variable of survival which has not been reported in any other study. Neo-adjuvant chemotherapy has been used in all cases with unresectable disease. Extensive seeding of the small bowel has been the most significant drawback for resection. Patients with histologically aggressive subtypes received also neo-adjuvant treatment. All patients receiving neo-adjuvant chemotherapy responded very well and were eventually selected for surgery.A number of patients with advanced or metastatic STS are benefited from conventional chemotherapy. Patients resistant to chemotherapy may be treated by targeted therapy [36, 37]. The most potent cytostatic agents for SPS are doxorubicin alone or combined with ifosfamide and have been used for palliation. Gemcitabine with docetaxel are equally potent cytostatic agents and have also been used for reasons of palliation [38]. We have used a combination with cis-platin and doxorubicin in the HIPEC regimen with concurrent intravenous administration of ifosfamide and mesna in a few patients.

The recurrence rate was unacceptably high reaching 53.5%. The majority of failures were loco-regional and most patients underwent secondary or tertiary cytoreduction.Half of the leiomyosarcomas, all rhabdomyosarcomas, the DSRCT, and the majority of ovarian carcinosarcomas developed recurrence. The patient with malignant histiocytoma was not recorded with recurrence. A few cases of liposarcomas and GIST relapsed. No variable was found to be related to recurrence. The rate of secondary and tertiary cytoreduction was 26.2%.

The weak points of the study are the retrospective nature and the inclusion of a small number of patients

8. Conclusion

It appears that extensive CRS may be performed successfully in a large proportion of patients with PS and may be beneficial for some histopathologic subtypes that have not been clearly defined so far. The role of HIPEC in PS has not been also defined. The heterogeneity of histopathology, the rarity of the disease, and the high rate of recurrence do not allow us to draw definitive conclusions. Further studies are required to understand and define the proper treatment of PS.

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