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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Peritoneal Sarcomatosis: Is There a Subset of Patients Who May Benefit from Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy?

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ABSTRACT

Background. Unlike novel molecular-targeted therapies for metastatic gastrointestinal stromal tumors (GIST), conventional treatments for peritoneal sarcomatosis (PS) are mostly ineffective. As with carcinomatosis of epithelial origin, a rationale base supports an aggressive locoregional treatment of PS, but the use of CRS and HIPEC in this setting is still controversial. We assessed the outcome of clinically and pathologically homogeneous subsets of patients with PS uniformly treated by cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

Methods. A prospective database of 37 patients who underwent CRS and close-abdomen HIPEC with cisplatin and doxorubicin or mitomycin-C was reviewed. PS originated from GIST (pre-imatinib era) in 8 patients, uterine leiomyosarcoma (ULS) in 11, retroperitoneal liposarcoma (RPLP) in 13, and other sarcoma in 5.

Results. CRS was macroscopically complete in 28 patients (75.7%). Operative mortality was 3.7% and morbidity 21.6%. After median follow-up of 104 (range, 1–131) months, peritoneal disease progression occurred in 16 patients, distant metastases in 5, and both in 13. For all patients, median overall survival was 26.2 months; 7 patients were alive at 46–130 months (ULS, $n = 4$; RPLP, $n = 2$; GIST, $n = 1$). RPLP had the best overall survival (median, 34 months) but 100% peritoneal relapse; GIST had dismal overall, local–regional-free and distant-free survival; ULS had the higher proportion of long survivors and best local–regional-free survival.

Conclusions. Overall, results of CRS and HIPEC did not compare favorably to those of conventional therapy. In a subgroup analysis, the combined approach did not change GIST and RPLS natural history. The interesting results with ULS may warrant further investigations.

Soft tissue sarcomas (STS) are rare mesenchymal tumors, accounting for 1% of all adult solid malignancies.[1] Up to 30% of STSs arise in the abdominopelvic cavity or the retroperitoneum. Retroperitoneal and both gastrointestinal or gynecological visceral sarcoma are associated with high rates of local–regional relapse after surgical resection, due to anatomical and biological features.[1] Peritoneal sarcomatosis (PS) refers to a condition in which the intra-abdominal STS spread is the dominant clinical picture. It may occur at first presentation or more often at the final stage of disease progression, especially when the primary tumor has been ruptured spontaneously or surgically.[2,3]

Although low-grade liposarcoma may have a prolonged clinical course and survival of gastrointestinal stromal tumors (GIST) has been dramatically improved by novel molecular-targeted therapies, prognosis of PS is generally poor and conventional treatments, namely debulking/palliative surgery, systemic/intraperitoneal chemotherapy, and radiotherapy, are largely ineffective.[2–5] As with

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peritoneal carcinomatosis originating from gastrointestinal or gynecological epithelial tumors, a strong rational basis supports an aggressive locoregional treatment approach in patients with PS and no extraperitoneal disease.[6] This innovative strategy involves peritonectomy procedures and multivisceral resections to remove all of the macroscopic tumor, in combination with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) and/or early postoperative intraperitoneal chemotherapy (EPIC) to sterilize microscopic residual disease.

The combination of cytoreductive surgery and perioperative local–regional chemotherapy has been successfully used to treat peritoneal mesothelioma and carcinomatosis of appendiceal, colorectal, and ovarian origin, but its use in the setting of PS is still controversial.[7–11] Due to the rarity of these conditions, limited published data on combined treatment are available.[12–20] Furthermore, a randomized trial failed to demonstrate any survival advantage with the administration of EPIC after complete tumor resection.[18] Nevertheless, several peritoneal malignancy management centers still offer this treatment option to patients with PS. The experience at the M.D. Anderson Cancer Center has been recently published and cases of PS also have been treated during the past years by the recently established center at the Pittsburgh University.[17,19]

An appraisal of the comprehensive treatment of PS is hampered not only by the small number of cases, but also the heterogeneity in histopathologic features and biologic behavior of different STS histo-types and the variation among centers in terms of eligibility criteria, study design, and treatment modalities. Therefore, we took advantage of our relatively large institutional series treated by the same standardized protocol with minimal treatment-related bias to assess the clinical outcome of homogeneous subsets of patients with PS in an attempt to identify which STS histotypes, if any, may be suited for this aggressive treatment approach.

PATIENTS AND METHODS

All of the patients included in the present study were treated according to a protocol approved by the Institutional Ethics Committee and signed a written, informed consent form. Data for the present analysis were collected from a prospective database. Additional information was retrieved from medical charts.

Selection Criteria

PS was defined as the presence of multiple peritoneal nodules at computed tomography (CT) scan, laparoscopy, or surgical exploration. Both patients with PS synchronous to primary tumor or recurrent PS were included. Diagnosis of primary sarcoma was made or confirmed by specialized pathologists at our institution. PS was confirmed by pathological examination at the time of combined treatment. Additional eligibility criteria included: age $\leq$75 years, performance status $\leq$2 according to Eastern Cooperative Oncology Group (ECOG) score, no significant comorbidities, no extra-abdominal or hepatic metastases, and peritoneal disease amenable to potentially complete surgical cytoreduction at preoperative CT scan.[21] Patients with local recurrence at the site of primary tumor excision were excluded.

Patient Population

From January 1996 to May 2006, 37 consecutive patients with PS were treated with cytoreduction and HIPEC by the same surgical team at the National Cancer Institute, Milan, Italy. Some of these patients were reported previously.[15,22,23] Before cytoreduction and HIPEC, 29 patients underwent a median of 1 (range, 1–5) previous resective operations; 15 patient received a median of 1 (range, 1–4) systemic chemotherapy regimens, for a median of 5 (range 2–18) courses of treatment; 4 patients received radiotherapy.

For the purpose of the current analysis, patients were categorized as follows: well-differentiated/de-differentiated retroperitoneal liposarcoma (RPLP) ($n = 13$); GIST ($n = 8$), including two patients diagnosed with gastrointestinal leiomyosarcoma before c-kit testing became routine clinical practice in our institution; uterine leiomyosarcoma (ULS) ($n = 11$), including one patient with high-grade endometrial stromal sarcoma; other sarcoma ($n = 5$), namely small-cell desmoplastic sarcoma ($n = 3$), sigmoid colon mixofibrosarcoma ($n = 1$), and pelvic wall leiomyosarcoma ($n = 1$). Patient characteristics are shown in Table 1, according to primary tumor.

Operative Treatment

The peritoneal cancer index (PCI) was used to score the extent of peritoneal involvement at surgical exploration.[24] Cytoreductive surgery was based on the technique originally described by Sugarbaker, with some modifications.[6,25] Briefly, the goal of the surgical cytoreduction was to remove all visible tumor by means of diaphragmatic, parietal anterior, and pelvic peritonectomy with greater and lesser omentectomy. Depending on disease involvement, multivisceral resections were performed, including cholecystectomy, splenectomy, sigmoid, right or total colectomy, and hysterectomy with salphingo-ophorectomy in women.

TABLE 1 Patient characteristics

Variable	Category	Overall	GIST	ULS	RPLS	Other
Sex	Male	14	4	–	6	4
	Female	23	4	11	7	1
Median age	Years (range)	51 (24–74)	47 (29–68)	50 (40–73)	53 (41–74)	34 (24–54)
ECOG score	0	31	7	9	11	4
	1	4	1	–	2	1
	2	2	–	2	–	–
Presentation	Primary	10	4	3	1	2
	Recurrent	27	4	8	12	3
Previous surgery	Only biopsy	7	–	3	1	3
	1 abdominal region dissected	8	5	–	2	1
	2–5 abdominal regions dissected	22	3	8	10	1
	>5 abdominal regions dissected	–	–	–	–	–
Previous systemic CT	Done	15	4	5	2	4
	Not done	22	4	6	11	1
Previous RT	Done	4	1	3	3	–
	Not done	33	8	7	10	5
Tumor grade	1	11	2	2	7	–
	2	8	1	1	5	1
	3	18	5	8	1	4
Mean PCI	(range)	14.7 (2–34)	17.4 (3–21)	14.2 (2–34)	13.5 (2–19)	14.6 (2–22)
Interval diagnosis HIPEC	Months (range)	15 (1–106)	18 (2–56)	5 (1–44)	19 (2–106)	13 (4–47)

GIST gastrointestinal stromal tumor, *ULS* uterine leiomyosarcoma, *RPLS* retroperitoneal liposarcoma, *ECOG* Easter Cooperative Oncology Group, *CT* chemotherapy, *RT* radiotherapy, *PCI* peritoneal cancer index, *HIPEC* hyperthermic intraperitoneal chemotherapy

HIPEC was performed according to the closed-abdomen technique at 42.5°C. Perfusate volume was 4–6 l, and average flow was 700 ml per min. Drug schedule was cisplatin (25 ml/m^2/l) plus mitomycin-C (3.3 mg/m^2/l) for 60 min or cisplatin (45 ml/l) plus doxorubicin (15 mg/l) for 90 min.[26] A 30% dose reduction was applied to patients older than age 70 years or those who underwent previous chemotherapy and/or extensive cytoreductive surgical procedures. The Performer LRT® [RAND, Medolla (MO), Italy] extracorporeal circulation device was used.

Completeness of cytoreduction (CCR) was classified at the end of the surgical phase according to Sugarbaker criteria, as macroscopically complete (CCR-0); nearly complete: residual disease ≤2.5 mm in any region (CCR-1); or grossly incomplete: residual disease >2.5 mm (CCR-2) or >25 mm (CCR-3).[24] Postoperative complications occurring within 30 days of the procedure were scored according to the National Cancer Institute Common Terminology Criteria (http://ctep.cancer.gov/forms/CTCAEv3.pdf).

All resected specimens were submitted to pathological examination. Tumors were histologically categorized following the World Health Organization (WHO) classification.[27] Tumor grade was assessed in the untreated tumors, according to the 3-tiered National Federation of Centers in the Fight Against Cancer (FNCLCC) classification, based on tumor differentiation (D), mitotic index (M), and the presence of necrosis (N).[28] Well-differentiated liposarcomas were scored as grade 1 (D1, M1, N0); differentiation of the de-differentiated component was scored as D3, as in a previous paper.[29] For the purpose of the present study, tumors were scored as low/intermediate or high grade, the latter included FNCLCC grade 3 STS, and high-risk GIST.[30]

All patients underwent postoperative follow-up. Physical examination and thoracic/abdominal CT scan were performed every 3 months during the first 2 years and every 6 months thereafter. Postoperative disease progression was confirmed at surgical exploration or by CT scan/ultrasound-guided biopsy. Alternatively, it was defined according to the Response Evaluation Criteria in Solid Tumor Group (RECIST).[31]

Statistics

The study endpoints were overall survival (OS), local–regional progression-free survival (RLPFS), and distant (extraperitoneal) progression-free survival (DPFS). The study period ended on December 31, 2009. Survival rates were calculated according to the Kaplan–Meier method and compared by two-tailed log-rank test.[32] OS was dated from the day

of cytoreduction with HIPEC to the time of death because of any cause; LRPFS and DPFS were dated from the day of cytoreduction with HIPEC to the time of postoperative local or distant disease progression, respectively. Patients with uneventful postoperative course were censored at the time of last follow-up visit or at the cutoff date, whichever came first. Patients who underwent grossly incomplete surgical cytoreduction (CCR-2/3) were considered to have immediate local disease progression. The date of death was used as the date of disease progression in two patients for whom the date of progression was unknown. Factors with $P < 0.1$ by univariate analysis were entered into a Cox proportional hazard model.[33] The backward elimination method was used to determine which clinical variables best correlated to survival. All statistical analyses were conducted by SPSS software version 8.0.0 for Windows (SPSS Inc., Chicago, IL). $P < 0.05$ was considered significant.

RESULTS

The completeness of cytoreduction was rated as CC-0 in 28 patients, CC-1 in 3, CC-2 in 4, and CC-3 in 2. Operative mortality occurred in one patient (2.7%) and grade 3–4 surgical complications in eight patients (21.6%). The most common surgical morbidity was small bowel perforation ($n = 4$), followed by duodenal perforation ($n = 2$). Reoperation rate was 16.2%. Bone marrow and renal toxicity occurred in three and one patients, respectively. Overall, grade 3–4 adverse events occurred in nine patients (24.3%).

In the overall series, median Kaplan–Meier estimated potential follow-up was 104 (range, 1–131) months. Median overall survival was 26.2 months; 5-year OS was 24.3%. At the time of the present analysis, peritoneal disease progression occurred in 16 patients, distant metastases in 5, and both in 13, accounting for a median LRPFS of 12 months (17.8% at 5 years) and a median DPFS of 80 months (54.4% at 5 years). In Table 2, patient outcome is detailed according to the different primary tumors. RPLS had the best OS but 100% peritoneal relapse. GIST were associated to the worst survival rates, with LRPFS and DPFS <6 months. ULS showed the greater proportion of long survivors and the higher LRPFS. Survival curves are shown in Fig. 1.

All three patients with small cell desmoplastic tumor died after 6.5–40 months from cytoreduction and HIPEC. Disease progression involved retroperitoneal lymph nodes at 9.3 and 15 months in two of them, and both peritoneum and lung in one at 6.5 months. Sites of distant relapse were the liver ($n = 4$) and lung ($n = 1$) for GIST, bone ($n = 1$) and lung ($n = 2$) for ULS, and lung ($n = 2$) and bone ($n = 2$) for RPLS.

Univariate and multivariate analysis of potential prognostic factors is shown in Table 3. Three variables (high tumor grade, preoperative systemic chemotherapy, CCR-1/3) univariately correlated to decreased OS; male sex and use of mitomycin-C combined with cisplatin reached border-line statistical significance. Use of mitomycin-C and CCR-1/3 (with weaker significance) univariately correlated to decreased LRPFS; high tumor grade correlated to decreased DPFS. After multivariate analysis, grading retained prognostic significance for reduced OS and use of mitomycin-C reached borderline significance for reduced LRPFS.

TABLE 2 Outcome results and pattern of failure according to primary tumor

	Overall	ULS	GIST	RPLP	Other
Completeness of cytoreduction					
CCR-0	28	10	7	9	2
CCR-1	3	–	–	2	1
CCR-2/3	6	1*	1	2	2
Patient status					
NED	4	3	1	–	–
AWD	4	2	–	2	–
DOD	29	6*	7	11	5
Median overall survival (mos.)	26.2	29.5	18.2	34.0	19.7
Local progression	29	6	7	13	3
Local-free survival (mos.)	12.1	15	5.9	12.1	6.7
Distant progression	16	3	5	4	4
Distant-free survival (mos.)	80	NR	5.5	NR	15.0

GIST gastrointestinal stromal tumor, *ULS* uterine leiomyosarcoma, *RPLS* retroperitoneal liposarcoma, *CCR-0* macroscopically complete cytoreduction, *CCR-1* residual disease ≤2.5 mm in any region, *CCR-2* residual disease >2.5 mm and <25 mm, *CCR-3* residual disease >25 mm, *NED* no evidence of disease, *AWD* alive with disease, *DOD* dead of disease, *NR* not reached

* One operative death

DISCUSSION

No effective treatment for peritoneal spread from intra-abdominal non-GIST sarcoma is currently available. The goal of the present study was to investigate outcome results and pattern of failure in clinicopathologically homogeneous subsets of patients with peritoneal sarcomatosis treated by uniform protocol of cytoreduction and HIPEC. Although the single disease entities accounted for relatively small numbers of cases, interesting information was provided, which may help to rationalize the clinical management of these conditions and to plan further prospective investigations of comprehensive treatment. Our data suggest that the multimodality approach was of no benefit for PS from low-grade retroperitoneal liposarcoma and GIST and yield encouraging long-term results in patients with disseminated uterine leiomyosarcoma.

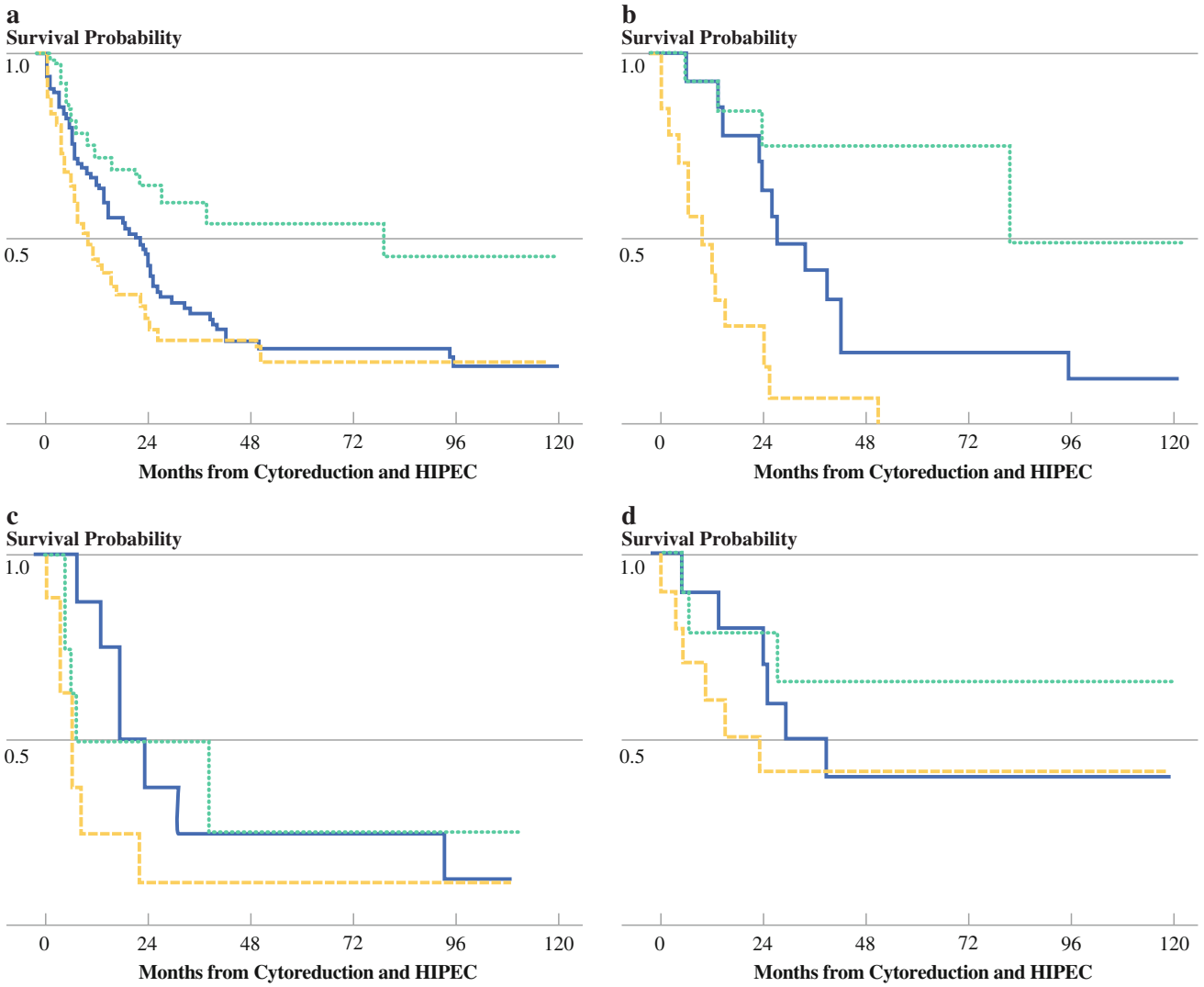

FIG. 1 Overall survival (*continue line*), local–regional progression-free survival (*dashed line*), and distant progression-free survival (*dotted line*) in the overall series (**a**), retroperitoneal liposarcoma (**b**), gastrointestinal stromal tumor (**c**), and uterine leiomyosarcoma (**d**)

To assess the role of cytoreductive surgery and HIPEC, two questions need to be addressed: what is the prognosis of PS treated with conventional therapies? Are the results of combined treatment better than those of conventional treatments? Poor literature information is available on the first issue. In all-type STSs, median survival was 23 and 6 months in 72 patients treated by Karakousis with complete or partial tumor resection, respectively[2]; it was 13 months in 51 patients treated by Billimoria with surgery alone or surgery with systemic chemotherapy and/or radiotherapy.[3] Regarding specific histo-types, survival was 12–26 months for isolated PS from gastrointestinal leiomyosarcoma/GIST, before the advent of targeted therapies.[34,35] Finally, median survival was 29 months for the control arm, which received complete CRS and no intraperitoneal chemotherapy in the French randomized trial.[18] Taken together, these data suggest that survival of PS ranges from 6 to 30 months with conventional treatments, depending primarily on optimal surgery and tumor biology.

Given the ineffectiveness of traditional treatments and the pharmacological advantages of intraperitoneal versus systemic chemotherapy administration (i.e., higher local–regional drug concentration with minimal systemic toxicity), a few authors have tested this treatment modality in combination with surgery.[12,13] In more recent years, the new concept of cytoreductive surgery combined with HIPEC has been developed by Sugarbaker. The intraoperative time setting allows optimal distribution throughout the abdominal cavity before the development of postoperative adhesions and prevents tumor cell entrapment in scar tissue, which can give contribute to disease recurrence.

TABLE 3 Univariate and multivariate survival analysis

	Overall survival			Local progression-free survival			Distant progression-free survival
	Univariate *P*	HR (95% CI)	Multivariate *P*	Univariate *P*	HR (95% CI)	Multivariate *P*	Univariate *P*
Sex (male vs. female)	0.064	0.9 (0.3–2.3)	0.794	0.204			0.858
Age (>51 vs. ≤51)	0.832			0.161			0.77
ECOG score (1–2 vs. 0)	0.277			0.51			0.872
Presentation (prim vs. rec.)	0.145			0.2			0.405
Interval diagnosis/HIPEC (>6 vs. ≤6)	0.396			0.252			0.367
Site (retroperitoneal vs. visceral)	0.747			0.297			0.188
Previous systemic CT (done vs. not done)	0.04	1.8 (0.8–3.9)	0.139	0.671			0.195
PCI (>14 vs. ≤14)	0.158			0.147			0.926
CCR (0 vs. 1–3)	0.039	1.6 (0.4–6.2)	0.475	0.051	1.1 (0.5–2.8)	0.752	0.912
Drugs (CDDP + mitomycin-C vs. CDDP + doxorubicin)	0.058	2.0 (.7–5.4)	0.154	0.033	2.3 (0.9–5.7)	0.075	0.303
Tumor grade (high vs. low/intermediate)	0.046	1.7 (1.0–2.7)	0.031	0.848			0.009

ECOG Easter Cooperative Oncology Group performance score; *HIPEC* hyperthermic intraperitoneal chemotherapy; *CT* chemotherapy; *PCI* peritoneal cancer index; *CCR-0* macroscopically complete cytoreduction; *CCR-1* residual disease ≤2.5 mm in any region; *CCR-2* residual disease >2.5 mm and <25 mm; *CCR-3* residual disease >25 mm; *CDDP* cisplatin

Additionally, mild hyperthermia has both intrinsic and synergistic effect with antiblastic drugs.[6,7]

Literature data on combined treatment are summarized in Table 4. The interpretation of results is made difficult by the variation among series, and sometimes within the same series, in terms of technique to deliver intraperitoneal chemotherapy (delayed administration, EPIC, HIPEC), drugs (cisplatin, doxorubicin, mitoxantrone, alone or in combination), completeness of surgical cytoreduction, study design (observational or randomized), and presence versus absence of liver metastases.[12–18] Furthermore, STSs consist of approximately 100 distinct pathological, biological, and clinical diagnoses, many of which may cause PS. Some authors have reported just the retroperitoneal versus visceral source of PS, and others only the site of origin, or the histological diagnosis.[14,15,17,18] Nevertheless, outcome has never been thoroughly assessed in well-defined patient populations affected by specific clinical entities, such as in the present study.

Limited survival benefit seems to be associated with combined treatment in most of the studies shown in Table 4, except for those series in which optimal cytoreduction was achieved.[15,18] The series by Berthet et al. from the Washington Cancer Institute was the first study to investigate CRS with HIPEC and/or EPIC.[14] Median survival was 20 months in the overall series of 43 patients, although only 16 patients received HIPEC, 14 received EPIC, and 13 no local–regional chemotherapy at all, due to grossly incomplete cytoreduction ($n = 8$), no PS ($n = 2$), or previous radiotherapy ($n = 3$). So far, the largest experience of multimodality treatment was collected by an Italian multi-institutional trial of 60 patients who underwent complete/nearly complete CRS and HIPEC with cisplatin and doxorubicin.[15] Median local progression-free and overall survival were 22 and 34 months, respectively, but the study also included local recurrences, which may represent an earlier disease stage. In a French trial, patients were randomized to receive either EPIC or no intraperitoneal chemotherapy after macroscopically complete cytoreduction.[18] Overall, local, and distant recurrence-free survivals were identical (29, 12.5, and 18 months, respectively). However, the use of a less aggressive normothermic approach and a statistical design intended to detect a survival difference >40% could have missed smaller survival improvements.

In the present series, patients with GIST achieved the worst survival results. All GISTs were treated before the new knowledge of molecular pathogenesis evolved into an effective therapy selectively targeting the abnormal pathways of this tumor. Before the year 2000, median survival was approximately 20 months for metastatic GISTs.[35] At present, since imatinib has become the worldwide standard of treatment for advanced/metastatic disease, median progression-free and overall survival has dramatically improved to approximately 2 and 5 years, respectively.[5] Although the development of secondary resistance still represents a major limitation and secondary surgery is

TABLE 4 Literature data on combined treatment of peritoneal sarcomatosis

Author	Patient	Residual disease	Intraperitoneal chemotherapy	Drug(s)	Median follow-up	Median survival	5-year survival	Primary tumor
Karakousis[12]	28	79% R0	Delayed	CDDP	12.6	14	7%	RPS = 18, VS = 10
Eilber[13]	35	100% R0	Delayed	mitox	18	24	46%	GIST = 34, RPS = 3
	19	1,000% R0	Delayed	mitox	20	12	5%	Uterine = 14, other = 3
Berthet[14]	43	63% <2.5 mm	HIPEC ± EPIC	CDDP ± dx	20	20	30%	GIST = 10, RPS = 16 uterine = 4, other = 13
Rossi[15]	60	100% <3 mm	HIPEC	CDDP + dx	28	34	38%	GIST = 14, RPS = 34, uterine = 12
Lim[17]	19	96% <2.5 mm	HIPEC	CDDP		17		GIST = 15, other = 4
	9		HIPEC + EPIC	CDDP + mitox		6		GIST = 2, other = 7
Bonvalot[18]	19	100% R0	EPIC	CDDP+dx	60	29	37%	RPS = 9, VS = 10
(control arm)	19	100% R0	None	–		29	37%	RPS = 6, VS = 13
Present series	37	76% R0	HIPEC	CDDP + dx/mC	104	26	24%	RPS* = 13, uterine = 11 GIST = 8, other = 5

R0 no macroscopic residual tumor, *HIPEC* hyperthermic intra-peritoneal chemotherapy, *EPIC* early postoperative chemotherapy, *CDDP* cisplatin, *mitox* mitoxantron, *dx* doxorubicin, *mC* mitomycin-C, *RPS* retroperitoneal sarcoma, *VS* visceral sarcoma, *GIST* gastrointestinal stromal tumor

* Well-differentiated/de-differentiated liposarcoma

under evaluation, it is difficult to foresee a future role for HIPEC, based on our findings.

Well-differentiated/dedifferentiated liposarcoma is the most common retroperitoneal sarcoma. The anatomic constraints of the retroperitoneal space limit the achievement of wide resection margins, resulting in higher local–regional recurrence rates and worse outcome, compared with STS at most other sites, despite their more indolent biology.[4] Systemic chemotherapy, external-beam/intraoperative radiotherapy are still investigational and recurrences are generally treated with serial debulking, although benefit reduces with subsequent failures and multifocal or disseminated abdominal spread in absence of distant metastases often represents the final stage of the disease.[1,4] Because these tumors are characterized by indolent biology, more aggressive surgical approaches to achieve local control may improve prognosis. In a recent paper, median survival was 13–100 months for recurrent RPLS, depending primarily on tumor biology.[4] It was 34 months in the present series. Although our patients with PS may represent a more advanced disease stage, the 100% rate of local–regional failure suggests that combined treatment was unable to change the natural history of the disease. A possible explanation of such poor results may be the peculiar behavior of RPLS, which spreads across retroperitoneal anatomical structures not accessible to the intraperitoneal chemotherapy, such as vessels and nerves.

Uterine leiomyosarcoma comprise approximately 4–9% of all uterine malignancies.[36] Up to 70% of patients with ULS confined to the uterus and nearly all with extrauterine disease at initial diagnosis will eventually recur, following a clinical pattern similar to epithelial ovarian tumors. Median survival of advanced or unresectable recurrent disease is less than 1 year.[36,37] The combination of gemcitabine and docetaxel has shown substantial activity in both first- and second-line therapy, with objective response rates of 28–35.8%.[38,39] Nevertheless, virtually no patient with advanced ULS can be definitively cured. In the present series, 5 of 11 patients were alive at 4–10 years after combined treatment, 2 of them with stable peritoneal recurrences for more than 2 years. In accordance with published data demonstrating that optimal surgery may provide long-term survival in selected patients with metastatic/recurrent ULS, this might support a possible role for the combined treatment approach.[40]

The results of the current study addressing potential determinants of outcome showed the correlation of tumor grade with both overall and metastasis-free survival. This is in agreement with some authors,[13,15] but not with others,[3,14,18] who argued that PS represents the most aggressive form of intra-abdominal sarcoma, irrespective of histopathological grading. Macroscopically complete cytoreduction correlated to better OS and LRPFS at

univariate analysis, presumably due to the limited HIPEC penetration into residual tumor tissue.[6,7] However, the reason why it failed to reach significance at multivariate analysis is not readily apparent. Interestingly, the combination of cisplatin and doxorubicin was the only borderline independent determinant of better local control. As a matter of fact, doxorubicin and ifosfamide, alone or in combination, represent the current frontline systemic therapy for STS.[1]

In conclusion, our findings and literature data suggest that complete cytoreduction might result in survival benefit for patients with low-grade PS, although the contribution of intraperitoneal chemotherapy is harder to ascertain. The encouraging results with uterine leiomyosarcoma may warrant further clinical investigations. The combination of cisplatin and doxorubicin seems more effective in achieving durable local control.

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