

Hyperthermic Intraperitoneal Intraoperative Chemotherapy after Cytoreductive Surgery for the Treatment of Abdominal Sarcomatosis

Clinical Outcome and Prognostic Factors in 60 Consecutive Patients

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BACKGROUND. Abdominal sarcomatosis is a rare nosologic entity with a poor prognosis. After a Phase I study on cytoreductive surgery combined with hyperthermic intraperitoneal intraoperative chemotherapy (HIIC), the authors reported the results of the treatment of 60 patients using this novel multimodal approach.

METHODS. Twenty-nine patients had multifocal primary disease and 31 patients had recurrent abdominal sarcoma. Tumor histology was represented by visceral ($n = 26$ [43%]) and retroperitoneal ($n = 34$ [57%]) sarcoma. All patients underwent cytoreductive surgery (with no or minimal residual disease) and 90-minute HIIC with doxorubicin (15.25 mg/L of perfusate) and cisplatin (43 mg/L). The clinical outcome and the prognostic value of 11 clinicopathologic variables were analyzed.

RESULTS. No postoperative deaths occurred. The morbidity rate was 33% and the moderate to severe locoregional toxicity rate was 15%. The median time to local disease progression and the median overall survival were 22 months and 34 months, respectively. Using multivariate analysis, histologic grading and completeness of surgical cytoreduction predicted patient prognosis, indicating that both local progression-free and overall survival were affected significantly by tumor aggressiveness and local disease control.

CONCLUSIONS. Although these results were encouraging, there was no definitive conclusion reached regarding the therapeutic activity of this locoregional treatment. In addition, the toxicity rate was substantial. In the absence of effective systemic agents, the therapeutic potential of cytoreductive surgery plus HIIC should be explored further in comparative trials. *Cancer* 2004;100:1943–50.

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Even without distant metastasis, patients with multifocal primary and recurrent sarcomas of the abdominal cavity have a poor prognosis.^{1–8} The proportion of patients with locoregional disease recurrence after surgical resection ranges from 35–82%, depending mainly on surgery completeness and tumor grade. In the literature, disease recurrence at the operative site and on peritoneal surfaces is a prominent cause of morbidity and mortality. Unfortunately, to our knowledge there is no evidence published to date that any adjuvant or neoadjuvant treatment (i.e., systemic chemotherapy or external beam radiation) affects the prognosis of these patients,^{9,10} partly because of the intrinsic radioresistance/chemoresistance of these tumors.^{11,12}

Therefore, an effort should be made to explore new therapeutic

modalities to improve the prognosis of these patients. The recent implementation of tyrosine kinase inhibitors (e.g., imatinib mesylate) is giving new hope to patients with locally advanced or metastatic visceral tumors originating from the stroma of the gastrointestinal tract (gastrointestinal stromal tumors [GIST]), once classified often as leiomyosarcomas of the gastrointestinal tract.⁸ On the basis of the encouraging preliminary results, this molecularly targeted therapy is being tested in the adjuvant and neoadjuvant setting, but to our knowledge no results are yet available.

With respect to systemic chemotherapy, locoregional drug delivery systems can yield high intraperitoneal drug concentrations and low systemic drug levels.^{13,14} Because the intraperitoneal route cannot guarantee adequate drug penetration into tumor deposits > 1–3 mm,^{15,16} cytoreductive surgery is the main prerequisite for intraperitoneal chemotherapy.¹⁷ Despite these premises, postoperative intraperitoneal chemotherapy has not been found to significantly improve the clinical outcome of patients with ovarian or colon carcinomatosis.^{18–22} The failure of postoperative intraperitoneal drug administration may be correlated with heterogeneous drug distribution caused by early postoperative adhesions entrapping tumor cells and protecting them from the chemotherapeutic agents.²³ In addition, some antineoplastic drugs (e.g., doxorubicin and cisplatin) act synergistically with each other^{24,25} and with heat,^{26,27} which led some authors to propose hyperthermic intraperitoneal intraoperative chemotherapy (HIIC) for the treatment of locally advanced intraabdominal malignancies.^{17,28} The results of cytoreductive surgery combined with HIIC for the treatment of gastrointestinal carcinomas have been encouraging.^{18,29–38} However, to our knowledge few formal clinical trials have been performed and the clinical series reported in the literature are heterogeneous with regard to histologic type, peritoneal involvement by the disease, extent of cytoreductive surgery, drug regimen, and HIIC features (e.g. technique, duration, and temperature). Therefore, to our knowledge there are no definitive conclusions regarding the use of cytoreductive surgery and HIIC.

Doxorubicin is considered to be one of the most active antineoplastic drugs currently available against sarcomas.³⁹ As a single drug regimen, it has been administered intraperitoneally in patients with advanced ovarian carcinoma, but patients develop high local toxicity.⁴⁰ Some studies demonstrated in preclinical models that doxorubicin activity is enhanced by the addition of cisplatin^{24,25} and/or hyperthermia.^{26,27,41} This potential synergy might be exploited to reduce the doxorubicin dosage (and thus minimize doxorubicin-related local toxicity) while still maintain-

ing the therapeutic activity of the cytotoxic regimen. Using this hypothesis, we conducted a Phase I trial in which the maximum tolerable doses of doxorubicin and cisplatin administered during HIIC were determined.⁴² Because of the favorable pharmacokinetic findings yielded in that trial, we initiated a multicentric study to evaluate the clinical outcome and analyze the prognostic factors of patients with abdominal sarcomatosis treated with this aggressive therapeutic approach. We report the clinical results of the 60 consecutive patients enrolled in the current study.

MATERIALS AND METHODS

Study Design

In our multicentric prospective study, 60 patients were enrolled by 4 Italian centers (University of Padova, National Cancer Institute of Milan, University of Turin, and Istituto Regina Elena, Rome). All institutions followed a common study protocol, which had been approved previously by the respective local ethical committees.

The main eligibility criteria were a histologically proven diagnosis of advanced (multifocal primary or local recurrent disease) intraabdominal visceral or retroperitoneal soft tissue sarcoma, tumor remnants < 3 mm after cytoreductive surgery, and the absence of distant metastasis as assessed by a thoracoabdominal computed tomography (CT)/magnetic resonance imaging (MRI) scan. In addition, informed consent form was obtained from all patients before they entered the study.

The treatment was comprised of cytoreductive surgery (with no macroscopic tumor remnants or residual tumors < 3 mm in greatest dimension) followed by HIIC with doxorubicin (15.25 mg/L of perfusate) and cisplatin (43 mg/L of perfusate).

When patients experienced disease recurrence, systemic chemotherapy and/or external beam radiotherapy was administered to the patients as indicated by the oncologist.

Cytoreductive Surgery

Tumor spread was scored at laparotomy using the peritoneal index, as described by Sugarbaker.⁴³ Briefly, the abdominal cavity was divided into 13 regions, each of which was assigned a score from 0 to 3 according to the size and extent of the tumor implants (peritoneal index range, 1–39).

Adequate cytoreductive surgery was required before patients underwent HIIC. Adequate cytoreductive surgery was defined as the tumor ablation (or electrocauterization) of all macroscopically visible disease, leaving in place no tumor residues (complete cytoreductive surgery) or tumor remnants < 3 mm in great-

TABLE 1
Locoregional Toxicity Grading System

Grade I	Abdominal pain after the 3rd postoperative day requiring analgesic drug (nonsteroidal antiinflammatory drugs) administration Ileus time \geq 3rd < 5th postoperative day
Grade II	Abdominal pain after 3rd postoperative day requiring major analgesic drug administration (morphine) Ileus time \geq 6th < 10th postoperative day
Grade III	Abdominal pain resistant to major analgesic drugs Ileus time \geq 11th < 15th postoperative day
Grade IV	Bowel leakage/perforation or persistent ileus requiring reoperation

est dimension (near complete cytoreductive surgery). When there was organ infiltration, an en bloc resection was recommended. Peritonectomy procedures⁴⁴ were performed as necessary. If bowel resections were required, anastomoses were performed after HIIC.

Hyperthermic Intraperitoneal Intraoperative Chemotherapy

The technique is described in detail elsewhere.⁴⁵ Briefly, a continuous closed circuit made of two inflow and two outflow catheters passing through the abdominal wall and operated by a roller pump was used to force the perfusate into the abdominal cavity. HIIC was performed after the laparotomy was temporarily closed (closed technique, *n* = 31 [52%]) or after a peritoneal cavity expander was used (open technique, *n* = 29 [48%]) that allows the operator to mix the perfusate and homogenize drug distribution within the abdominal space, as suggested by Fujimura et al.⁴⁶ Perfusate containing the cytotoxic drugs was heated with a heat exchanger incorporated in the perfusion system. Four thermal probes were placed inside the abdominal cavity to monitor perfusate temperature in the four abdominal quadrants throughout HIIC. Once the working temperature (> 41 °C) was reached, the drugs (doxorubicin and cisplatin) were bolus injected into the circuit and the perfusion was initiated. The drug dosages were 15.25 mg/L and 43 mg/L of perfusate, respectively, for doxorubicin and cisplatin.

Clinical Outcome Evaluation

Postoperative morbidity (surgery-related complications, locoregional and systemic toxicity) and mortality rates were recorded. Locoregional toxicity was graded according to a modified version of the Ozols et al. system⁴⁰ (Table 1). Systemic toxicity was classified using the World Health Organization scale.

Response to treatment was evaluated as local pro-

TABLE 2
Patients' (*n* = 60) Characteristics at Presentation

Characteristics	No. (%)
Gender	
Males	25
Females	35
Mean age (range)	54 (18–72 yrs)
No. of Patients who dropped out	0
Tumor histology	
GIST	14 (23)
Retroperitoneal sarcoma	34 (57)
Uterine sarcoma	12 (20)
Previous treatments	
Surgery	25 (40)
Systemic chemotherapy	15 (25)
Radiotherapy	6 (10)
Combination	6 (10)
Mean time from primary surgery (range)	21 (6–48 mos)
Mean peritoneal index (range)	7.7 (2–21)
Metastatic disease	0

GIST: gastrointestinal stromal tumors.

gression-free survival and overall survival. Local disease progression was established by CT/MRI scans performed every 4 months after HIIC. Positron emission tomography (PET) was used when CT/MRI scans did not provide firm conclusions.

Statistical Analysis

Patient data were collected and analyzed by the University of Padova. No patient was lost to follow-up. The median follow-up was 26 months (range, 9–70 months). A Kaplan–Meier survival curve was fitted to the data and tested using a log-rank test for differences between curves. The response variable was survival in months for clinicopathologic features.

Variables with the most robust statistical significance (*P* ≤ 0.2) after univariate analysis were selected to perform multivariate analysis, for which a Cox proportional hazards model was used. All statistical analyses were conducted using StatView for Windows, version 5.0 (Abacus Concept, Berkeley, CA).

RESULTS

Patient Characteristics

From 1997 to 2002, 60 consecutive patients were enrolled in the current study (Table 2). No significant differences between centers was found with regard to the characteristics of the patients. There were 25 men and 35 women with a mean age of 54 years (range, 18–72 years). Twenty-nine patients had multifocal primary disease, whereas the remaining 31 patients were referred to any of the four centers with local recurrent disease. Sarcomatosis arising from GIST, uterine sar-

coma (leiomyosarcoma [$n = 8$] and endometrial stroma sarcoma [$n = 4$]), and retroperitoneal soft tissue sarcoma were present in 14 (23%), 12 (20%), and 34 (57%) patients, respectively. In the retroperitoneal soft tissue sarcoma group, 20 patients (33%) had liposarcoma, 6 patients (10%) had malignant fibrous histiocytoma, 4 patients (7%) had malignant schwannoma, 2 patients (3%) had fibrosarcoma, and 2 patients (3%) had small round cell desmoplastic sarcoma. Using the criteria of nuclear morphology, number of mitoses, and the presence of necrosis, tumor specimens from 29 patients (48%) were classified as high-grade sarcomas and tissue specimens from 31 patients (52%) were classified as low-grade sarcomas.

Before HIIC, 52 patients (85%) had received previous treatment. Twenty-five patients (40%) had received surgery, 15 (25%) had received systemic chemotherapy, 6 (10%) had received radiotherapy, and 6 (10%) had received a combination of treatments.

Cytoreductive Surgery

At laparotomy, the mean number of abdominal regions with tumor spread was 3.2 (range, 2–7), the mean disease extension was 2.4 (range, 1–3), and the mean peritoneal index was 7.7 (range, 2–21). Cytoreductive surgery was comprised of peritonectomy (of 1–4 abdominal regions), partial holed organ resection, and partial/complete parenchymal organ resection (alone or in combination) in 47 patients (78%). Forty-one patients (68%) underwent complete cytoreductive surgery (no macroscopically evident tumor remnants) and 19 patients (32%) underwent near complete tumor cytoreduction (tumor residuals < 3 mm in greatest dimension).

Hyperthermic Intraperitoneal Intraoperative Chemotherapy

All patients underwent 90-minute HIIC. The mean perfusate temperature and flow were 41.4 °C (range, 41.0–42.1 °C) and 850 mL/min (range, 700–1100 mL/min), respectively. The mean doxorubicin and cisplatin dosages were 69 mg (range, 53–91 mg) and 197 mg (range, 150–258 mg), respectively, depending on the perfusate volume. Considering both HIIC and cytoreductive surgery, the mean duration of surgery was 7.2 hours (range, 5.9–11 hours).

Morbidity and Mortality

No postoperative deaths occurred. Surgical complications were recorded in 14 patients (23%) and were comprised of 8 anastomotic leaks, 4 intraabdominal abscesses, 5 hemoperitoneums, and 2 pancreatic fistulae. Grade I, II, III, and IV locoregional toxicity was observed in 36 patients, 6 patients, 2 patients, and 1

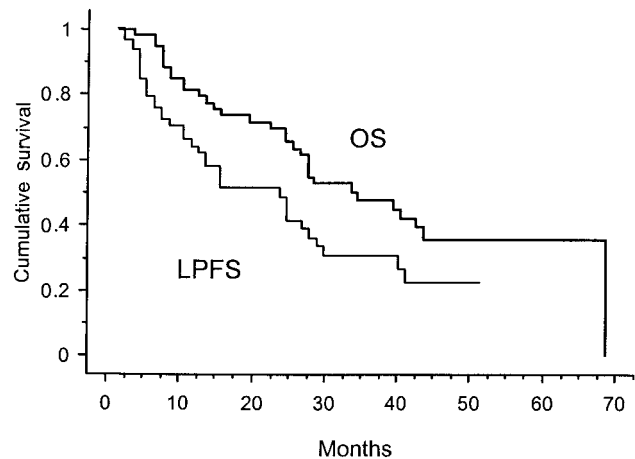


FIGURE 1. Overall survival (OS) and local progression-free survival (LPFS) analysis of 60 patients who underwent cytoreductive surgery combined with hyperthermic intraperitoneal intraoperative chemotherapy for intraabdominal sarcomatosis.

patient, respectively. Systemic toxicity occurred in two patients who had Grade 2 myelosuppression (leukopenia) and in four patients who had Grade 2 renal failure. With regard to the surgical complications and the moderate to severe (Grade ≥ 2) locoregional and systemic toxicity, the morbidity rate was 33% ($n = 20$). The mean hospital stay for all patients was 12 days (range, 9–51 days).

Survival Analysis

After a median follow-up of 28 months (range, 9–70 months), 32 patients (53%) had died of disease (19 of whom developed locoregional tumor recurrence only and 11 of whom developed locoregional and distant tumor recurrence), 12 (20%) were alive with disease (8 with locoregional disease only and 4 with locoregional and distant disease), and 16 (27%) were alive without evidence of disease. For two patients with inconclusive CT/MRI scans, locoregional disease recurrence was confirmed by PET evaluation.

Overall and local progression-free survival are shown in Figure 1. The estimated median overall survival was 36 months and the median time to local disease recurrence was 24 months.

Eleven clinicopathologic variables that could potentially influence patient survival were analyzed. Of these, histologic grading (high vs. low grade) and the type of cytoreduction (complete cytoreduction vs. near complete cytoreduction) were the only variables that were found to predict both overall and local progression-free survival on multivariate analysis (Table 3).

TABLE 3
Influence of 11 Prognostic Factors on Overall and Local Progression-Free Survival in 60 Patients with Abdominal Sarcomatosis Who Underwent Cytoreductive Surgery and HIIC^a

Characteristics	Overall survival		Local progression-free survival	
	Univariate	Multivariate	Univariate	Multivariate
Age (< 50/≥ 50 yrs)	> 0.2	—	> 0.2	—
Gender (M/F)	> 0.2	—	> 0.2	—
Previous treatment (yes/no)	> 0.2	—	> 0.2	—
Post-HIIC treatment (yes/no)	> 0.2	—	> 0.2	—
Histology (liposarcoma/GIST/other)	> 0.2	—	> 0.2	—
Grading (high/low)	0.01	0.03	0.02	0.03
Peritoneal index (≤ 6/> 6)	> 0.2	—	> 0.2	—
Presentation (primary/recurrence)	0.15	NS	0.08	NS
Surgery (CCS/NCCS)	0.02	0.04	0.02	0.02
Temperature (≤ 41.3/> 41.3 °C)	> 0.2	—	0.18	NS
DXR dose (≤ 60/> 60 mg)	0.06	NS	0.13	NS

HIIC: hyperthermic intraperitoneal intraoperative chemotherapy; M: male; F: female; GIST: gastrointestinal stromal tumors; NS: not significant ($P \geq 0.05$); CCS: complete cytoreductive surgery; NCCS: near complete cytoreductive surgery; DXR: doxorubicin.

^a Factors characterized by $P \leq 0.2$ at univariate analysis were selected to perform the multivariate analysis.

DISCUSSION

Patients with abdominal sarcomatosis (multifocal primary or recurrent sarcoma) are at a high risk of developing disease progression and their natural history is usually characterized by a poor prognosis.¹ To our knowledge, no current therapy has been proven to prolong local progression-free survival or overall survival. The rarity of abdominal sarcomatosis is the main reason for the lack of comparative studies, which in turn explains the absence of standardized guidelines in the treatment of these patients. Although investigators are encouraged by the clinical administration of tyrosine kinase inhibitors for the treatment of GIST, larger studies and longer follow-up times are warranted to prove the efficacy of this molecularly targeted therapeutic approach.⁸ Furthermore, in addition to GIST or other rare sarcomas (e.g., dermatofibrosarcoma protuberans), patients with soft tissue sarcomas have not been shown to receive any benefit from tyrosine kinase inhibitor therapy, even if those tumors are *c-kit* positive.

For other histologic tumor types, only complete surgical excision of the tumor mass had been reported to improve a patient's prognosis.²⁻⁷ Adjuvant treatments are needed to improve the results obtained with surgery alone. However, neither systemic chemotherapy nor external beam radiation appear to meet the expectations. Novel approaches, such as intraoperative radiotherapy, preoperative external beam radiotherapy combined with postoperative brachytherapy, and photodynamic therapy, have been proposed to ameliorate the life expectancy of these patients, but

to our knowledge there are not enough clinical data from which to draw any definitive conclusions.⁴⁷⁻⁵¹

HIIC has been used mainly to treat the intraperitoneal spread of gastrointestinal/ovarian carcinoma^{38,45,52} and peritoneal mesothelioma.^{53,54} In our Phase I study of doxorubicin/cisplatin-based HIIC,⁴² we used this multimodality approach to treat patients with abdominal sarcomatosis. In the absence of evidence demonstrating the effectiveness of any other treatment, we believed that HIIC possessed the appropriate pharmacokinetic features to be potentially of benefit for these patients. To our knowledge, this is the largest series of patients treated with HIIC for abdominal sarcomatosis reported to date. We believe the only published study to investigate the same therapeutic approach was performed by Berthet et al.⁵ In that study, 43 patients were enrolled, but only 16 underwent HIIC.

In the current study, postoperative complications (23%), locoregional toxicity (15%), and overall morbidity (33%) rates were comparable with those observed by other investigators in similar studies in which patients with other malignancies received cytoreductive surgery plus HIIC.^{45,55,56} Because this toxicity rate is substantial, this therapeutic modality should be limited to investigational studies. In contrast with the findings of other authors,^{1,3,8,57} univariate analysis of prognostic factors demonstrated that the extent of tumor spread and the type of presentation (i.e., primary vs. recurrent disease) were not predictive of survival (Table 3). These results might be explained by the relatively small sample of patients in the current study

or by the antineoplastic effect of HIIC, which might have minimized the differences reported in other studies in which HIIC was not included in the therapeutic regimen. Finally, tumor burden, which is a significant prognostic factor in the experience reported by Berthet et al.,⁵ might not have affected survival in the current series because we enrolled only patients with cytoreducible disease, thus excluding subjects with a larger tumor burden.

Multivariate analysis confirmed the pivotal role played by surgery in the control of the disease by demonstrating a significant advantage for the patients who received complete versus near complete cytoreduction. Moreover, the importance of the intrinsic aggressiveness of tumors was underscored by the different prognosis of high-grade versus low-grade malignancies (Table 3).

Despite the heterogeneity of the histologic tumor types encompassed by this nosologic entity, the clinical course of patients with sarcomatosis is similar.^{1,58} However, this heterogeneity might lead to an underestimation of the antineoplastic activity of HIIC, which might be clouded by the intrinsic differences in the drug sensitivity proper of each tumor type group (i.e., GIST vs. retroperitoneal sarcomas vs. uterine sarcomas). It is also difficult to compare survival findings with those observed in patients treated with other therapeutic approaches. In fact, the studies reported in the literature are heterogeneous in terms of disease stage at the time of presentation, previous treatments, and treatments at the time of disease recurrence. For instance, in the current series, most patients had unsuccessfully undergone one or more standard treatments before HIIC, whereas other authors report the results of first-line treatments.^{59,60} In some series, all or most patients had primary tumors only,⁵⁹⁻⁶¹ whereas we only report the results for patients with locally advanced (multifocal/recurrent) disease. The results of what to our knowledge is the only trial of HIIC for patients with sarcomatosis⁵ is not comparable with the results of the current study because of the heterogeneity of the treatments performed (i.e., HIIC, early postoperative intraperitoneal chemotherapy, and a combination thereof). Finally, most investigators have reported on single tumor type series (GIST, retroperitoneal sarcomas, or uterine sarcomas).

Although we are aware that the comparison of the current study results with those from other series^{3,8,61-63} can be undermined by selection bias, we found that the median time to local disease progression and the median overall survival (24 months and 36 months vs. 12-24 months and 24-28 months, respectively) in the current study were encouraging. In a study of the prognostic factors of patients with sarco-

matosis, Bilimoria et al.¹ found that the extent of disease drastically affected overall survival, in particular in patients with high-volume sarcomatosis, who demonstrated a median survival time of 12 months. Although we did not adopt the same method for assessing disease volume, the mean peritoneal index observed in the current trial (i.e., 7.7) indicates that a large volume of tumor was present in most of our patients. Confirming other the findings of other studies,^{2,8,9} we observed that the type of surgery affected both the local progression-free survival and overall survival of patients with locally advanced intraabdominal sarcomas. This suggests that local disease control is a major determinant of the natural history of this condition, thus supporting the development of locoregional treatments. Although we did not demonstrate that doxorubicin/cisplatin-based HIIC has any significant advantage compared with standard treatments for abdominal sarcomatosis, we believe that, in the absence of effective systemic agents, the therapeutic potential of this locoregional drug delivery system should be explored further in comparative trials to sterilize minimal tumor residuals left in place after surgery. One strategy to enhance the antineoplastic potential of HIIC might be to increase the drug penetration into tumor remnants during HIIC by using novel tumor-targeted drug formulations such as liposomes⁶⁴ or thermal-sensitive liposomes.⁶⁵ Liposomal doxorubicin is already commercially available⁶⁶ and preclinical studies currently are underway in our laboratory to provide a robust rationale for its implementation in an HIIC-based clinical protocol. Because the Gompertzian kinetics limit the effect of single-shot intraperitoneal chemotherapy, the multimodal approach with very aggressive cytoreductive surgery, hyperthermia, and novel cytotoxic agents might address this issue. With this in mind, the combination of conventional chemotherapeutic agents with biologic response modifiers such as tumor necrosis factor- α , which is known to be highly active against soft tissue sarcomas of the extremities,⁶⁷ has been tested in a human model of HIIC.⁶⁸

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