The Consensus Statement on the Locoregional Treatment of Abdominal Sarcomatosis

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Abdominal sarcomatosis (AS) is a rare condition characterized by soft tissue sarcoma spreading throughout the abdomen, in the absence of extra-abdominal dissemination. Retroperitoneal sarcomas, pelvic sarcomas, particularly uterine leiomyosarcoma, and gastrointestinal stromal tumors (GISTs) most frequently give rise to AS. Systemic chemotherapy is the standard of care for AS from non-GIST sarcomas, but with an essentially palliative aim and major limitations. Innovative targeted therapies has deeply affected the natural history of GIST, at least in prolonging survival in responsive patients. In this context, the notion that abdominal spread in the lack of extra-peritoneal lesions may typically occur in a number of patients, along with the dismal prognosis generally carried by AS, has prompted a few centers to perform cytoreductive surgery and perioperative intraperitoneal chemotherapy. To date, the rarity of these presentations makes it difficult to evaluate the clinical results and the role of combined local-regional treatment is still a matter of debate. This article presents the results of a group of experts from around the World trying to achieve a consensus statement in AS comprehensive management. A questionnaire was placed on the website of the 5th International Workshop on Peritoneal Surface Malignancy and the experts voted via internet.


INTRODUCTION

Abdominal sarcomatosis (AS) may be defined as the spread of a soft tissue sarcoma throughout the abdomen, in the absence of any extra-abdominal dissemination, or at least other sites of disease of major clinical concern. This gives rise to presentations in which the abdominal spread of disease is the dominating clinical factor, thus the main therapeutic challenge [1]. The perspective may be palliative or curative, the former situation being more frequent than latter.

Retroperitoneal soft tissue sarcomas are the most frequent sarcomas to give rise to disseminated abdominal disease [2]. Indeed, the local regional risk of a retroperitoneal sarcoma may well be in the 70% range in the long term. Liposarcomas are especially at risk, given their inherent anatomic characteristics (average tumor size, multinodularity or even multilocularity, etc.) and their tendency to remain confined to the abdomen in many cases throughout their natural history. Even pelvic tumors may result in peritoneal sarcomatosis, such as a uterine leiomyosarcoma relapsing with scattered tumor masses throughout the abdomen. Gastrointestinal stromal tumors (GISTs) essentially metastasize to two sites, peritoneum and the liver, the former in the lack of the latter in a number of patients. Other rare mesenchymal entities may metastasize throughout the abdomen, such as the desmoplastic small round cell abdominal tumor of young adults or adolescents, typically spreading with multiple tumor nodules over the peritoneal surface. All these tumors are rare. Their abdominal spread in the lack of lesions outside is even less frequent, though it may typically occur, indeed, in a number of patients. Finally, the prognosis of AS is generally dismal, although liposarcomas may run a slow course, and GIST are now amenable to effective medical therapies which at least prolong significantly survival.

Medical Therapies

Disseminated disease spreading throughout the abdomen makes the patient metastatic, and thus a candidate for medical therapies by definition. At the moment, chemotherapy of adult soft tissue sarcomas is based on anthracyclines and Ifosfamide, given either alone or in combination (Type 1 evidence). The response rate is in the 20–40% range, and median survival is in the 1-year range. Gemcitabine plus/minus Docetaxel may exert a palliative effect especially in leiomyosarcoma (Type 3 evidence). The new marine agent Trabectedin (ET-743) is active in liposarcoma and leiomyosarcoma, that is, the two main retroperitoneal mesenchymal entities, with an exceedingly high activity in myxoid liposarcoma, which however is rare in the retroperitoneum (but an abdominal widespread extent of disease, even in the lack of lesions elsewhere, may occur following a primary tumor in a limb; Type 3 evidence). Imatinib is exceedingly effective in GIST, with a progression-free interval and an overall survival, respectively, in the 2-year and 5-year range if the disease is metastatic. Surgery of residual disease is often carried out following optimal response of GIST to Imatinib, though, possibly, peritoneal lesions may benefit less than liver metastases from such an approach, which in any case remains investigational (Type R basis evidence). Medical therapy is active, but generally of limited prognostic meaning, in desmoplastic small round cell abdominal tumor. Therefore, medical therapies have some activity against peritoneal sarcomatosis, but always with an essentially palliative aim, major limitations, and variability across tumor entities. A huge distinction can be made between GIST and other adult soft tissue sarcomas, because the natural
history of GIST has been deeply affected by the medical therapy, while this is still not the case for other sarcomas. Integrated approaches are often resorted to, often using surgery in the case of tumor response to medical therapies, and/or medical therapy in the case surgery is unfeasible. Surgery is obviously the treatment mainstay in most cases with a localized disease stage, but the surgeon is well aware of the risk of sarcomatosis, which may be inherent to the natural history of disease, and also a consequence of complications occurring during surgery (tumor rupture, etc.). Therefore, the value of adjuvant procedures has been long explored. Unfortunately, as of today, no adjuvant medical therapy has been proved of value in these diseases [3]. Prospective trials on adjuvant Imatinib are ongoing in intermediate-high risk GIST patients [4,5]. On the other hand, patients with adult soft tissue sarcomas are often offered adjuvant chemotherapy in several institutions across the world when the disease is high-risk, as is the case by definition in most cases of high-grade retroperitoneal, or pelvic, sarcomas. However, we lack any formal proof of efficacy thereof. Local regional drug delivery systems can yield high intraperitoneal concentrations of chemotherapeutic agents, while keeping low their systemic levels. As the intraperitoneal route cannot guarantee an adequate drug penetration into tumor deposits larger than 1–3 mm, cytoreductive surgery is the main prerequisite for any intraperitoneal chemotherapy. In addition, by entrapping cancer cells and preventing them from being reached by chemotherapeutic agents [6], early postoperative adhesions may limit the effect of intraperitoneal therapies when given postoperatively. This has led to place these therapies immediately after surgery (early postoperative intraperitoneal chemotherapy: EPIC). Furthermore, the notion that some antineoplastic drugs act synergistically with others, as well as with heat, led some authors to propose hyperthermic intraperitoneal chemotherapy (HIPEC). The rarity of these presentations makes it difficult to undertake formal clinical trials. However, only the joined efforts of several institutions might achieve the goal. At the moment, medical therapy is the standard of care for these patients. The histological entity dictates which medical treatment to select, and/or clinical studies may be open in the various presentations. Following optimal tumor response, surgery is often resorted to in sarcomas, and may well be used also in these patients. Its combination with HIPEC should be considered investigational in retroperitoneal and/or pelvic sarcomas. The major benefit gained from Imatinib, and the availability of further second-line molecularly targeted agents, in the lack of any formal proof of efficacy of surgery for residual disease, makes it difficult, at the moment, to foresee that HIPEC may make any difference in advanced GIST patients, even when the disease is confined to the peritoneum.

A prospective study on the combination of aggressive cytoreductive surgery with HIPEC might be foreseen in principle, if a collaborative effort can be put in place. Eligible for such a trial could be patients with: (1) histologically proven multifocal peritoneal implants of non-GIST adult soft tissue sarcoma; (2) tumor remnants <3 mm following cytoreductive surgery; (3) absence of distant metastasis on CT/MR imaging. Patients’ selection should be based on an accurate preoperative work-up encompassing thoraco-abdominal CT scan. Intraoperative staging should include a peritoneal cancer index. Cytoreductive surgery should be performed according to the criteria by Sugarbaker [15]. HIPEC should be based on Doxorubicin and Cisplatin, according to the results of a previously reported Phase I study [16,17]. In the event such a clinical trial provides interesting results, further investigations with randomized confirmatory studies and/or on new pharmacological regimens could be pursued.

Results of Web Based Voting on Conflicting Points
This section reports and comments on the results of the peritoneal sarcomatosis consensus group, which was composed of 13 physicians from around the World. A questionnaire was placed on the website of

Intraperitoneal Chemotherapy

The first published study investigating this therapeutic approach in patients with PS is attributed to Berthet et al. [11]. These authors combined complete gross resection through a peritoneectomy procedure with early peritoneal chemotherapy with or without hyperthermia. Only 16 out of 43 underwent HIPEC. Overall, the 43 patients achieved a median survival of 20 months. Only the completeness of cytoreductive surgery had a significant impact on survival. Eilar et al. [12] used a similar aggressive surgical approach for recurrent abdominal sarcoma, including first recurrence with/without sarcomatosis, but intraperitoneal chemotherapy was delayed (1–2 weeks after complete surgery) with the risk of postoperative adhesions preventing complete bathing of the peritoneal cavity. The 35 patients having intraperitoneal disease alone showed a median survival of 24 months. The median survival of patients treated in these two studies does not differ from that reported by Bilimoria, who treated 51 patients with sarcomatosis or GISTs at the MD Anderson Cancer Centre by means of surgery and conventional chemo/radiotherapy, thus obtaining a median survival of around 22 months [1]. Bonvalot et al. [13] recently published a randomized trial on 19 patients with peritoneal sarcomatosis treated with surgery alone, versus 19 who underwent surgery followed by intraperitoneal chemotherapy with doxorubicin and cisplatin for 5 days. After a median follow-up of 60 months, the local relapse-free, metastatic relapse-free and overall survival were similar in the two groups. So far, the most relevant experience reported with surgery combined with HIPEC is from the Italian Society for Locoregional Treatments on Oncology (SITILO) [14]. In a study, 60 patients affected by advanced (multifocal primary or locally recurrent) intraabdominal visceral or retroperitoneal soft tissue sarcomas underwent optimal cytoreductive surgery (tumor remnants diameter <3 mm) followed by HIPEC with doxorubicin and cisplatin. The postoperative complication rate was 23%, locoregional toxicity 15%, and overall morbidity 33%. The median time to local disease progression and the median overall survival were 22 and 34 months, respectively. A multivariate analysis showed a significant advantage for patients who had undergone complete versus near-complete cytoreduction. Moreover, the importance of inherent tumor aggressiveness was underscored by the different prognosis of high versus low grade malignancies. Although in this group of patients an improved median overall survival was observed in comparison to other case series (34 vs. 20–29 months), these results should be interpreted by considering: (1) heterogeneity of histological types across the case series; (2) different inclusion criteria; (3) different treatments (HIPEC end EPIC). One possible explanation for these poor results in PS might lie in the natural history of sarcomas, which tend to spread across anatomical structures as nerves and vessels, which in the abdomen are retroperitoneal, and are therefore not accessible to peritoneal bathing. It may be concluded that, at present, there is no sufficient evidence supporting the treatment of patients with peritoneal sarcomatosis with HIPEC or EPIC, even if the former may be slightly more effective (Type 3 evidence). This treatment modality is highly demanding both for patients and health resources, and thus should be all the more considered investigational for patients with multiple peritoneum implants (true peritoneal sarcoma).
the 5th International Workshop on Peritoneal Surface Malignancy and the group members voted via internet. Questions generally asked for a ranking of answers on a 1–5 scale where 1 was considered NOT important and 5 MOST important. For the purposes of clarity in presentation of the results of the consensus, the answers 4 and 5 have been added together as were answers 1 and 2 and the results are expressed as percentages of the total respondents. The percentages were rounded up and down to the nearest whole number.

In some cases meaningful data could not be obtained from the questionnaire and this data is not reported here.

**Preoperative Work-Up**

What investigations are optimal to define extent of disease? (Tables I–III).

**Eligibility**

Six questions were asked regarding some of the conflicting indications and/or situations that would make a patient with peritoneal sarcomatosis a candidate for cytoreductive surgery and HIPEC.

(1) With regard to the non-GIST sarcomas, may we foresee a role for HIPEC in the era of molecularly targeted therapies?

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<td>(1)</td>
<td>67%</td>
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(2) With regard to the GIST model, may we foresee a role for HIPEC in the era of molecularly targeted therapies?

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(3) With regard to the GIST model, may we foresee a role for HIPEC in patient non-responsive to targeted therapies?

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(4) Referring to retroperitoneal sarcomas, pelvic sarcomas, GIST, is there any clinical presentation in which abdominal sarcomatosis could be treated today with HIPEC outside a clinical study? In other words, as of today, should we consider HIPEC:

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(5) As of today’s knowledge, which is the selective contribution of cytoreductive surgery, ablative perfusion and hyperthermia to the potential efficacy of HIPEC, if any, in abdominal sarcomatosis?

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(6) With regard to non-GIST sarcomas, which role for HIPEC may we foresee within combined approaches incorporating pre/postoperative chemotherapy?

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**State of the Art of the Methodology**

The following questions were presented to the voters concerning the technical aspects of the local-regional therapy.

Sixty-two percent of the voters defined complete cytoreduction as the presence of a residual disease <2.5 mm (CC-1).

Three quarters of the voters were of the opinion that there would be a role of maximal palliative cytoreduction in cases not amenable to radical surgery.

Regarding the advisable extent of radicality the majority of the panel (92%) voted that a limited peritonectomy to affected area would be sufficient, rather than performing a complete peritoneal resection even in the absence of macroscopic disease.

Seventy-three percent of the panel was of the opinion that HIPEC would not be performed in inoperable cases.

Hundred percent of the panel voted that the combination of chemotherapies would be better than single agent to use in HIPEC. The preferred combination was cisplatin + doxorubicin.

**Follow-Up**

Ninety-one percent of the panel voted CT scan as the preferred imaging modality for the follow-up.

In case of asymptomatic recurrence three quarters of the voters favored the surgical approach and 92% favored the systemic chemotherapy.

**FUTURE INVESTIGATIONS**

Ninety-two percent of the panel was of the opinion that a prospective multicentric randomized trial testing the efficacy of
Cytoreductive surgery and HIPEC with cytoreductive surgery alone. The rate of voters agreed that the patients should be randomized to CRS + HIPEC versus CRS alone.

DISCUSSION OF RESULTS

The great majority of the experts, accounting for more than 90% of voters, agreed that physical examination and CT-scan of the chest abdomen and pelvis are of the utmost importance to define the extent of peritoneal involvement by sarcomatous tumor. Furthermore, there was a general agreement that additional diagnostic tools, such as MRI imaging, PET-scan, laparoscopy and endoscopy play a limited role in the preoperative work-up of potential candidates to local-regional treatment. However, it is surprising that only 25% stated that there should be an effort to document a Peritoneal Cancer Index on the preoperative CT scan, while for 67% of voters such an issue is not relevant.

Concerning the local-regional treatment of abdominal sarcoma, the most controversial issue is presently represented by the availability of innovative targeted therapies which has shown favorable effectiveness at least in prolonging significantly survival for patients affected by GIST [18]. This, along with the lack of formal proof of the efficacy of the combined modality approach in this clinical setting, led the majority of the experts to conclude that today HIPEC should be considered a merely investigational option to be performed in case of recurrent disease presentation with the aim to achieve better local control, but with no impact of long term survival. Accordingly, when the role of surgical cytoreduction and HIPEC in the management of the different sub-types of sarcoma was discussed, no agreement was reached on the use of the intraperitoneal perioperative chemotherapy in patients affected by GIST responsive to the molecular therapy. By contrast, two-third of voters favored the hypothesis of a combined treatment approach to treat non-GIST sarcomas or GIST not responsive to the molecular therapy.

The rarity of abdominal sarcomas and the controversies surrounding their local-regional aggressive management have resulted in a limited number of patients treated by a multimodality approach being reported in the literature [12–14,19–24]. Consequently, many technical aspects of the comprehensive procedure still have to be optimized. Nevertheless, according to the base principles of peritoneal surface tumor management, the expert panel emphasized that maximal cytoreductive surgical efforts should be paid to reduce the volume of residual disease as much as possible, or at least to diameter less than 2.5 mm. Analogously, due to the well-known limited tumor penetration of locally applied chemotherapy, they agreed that HIPEC would not be performed in patients not amenable to significant surgical cytoreduction.

In conclusion, treatment of peritoneal recurrence following surgical resection of intraabdominal sarcomas presents a significant challenge to clinicians. Although the rarity of this disease presentation makes it difficult to undertake formal clinical trials a prospective multicentric randomized trial testing the efficacy of CRS + HIPEC in the treatment of peritoneal sarcomatosis was considered advisable by the majority of the expert panel and it would ideally compare the combination of cytoreductive surgery and HIPEC with cytoreductive surgery alone.

REFERENCES
