

# Cytoreductive surgery and HIPEC in the treatment of peritoneal metastases of sarcomas and other rare malignancies

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**ABSTRAKT:** Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in intraperitoneal dissemination of colorectal carcinoma, pseudomyxoma peritonei or gastric cancer is becoming standard practice. The evaluation of the effectiveness of such management in other cancers is still the subject of clinical trials. It is particularly difficult to assess the effectiveness of CRS and HIPEC in the treatment of intraperitoneal spread of rare types of malignancies such as sarcomas or small intestine cancer. The available, mainly retrospective, studies have been reviewed and discussed. They confirm the efficacy of cytoreductive procedures, especially if complete surgical cytoreduction (CC-O/1) has been achieved, however, the effectiveness of HIPEC requires further prospective studies.

**KEYWORDS:** Sarcoma, DRISCT, small bowel adenocarcinoma, peritoneal carcinomatosis, cytoreductive surgery, HIPEC

## ABBREVIATIONS

TCRS - cytoreductive surgery  
CRC - colorectal cancer  
CC - completeness of cytoreduction  
DFS - disease-free survival  
DRISCT - desmoplastic round small cell tumor  
EPIC - early postoperative intraperitoneal chemotherapy  
GIST - Gastrointestinal stromal tumor  
HIPEC - hyperthermic intraperitoneal chemotherapy  
OS - overall survival  
PCI - peritoneal cancer index (Sugarbaker)  
GC - gastric cancer  
BC - breast cancer  
TKI - tyrosine kinase inhibitors  
WART - whole abdominal radiation therapy

## INTRODUCTION

Clinical studies confirming the efficacy of cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of peritoneal metastases of cancers including colorectal cancer (CRC), gastric cancer (GC) or ovarian cancer have become a trigger for further research of efficient therapies for metastases of other malignant diseases [1]. Unfortunately, this experience does not translate into the treatment of sarcomas or other rare types of malignancies. The incidence of these malignancies is so low that it is difficult to find any longer case series being reported, not to mention the potential planning of prospective studies. In his retrospective assessment, Honore presented 31 patients with isolated intraperitoneal spread of as many as 15 rare tumors including DRISCT, adrenocortical carcinoma, mucinous urachal adenocarcinoma or nonseminomatous germ cell tumor [1]. The isolated cases of cancer included in the study were observed mainly in young patients; according to the authors, this might be the reason for atypical qualifications for the treatment. However, the results (median survival 37 months, 5-year survival 33%) cannot be explained by the patients' age. Therefore, attempts

at the treatment of intraperitoneal spread of malignancies made to date are promising enough for potential treatment with CRS + HIPEC to be considered.

## SARCOMAS

Sarcomas constitute a group of rare and histologically diverse tumors accounting for 2% of all malignancies. The published material is based on short case series and therefore difficult in terms of comparative assessment. More can be said of two specific types of sarcoma, namely DRISCT and GIST, and therefore these tumors will be discussed separately.

About 18% of abdominal sarcomas may produce metastases within the peritoneal cavity. Most of these cases (84%) consist of metastases of retroperitoneal sarcomas [2]. It is believed that the tumors most commonly spread by direct continuity, less commonly along blood circulation and, occasionally, along the lymphatic system. The efficacy of systemic treatment of intraperitoneal spread remains low while radiation therapy involving extensive irradiation of small bowel is burdened by a high risk of complications. In the past, the most common treatment consisted in surgical decompression of the peritoneal cavity. However, the management did not bring about the expected results and the mean survival times did not exceed 9 to 13 months [3,4]. An improvement in the survival times could only be observed in patients in whom macroscopically radical (CC-0) resection of lesions could be performed; in these cases, mean survival times were 23-29 months (4,5) with 5-year survival rates as high as 40%, particularly when the disease was of limited extent [5].

In light of the efficacy of complete surgical cytoreduction, consideration was given to whether inclusion of chemotherapy would contribute to further improvement of outcomes. The only randomized prospective trial that compared CRS combined with chemotherapy to CRS alone in the treatment of metastatic sarcomas could not confirm any beneficial effect of chemotherapy (6). The study was conducted in a population of 38 patients divided into 2

**Tab. I.** List of bibliographic references reporting the use of CRC+HIPEC in intraperitoneal spread of sarcoma.

| AUTHOR (REFERENCE NO.) | PUBLICATION YEAR | NUMBER OF PATIENTS | CRS COMPLETENESS (% CC 0-1) | MEAN SURVIVAL (MONTHS) | 5-YEAR SURVIVAL (%) | PROGNOSTIC FACTORS  |
|------------------------|------------------|--------------------|-----------------------------|------------------------|---------------------|---|
| Rossi [10]             | 2004             | 60                 | 100                         | 34                     | 38                  | Disease staging<br>Degree of cytoreduction (CC 0 vs. CC1) |
| Baratti [11]           | 2010             | 37                 | 87                          | 26,2                   | 24,3                | Disease staging<br>Degree of cytoreduction                |
| Salti [12]             | 2012             | 13                 | 70                          | 12                     | b.d.                | Degree of cytoreduction PCI <10<br>Disease staging        |
| Baumgartner [13]       | 2013             | 15                 | 100                         | 22,6                   | 35                  | Tumor size<br>Time to peritoneal metastasis               |
| Sommariva [14]         | 2013             | 15                 | 100                         | 27,0                   | 29,0                | Gender (females)  |
| Randle [15]            | 2013             | 7                  | 60                          | 21,6                   | 43                  | Completeness of cytoreduction                             |

equally-sized groups. One half of the population received early postoperative intraperitoneal chemotherapy (EPIC, doxorubicin 0.1mg/kg and cisplatin 15 mg/m<sup>2</sup>/day for 5 consecutive days). No significant difference could be observed between the groups in terms of OS as well as DFS although the study population was too small for demonstration of the assumed 40% difference in the OS. The lack of efficacy and uncertain distribution of the cytostatic agent could have been due to both postoperative adhesions and the clogging of drainage tubes. A bigger hope is raised by HIPEC being administered as an adjuvant to CRS. However, most available data originate from retrospective assessment of subgroups from centers which studied the outcomes of HIPEC in the treatment of metastatic cancers. In a prospective, single-site study, Lim [7] assessed the efficacy of HIPEC by applying two treatment regimens including cisplatin at a dose reduced due to nephrotoxicity from 150 to 90 mg/m<sup>2</sup>/ 90 min (19 patients) and additionally mitoxantron 20 mg/m<sup>2</sup> (9 patients). The CC-0 response rates in the study groups were 94.7 and 100%, respectively. Surgical complications were respectively observed in 3 (16%) and 4 (44%) of NCI stage III and IV patients (8). Post-chemotherapy complications were much more common. Most prevalent complications within the first group included intestinal disturbances (58%), hepatotoxicity (58%) and renal failure (37%) which was the cause for cisplatin dose being reduced already after administration to the first patient. Within the second group, the most common complications included hematological complications (89%) followed by intestinal and hepatic complications (66% each). Only 1 death was observed in the second group, its relationship to the treatment being unclear. The reported mean OS values (16.9 and 5.5 months, respectively) are difficult to interpret due to the small study population; the values are not higher than these reported following CRS alone; however, the safety of the HIPEC treatment raises hopes for further research being conducted.

In recent years, several further studies were published on the subject. Unfortunately, the analysis of their results is difficult due to small and non-homogeneous patients populations, different cancer staging criteria, different scopes of cytoreduction and different therapeutic approaches (normothermic vs. hyperthermic, open vs. closed method). The study populations ranged from several up to 60 patients, mean OS times ranged from 12 to 34 months, and 5-year survival rates in selected groups was as high as 40%. Most common prognostic factors as reported by the authors include the completeness of cytoreduction (CC-0/1), the staging of the disease, and the disease-free survival times.

Biilimoria [4] examined a group of 51 patients to identify two dif-

ferent and prognostically significant stages of the disease: a restricted disease with not more than 10 peritoneal lesions of size not larger than 5 cm, and an extensive disease with >20 lesions of any size. The 5-year survival times in both groups were 82 and 24%, respectively. These observations were confirmed by the retrospective analysis conducted by Anaya et al. [8] who observed that the number of peritoneal lesions was an independent prognostic factor along with histological malignancy grading or the completeness of cytoreduction. Table 1 lists the results from available publications. The conclusions from the available studies are suggestive of caution being taken when qualifying patients with peritoneal sarcoma metastases to HIPEC treatment while highlighting the importance of cytoreductive surgery, particularly in case of CC-0 completeness being achieved [9]. Due to the small population of subjects available for collection at a single site, only multicenter studies would facilitate the development of novel management standards (Tabl I.).

## DESMOPLASTIC SMALL ROUND CELL TUMOR (DSRCT)

Desmoplastic small round cell tumor (DSRCT) is a very rare sarcoma first described in 1989 by Rosai [16]; it is diagnosed mostly in young males (F:M ratio = 1:4). Peak incidence occurs between the ages of 20 and 40 (although cases were reported as early as in children below 10 years of age). DSRCT is associated with a very aggressive course and poor prognosis, with median survival in the range of 17-25 months [16] and the number of cases reported to date is as low as several hundred. The most common primary location consists of abdominal cavity with extensive involvement of the peritoneum and infiltration of extraperitoneal organs. The rapidly formed distant metastases are located usually within the liver and lungs. t(11;22)(p13;q12) translocation is an identified cytogenetic marker of DSRCT. Due to the rare nature of the disease, no uniform management standards are available [17]. Most commonly, recommendations include induction chemotherapy, cytoreductive surgery, and radiation therapy. The usefulness of HIPEC as an adjuvant to CRS in this indication remains the subject of examination. Angarita [18] et al. performed a retrospective analysis of 20 patients (age median of 29 years) in a period of 16 years, with median survival of 22 months. The treatment varied, with CRS being performed only in 5 patients to achieve OS extension (HR:0.1, 95%C.I. 0,03-0.7, p+0.02). Lar et al. [19] evaluated the experience of a single center with a total population of 61 DSRCT patients (91% M) with median age of 19 years (7-58)

**Tab. II.** List of bibliographic references reporting the use of CRS+HIPEC in intraperitoneal spread of SBC

| AUTHOR (REFERENCE NO.) | PUBLICATION YEAR | NUMBER OF PATIENTS | CRS COMPLETENESS (%CC 0-1)   | MEAN SURVIVAL (MONTHS) | 3-YEAR SURVIVAL (%) | PROGNOSTIC FACTORS   |
|------------------------|------------------|--------------------|------------------------------|------------------------|---------------------|--|
| Marchettini [32]       | 2002             | 6                  | 100                          | 12 (6–57)              | 33                  | no data  |
| Chua [33]              | 2009             | 7                  | 100                          | 25 (5–46)              | 20                  | Histological type (signet ring cell)   |
| Sun [30]               | 2013             | 17                 | 82,3                         | 18,4 (5–52)            | 23                  | Disease extent Degree of cytoreduction Duration of surgery Patient condition |
| van Oudheusden [34]    | 2014             | 16                 | 93,8                         | 31 (3,4–93,4)          | 50                  | no data  |
| Liu [35]               | 2016             | 21/31 <sup>1</sup> | 100 <sup>1</sup> (out of 21) | 36 <sup>1</sup> (9–95) | 35,5 <sup>1</sup>   | PCI < 15 Histological malignancy grading Degree of cytoreduction             |

<sup>1</sup> 31 of CRS patients, 21 with CCo/1 and HIPEC. OS and 3-year survival rates presented for the entire group of patients diagnosed with SBC regardless of the degree of cytoreduction

who received combination treatment (CRS, chemo- and radiotherapy) before introduction of HIPEC (in years 1972-2003). The 3- and 5-year survival rates were 44 and 15% respectively for the entire study population; however, the analysis of the impact of the treatment showed that only CRS had a significant influence on the survival (3-year OS 58% vs. 0% for patients not subjected to CRS).

The reports on the treatment regimens extended to include HIPEC originate mainly from a single site, i.e. the Anderson Cancer Center in Houston, TX [20,21]. The relevant experience was summarized by Osborne [22] who presented a group of 32 patients (M-28, F-4) treated at that site. At diagnosis, the disease had extraperitoneal extent in nearly one half of patients (15/32, due to hepatic or distant metastases). All patients were subjected to inductive chemotherapy and cytoreductive surgery (cisplatin 100 mg/m<sup>2</sup>, temp. 40-41 deg. C for 90 min) and, following a recovery period (median 1.4 months), radiation therapy to the entire abdominal cavity (30 Gy in fractionated doses of 1.5 Gy with possible boost of up to 40 Gy for residual changes). No HIPEC-related deaths were observed although toxicity was observed in as much as 84% of NCI stage 3 and 4 patients throughout the treatment period. The median OS in the study group was 60 months and the 3-year OS rate was 64%. The median DFS was 10 months for all patients. Disease progression was diagnosed upon the last follow-up visit in 20 patients; of these, extraabdominal location was observed in 5 patients. The most common location of tumor spread consisted of isolated liver metastases. According to the authors, the longer the interval between diagnosis and treatment initiation or the longer the intervals between individual treatment stages, the higher the risk of local recurrence of the disease [22]. In the discussion, the authors highlighted that previously published series of DSRCT cases reported median time to intraabdominal recurrence being 8 to 9 months while the inclusion of HIPEC extended this period to 11.7 months. However, local disease control within the abdominal cavity did not translate into longer OS since distant metastases had been formed in the patients. Particularly bad prognoses were reported for patients with initial secondary lesions developing within the liver.

Honore et al. [23] analyzed a group of 107 patients from 7 French sites; among these, 48 patients subjected to at least CC-1 grade cytoreductive surgery were identified. The group consisted predominantly of males (73%) with median age of 22 years (3-57) and median PCI value of 9 (2-27). Intraperitoneal chemotherapy was administered to 11 patients from the group of patients subjected to complete cytoreduction (EPIC in 2 patients, HIPEC in

9 patients). Platinum derivatives were used as chemotherapeutic agents in all patients while mitomycin, irinotecan, and adriamycin were additionally administered to 3, 2, and 2 patients, respectively. The median OS in the study group was 42 months while the 2- and 5-year OS rates were 72% and 19%, respectively. Only WART was confirmed as having an impact on DFS in multifactorial analysis (p=0,0014), while no impact could be demonstrated for PCI or intraperitoneal chemotherapy.

## GIST

GIST is the most commonly diagnosed of gastrointestinal sarcoma (24) that may involve intraperitoneal spread. Until 2002, i.e. until the introduction of the first tyrosine kinase inhibitor (TKI), imatinib, attempts at CRS + HIPEC combination treatment were made albeit with no encouraging results. In a retrospectively analyzed group of 15 patients with peritoneal sarcomatosis, Sommariva et al. [14] identified 2 patients with gastric GIST (following a repeated histopathological examination) who were able to achieve long survival times despite not receiving imatinib (77 and 134 months, respectively) and despite the fact that both these patients died as the result of disease progression. Overall two-year survival rates were at the level of 38-42% (3) while the median overall survival was about 13 months (4-42). Since the introduction of TKIs, chances for long-term survival in this group of patients are associated with the efficacy of systemic treatment. Significantly longer disease-free as well as overall survival times were observed in the selected group of patients presenting with good response to preoperative TKI treatment and subjected to CRS [25,26]. The largest number of diffuse GIST patients (16 patients, 18 procedures) was summarized by Bryan [27]. All patients had undergone CRS, with macroscopically complete cytoreduction achieved in 72% (13/18). HIPEC (mitomycin C, 40 mg, 40 deg. C, 60-120 min) was administered after the procedure. A retrospective analysis confirmed mainly the beneficial effect of complete cytoreduction on the survival of patients who had presented with good response to TKI treatment. The safety of the treatment did not differ from that in the group of patients treated for epithelial cancers (mortality 5.6%, major complications 33.3%). Preoperative resistance to TKIs was found to be associated with poor prognosis (median survival of 1.3 years). No confirmation could be obtained regarding HIPEC having any impact on improved survival; currently, the authors recommend CRS being performed in stable disease before the development of drug resistance symptoms.

## SMALL BOWEL ADENOCARCINOMA

Small bowel cancer (SBC) is rare (accounting for 1-3% of gastrointestinal tract malignancies) and, when diagnosed at the stage of intraperitoneal spread, is always associated with poor prognosis [28,29]. SBC usually develops within the duodenum. Since the duodenum is located outside the peritoneal cavity, intraperitoneal spread is usually a consequence of ileal or jejunal tumors and constitutes the most common route for the spread of this malignancy [24,30]. Due to the biology of the tumor as well as to its usually late diagnosis, the median survival according to the available sources is 12 to 20 months. This is associated with the oligosymptomatic course of the disease as well as to difficult diagnostic access to the small intestine. Although the expansion of available diagnostic techniques by double balloon enteroscopy or capsule enteroscopy facilitated the evaluation of this segment of the gastrointestinal tract, the limited availability of tests makes SBC being diagnosed late in its natural history, i.e. at the stage intraperitoneal or lymph node spread (1/4 of patients) [28]. The therapeutic management regimens copied after those used in colorectal cancer are inefficient in controlling the disease [31]. The success of cytoreductive therapy in combination with HIPEC in CRC raises hopes for similar results being obtained for SBC (tabl. II).

The literature published to date contains reports of four studies conducted in patients treated with CRS in combination with intraperitoneal chemotherapy (HIPEC or EPIC). The first group of patients with intraperitoneal spread of SBC (6 cases) was presented by Marchettini [32]. Primary tumor locations were equally divided between the ileum and the jejunum. Complete cytoreduction (CC-0) was obtained in all these patients. Intraperitoneal chemotherapy consisting of mitomycin C 12.5 mg/m<sup>2</sup> was administered for 90 minutes at 42 deg. C. The treatment was continued according to EPIC regimen consisting of intraperitoneal administration of 5-FU (650 mg/m<sup>2</sup>) for 5 days. No treatment-related deaths were observed; no data on complications are available. Median overall survival was 12 months; two patients died because of intraperitoneal recurrence. Chua [33] presented a heterogeneous group of 7 patients; 6 of these patients were subjected to pre- or post-operative chemotherapy, including HIPEC (mitomycin C 10-12/5 mg/m<sup>2</sup> for 90 min, open method) in 5 patients and additional EPIC (5-FU 650 mg/m<sup>2</sup> for 5 days) in 4 patients and EPIC only in 2 patients. Complete cytoreduction (CC-0) was obtained in all patients. The most important prognostic factor was histological malignancy grading (G3- signet ring cell carcinoma), with median survival of 5.5 months as compared to 25 months in the entire group. No treatment-related deaths were observed; major complications were observed in 2 patients (29%) while minor complications were observed in 5 patients (71%).

The efficacy of HIPEC in the largest reported group treated at a single site [30] was difficult to assess due to the fact that 16 out of 17 patients received chemotherapy before and/or after CRS. Among the study patients, primary tumors were located in the jejunum in 9 cases (47%), ileum in 7 cases (35%) and duodenum in 1 patient (6%). CC-0/1 cytoreduction could be obtained in 14 patients (82.3%) to be followed by HIPEC with mitomycin C at the dose of 30 mg/60 min with subsequent increase to 40 mg over the next 60 min at > 39 deg. C. In three patients, the treatment was repeated due to disease recurrence. No postoperative deaths were recorded in the study group with complications, mo-

stly consisting of neutropenia, being observed in 8 patients (47%). Intraperitoneal recurrences were observed in 15/17 patients. Van Outhesden [34] examined a group of 16 patients from different Dutch sites. Distribution of tumor locations was similar to that observed in Sun's study: 7 cases (43.8) were located within the jejunum, 8 cases (50%) were located within the ileum, and 1 case (6,3%) was located within the duodenum. Patients qualified for the treatment included those in whom the disease was detected in < 5/7 abdominal regions (Dutch classification). CC-0 cytoreduction could be obtained in most patients (93.8%). Chemotherapy consisting of mitomycin C at the dose of 35 mg/m<sup>2</sup> was administered in open procedure for 90 minutes at 41-42 deg. C. In addition, 9/16 patients (56.3%) received systemic treatment after the surgery. No postoperative deaths were recorded with major (grade 3) complications being observed in 4 patients (25%). The median OS was 30.8 months (3.4-94.4) while the median DFS was 9.5 months (4.6-14.4). Intraperitoneal locations of recurrent disease were observed in 7 out of 8 recurring patients. According to the Dutch National Cancer Registry a total of 281 SBC cases were diagnosed in the Netherlands in the analyzed period (2005-2012); of these only 19 cases (5%) were qualified for HIPEC and only 16 patients actually received the treatment. The largest reported group consisted of 31 small bowel tumors including 25 small bowel cancers was presented by Liu [35]. Most primary tumors (all but one) were located within the jejunum or ileum; the mean PCI was 15. CC-0/1 cytoreduction was achieved in 21 out of 31 patients; only these patients were qualified for open HIPEC treatment. All patients received mitomycin at the dose of 15mg/m<sup>2</sup>; 10 patients additionally received cisplatin at the dose of 60 mg/m<sup>2</sup> for 40 minutes at 42.9-43.5 deg. C. The treatment was readministered due to disease recurrence in 7 cases. Systemic treatment was administered to 28 patients. No treatment-related deaths were reported. CRC+HIPEC-related complications were observed in 14 patients (66%), including intestinal fistula in 4 patients, fever in 3 patients, infection in 2 patients, dysuria in 2 patients, biliary fistula in 1 patient and pleural effusion in 1 patient. In 8 patients (38%), the complications were classified as NCI grade 3/4. The authors analyzed the group as a whole, reporting survival times regardless of the treatment method, and therefore the only conclusion was the positive impact of CC-0/1 and HIPEC on the outcome prognosis.

Table 2 presents detailed data and long-term outcomes from 5 patients. The presented short series of cases and non-unified treatment regimens such as for example in relation to perioperative systemic treatment do not warrant any specific conclusions related to the role of HIPEC in the treatment of SBC; however, it should be noted that the reported OS values compared to the historical data form patients not receiving HIPEC treatment suggest that indications for HIPEC treatment should be considered on a case-by-case basis in all patients with intraperitoneal spread of cancer.

## SUMMARY

In the Peritoneal Surface Oncology Group International (PSOGI) study of data collected in years 1990-2016 at 53 sites worldwide, a total of 850 procedures performed in 781 patients with peritoneal metastases of rare malignancies were analyzed. Most cases pertained to rare ovarian tumors (224 patients), sarcomas (189), NET (127), GIST (47), cholangiocarcinoma (39), urachal adeno-

carcinoma (35), and DSRCT (34). Median survival in the entire population was 39.45 (33.18–44.05) months. Factors listed by the authors as having an adverse impact on the OS in unifactorial analysis include PCI (PCI<10: 46.1% >14: 31.9%;  $p=0.037$ ), degree of cytoreduction ( $p<0.0001$ ), diagnosis ( $p<0.0001$ ), tumor differentiation grade ( $p=0.0004$ ), lymph node involvement ( $p<0.0001$ ), duration of HIPEC (>60 min,  $p<0.0001$ ) and the surgical technique (closed method,  $p=0.0004$ ). In a multifactorial analysis, these correlations were confirmed for pre- and post-operative chemotherapy, lymph node involvement, degree of cytoreduction and etiology of the tumor [36].

The growing importance of CRS and HIPEC in the treatment of intraperitoneal spread of sarcomas, small bowel cancer, or other rare malignancies requires more evaluation due to the limited number of available studies. The available publications confirm only the significant impact of cytoreductive surgery on extended survival (especially in case of radical CC-0 cytoreduction); due to the small number of published case series, it's difficult to draw any conclusions regarding the role of HIPEC. However, the available reports raise hopes that the assessment of a larger number of patients in multicenter, prospective studies would facilitate development of management standards also for these rare and difficult cases.

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