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Peritoneal metastases of rare carcinomas treated with cytoreductive surgery and HIPEC – A single center case series

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HIGHLIGHTS

- The difficulties in deciding of whether to perform CRS and HIPEC for PSM arising from unusual malignancies are remaining.
- Perioperative morbidity for extensive surgical treatment and HIPEC is acceptable in specialized PSM centers.
- The prospective registration in tumor registries could help to better define the indications for CRS and HIPEC in rare PSM.

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ABSTRACT

Introduction: In selected cases, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is an established treatment for patients suffering from peritoneal metastases from colorectal, ovarian, gastric or appendiceal origin. The effectiveness of this extensive has not been elucidated within other rare diseases by now.

Methods: We conducted a retrospective analysis of patients treated with CRS for peritoneal carcinomatosis during the period between July 2010 and September 2015. Exclusion criteria were adenocarcinomas of the stomach, colon, neoplasms of the appendix, mesothelioma and ovarian cancers. Aim of this study was to examine the feasibility, complication rate and survival of patients with rare diseases.

Results: A total of 14 Patients were included: Four rare gynecological tumors, three adenocarcinomas of the small intestine, three retroperitoneal sarcomas, one cholangiocellular carcinoma, one neuroendocrine gastric tumor, one malignant peripheral nerve sheath tumor and one cancer of unknown primary syndrome. In 12 of 14 patients a macroscopically complete tumorresection could be achieved. No patient died during hospitalization. Seven of 14 patients experienced general complication of grade III according to NCI CTCAE V4.0, while two experienced complications of grade IV. Median follow-up and one year overall survival were 15.5 months and 46.8%, respectively.

Conclusion: For patients with rare tumors, CRS and HIPEC is feasible with an acceptable perioperative morbidity and mortality. To improve knowledge in patient selection and outcome, rare tumors treated with CRS and HIPEC should be documented in central databases (as for example BIG RENAPE, Pierre-Benite, France).

1. Introduction

The key factor for improving of survival in patients with peritoneal surface malignancies (PSM) was the development of cytoreductive surgery (CRS) and intraperitoneal (IPC) or hyperthermic intraperitoneal chemotherapy (HIPEC) in recent decades. It is the gold standard for curative treatment of primary peritoneal malignancies, low-grade appendiceal mucinous neoplasm (LAMN), peritoneal mesothelioma and PSM from colorectal origin [1–6]. The indication for CRS and HIPEC in patients with PSM from ovarian or gastric carcinoma, or neuroendocrine sarcoma remains contended [7]. There are several ongoing studies, which aim to answer this question and many excellence centers do not recommend HIPEC for these indications outside of clinical trials. The treatment for PSM

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arising from other origins is even more exceptional and lacks data in the literature, which exceeds clinical case reports. While these exceptional cases of PSM of non-gastrointestinal origin are often presented with diffuse extraperitoneal dissemination, only a few of these cases can be considered for complete cytoreduction and HIPEC. The decision for this procedure has to be taken in an individual approach.

The aim of this study was to analyze morbidity, mortality of CRS and HIPEC as well as long-term results in patients with PSM of unusual origin.

2. Material and methods

This retrospective study included all consecutive patients who were treated with CRS and HIPEC between July 2010 and September 2015 at Campus Mitte, Charité, Universitätsmedizin-Berlin, Germany. Patients with gastric, colorectal, ovarian and appendiceal cancer were excluded as patients with LAMN or mesothelioma.

Routine preoperative examination was performed in every patient; CT scans of the chest, abdomen, and pelvis and tumor markers (CEA, CA19-9, and CA 125) were obtained. The surgical procedure was recommended for all patients without evidence of extraperitoneal metastases if complete cytoreduction (CC) was deemed feasible by the operating surgeon. Each therapeutic decision was preoperatively discussed in the multidisciplinary tumor board, including oncologist, radiologist, radiotherapist, and visceral surgeon. The extent of peritoneal involvement was assessed through the Peritoneal Cancer Index (PCI) [8]. The assessment took place directly after explorative laparotomy and just before cytoreductive procedures and was performed by B.R. for every patient. B.R. performed more than 300 CRS and HIPEC procedures and is an experienced surgeon in the field PSM. The PCI score was simultaneously recorded and calculated by an assistant.

Definitive CRS was carried out to achieve complete cytoreduction using, but not limited to, the following procedures: exploratory laparotomy, abdominal wall resection, abdominal and pelvic lymphadenectomy, appendectomy, cholecystectomy, bilateral adnexectomy with hysterectomy, cytoreductive surgery and biopsy of peritoneal implants, enterolysis, and ureterolysis. The peritonectomy procedures included diaphragmatic, parietal, and pelvic peritonectomy and omentectomy. Resection of hollow viscus and/or organs was performed if they could not be cleared of disease or were affected by the primary cancer. Every effort was made to avoid extensive small bowel resection and/or ostomy formation to preserve quality of life. Complete cytoreduction was defined as nodules less than 2.5 mm in size (CC = 1) or the absence of visible tumor nodules (CC = 0). Cytoreduction was followed by immediate HIPEC. HIPEC protocols differed according to different tumor entities. HIPEC was delivered for 60 min in most of the cases (83.3%) and in a closed abdomen technique in 71.4% of the patients. An open circulation system was used for the remaining 28.6% of patients. Complications were retrospectively classified regarding to Dindo/Clavien [9]. Grade $\geq$ 2b complications were considered severe. Medical complications were classified by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE V4.0).

Clinical data were collected during follow-up visits and no patient was lost to follow-up. The study was approved by the ethics committee of the Charité, Universitätsmedizin – Berlin, Germany (EA1/009/16). The study was registered in accordance with the Declaration of Helsinki 2013 (UIN: researchregistry1938). The case series is reported in line with the PROCESS criteria [10]. All statistical analyses were performed using either SPSS 23.0 (International Business Machines Corporation, Armonk, NY) or Prism 6.0 (Graphpad Software, Inc., La Jolla, CA). Continuous descriptive data are given as mean and standard deviation. Categorical data are given as frequencies and proportions. Univariate analysis of time to event data was performed using Log-Rank tests to compare several groups. Univariate results were visualized by Kaplan-Meier curves. A p-value below 0.05 was considered significant.

3. Results

Between July 2010 and September 2015, 14 patients underwent CRS and HIPEC of unusual origin, representing 5.7% of all patients treated with HIPEC during the same period. There were 7 female (50%) and 7 male (50%) patients, with a mean age of 52 years (±12.8). Seven unusual histologic origins of PSM were included. The patient demographics are stated in Table 1. The mean time from diagnosis to CRS and HIPEC was 17.4 months (±35.6) whilst 8 patients (57%) were treated with systemic chemotherapy preoperatively. In all 14 patients PSM was the only metastatic side. The mean intraoperative peritoneal cancer index was 12.2 (±4.8). A complete tumorresection without macroscopic visible remnants could be achieved in 12 patients (86%). The mean operation time was 6.5 (±1.9) hours. HIPEC was performed in 10 (71%) patients in a closed abdomen technique and in 3 (21%) patients using the open coliseum approach. In one patient HIPEC was not performed. The duration of circulation was in 12 patients (79%) 60 min and in one patient 30 min. The mean temperature of the chemoperfusion was 40.9 °C (±0.8). Eight (57%) patients were treated with a postoperative systemic chemotherapy after recovery of the surgical procedure. Postoperative morbidity was 50%. Surgical complications $\geq$2b occurred in one patient developing fascial dehiscence treated with operation. Non-surgical complications were found in 8 patients (1 cardiac, 3 gastrointestinal, 4 infectious, 5 respiratory disorders and 2 other complications). No patient died postoperatively. The median hospital stay was 13 (range: 8–34) days. The median follow-up was 16 months, whilst 8 (57%) patients died and 6 (43%) patients were alive. Every still living patient developed a peritoneal tumor recurrence or tumor progression. Patient's

Table 1
Patient demographics, comorbidities and ASA = physical status classification system of the American Society of Anesthesiologists.

Descriptive	
Patient	
female [%]	50 (7/14)
age [years]	50.9 ± 13.0
PCI	14.0 ± 7.8
Primary malignancy [%]	
adenocarcinoma small bowel	21.4 (3/14)
sarcoma	21.4 (3/14)
gynecologic tumor	28.6 (4/14)
cholangiocellular carcinoma	7.1 (1/14)
Gastric neuroendocrine tumor	7.1 (1/14)
CuP-syndrome	7.1 (1/14)
malignant peripheral nerve sheath tumor	7.1 (1/14)
Comorbidities [%]*	
None	42.9 (6/14)
Pulmonary	28.6 (4/14)
Cardiac	21.4 (3/14)
Renal	7.1 (1/14)
Metabolic	7.1 (1/14)
Artheriosclerosis	0 (0/14)
Hepatic	0 (0/14)
Orthopaedic	0 (0/14)
ASA [%]	
I	0 (0/14)
II	64.3 (9/14)
III	35.7 (5/14)
IV	0 (0/14)

demographics, complications and follow-up are illustrated in Table 2.

Univariate analysis could not identify predictive factors for survival.

4. Discussion

The development of the treatment of PSM by CRS and HIPEC is ongoing and has demonstrated a survival benefit for many indications while proving to be ineffective for others [7,11]. However, for PSM arising from unusual origins, the evaluation of the benefit of CRS and HIPEC is more complex. This work illustrates nearly six years of experience in the treatment of PSM in a national reference center. During this time only 14 patients were treated with CRS and HIPEC from seven unusual origins. The comparison between chemotherapy (palliative) treatment and CRS and HIPEC is very difficult due to the more or less strict patient selection in the CRS and HIPEC studies. We aim to discuss our results with the already published data about CRS and HIPEC for these rare diseases.

4.1. Adenocarcinoma small bowel

There was a large national study of the Netherlands published in 2015 demonstrating the effect of CRS and HIPEC in 16 patients with PSM arising from small bowel cancer. They observed 50% tumor recurrence and achieved a median survival of 31 months, which seems comparable with PSM from CRC [12]. There are three further case series including six, seven and 17 patients and illustrating a median survival between 12 and 25 months [13–15]. Differences of these studies are most likely due to stricter patient referral and selection. Overall 5-year survival in all small bowel adenocarcinoma patients is 37% [16]. Metastasized small bowel cancer has a median survival of <13 months, with high recurrence rates mainly in the first year [17]. Our study showed three patients whilst one patient died after 12 months due to tumor progression. The other two developed tumor recurrence and are after five and 33 months alive.

4.2. Cholangiocellular carcinoma

Cholangiocellular carcinoma are known to be highly malignant with a median survival for best supportive care of 2.5 months [18]. Chemotherapeutic regimes usually contain gemcitabine and capecitabine and showed improved survival rates of 9.3–14 months [19–21]. A French retrospective study of iterative CRS and HIPEC procedures reported one patient, amongst others with peritoneal tumor recurrence of cholangiocellular carcinoma treated with CRS and HIPEC [22]. Unfortunately, there was no sole survival of this patient mentioned. One patient in our study cohort showed a survival with 12.7 months after CRS and HIPEC.

4.3. Retroperitoneal sarcoma

Peritoneal metastases of primary retroperitoneal tumors are rare, and most of them occur as implant metastases described as local recurrence after surgical procedures. The aggressiveness or differentiation of the tumor varies between well differentiated liposarcoma to less or barely differentiated leiomyosarcoma or malignant fibrous histiocytoma. Peritoneal sarcomatosis has traditionally been viewed as a terminal disease with median survival of less than 1 year, with surgery only reserved for associated complications such as intestinal obstruction and ureteral obstruction [23–25]. Bilimoria et al. found the median survival of patients with sarcomatosis treated with palliative surgery and/or chemotherapy to be 13 months with the only negative prognostic factor being tumor volume [23]. This result is in line with other published reports describing the experience with palliation have found the median survival to range from 7 to 15 months [24,25] and are comparable with 6.1 months shown in our study. The addition of intraperitoneal chemotherapy to cytoreductive surgery (CRS) has not been shown to improve on the results achieved with CRS alone and is therefore currently not recommended in the treatment of sarcomatosis except in well-selected patients with low tumor burden after complete cytoreduction and as part of an experimental protocol preferably in centers with expertise in peritonectomy procedures using hyperthermic intraperitoneal chemotherapy (HIPEC) as the intraperitoneal chemotherapy modality [26].

4.4. Embryonic rhabdomyosarcoma

There is only one case published who was treated with CRS and HIPEC and showed a postoperative survival of 15 months [27]. A recently published series described the performance of CRS plus HIPEC in seven patients with rhabdomyosarcoma of unspecified histological subtype. The authors showed that this etiology was individually associated with a very poor prognosis, having an overall 1- and 2-year survival of 29% and 14% respectively [28].

Table 2
Patient demographics, complications and follow-up (n.q. = not quoted; n.a. = not available).

tumor origin	total	PCI	Operation time [hours]	Patient age [years]	CCR	complications stadium 3–4 (NCI CTCAE)	Median tumor free interval [months]	status	median follow-up [months]
adenocarcinoma small bowel	3	10.5 ± 0.5	7.2 ± 0.5	56.8	0	infectious [n = 1] surgical [n = 1]	9.4	alive: n = 2 death: n = 1	22.8
sarcoma	3	10 ± 5	6.4 ± 1	55.4	0: n = 2 2: n = 1	gastrointestinal [n = 1] respiratory [n = 1] others [n = 2]	n.a.	death: n = 3	6.1
gynecologic tumor	4	11 ± 0	5.9 ± 0.1	49.4	0	gastrointestinal [n = 1] respiratory [n = 2]	19.8	alive: n = 3 death: n = 1	35.1
cholangiocellular carcinoma	1	10	4.4	67	0	–	12.1	death	12.7
Gastric neuroendocrine tumor	1	16	7.5	62	0	cardial [n = 1] gastrointestinal [n = 1] infectious [n = 1]	13.5	alive	48.9
CuP-syndrome	1	n.q.	9.8	46	1	infectious [n = 1] respiratory [n = 1]	11.8	death	19.6
malignant peripheral nerve sheath tumor	1	4	4.2	42	0	infectious [n = 1] respiratory [n = 1]	5.3	death	10

4.5. Endometrial cancer

One HIPEC for a case of PSM of endometrial origin was performed in our series. In the literature, 30 cases from six other retrospective studies have been reported [27,29–33]. Aggregated data from these series shows that 14 patients are alive without recurrence after a median follow-up of 30 months while nine died of early recurrence within the first postoperative year. There are no published data to confirm a potential benefit of the addition of HIPEC to CRS, although we could not identify any way to discriminate the different profiles of aggressiveness.

4.6. Granulosa cell tumor & yolk sac tumor & tubal clear cell carcinoma

One recent study showed the performance of CRS and HIPEC in pediatric ovarian tumors in 3 patients with yolk sac tumor and in one patient with granulosa cell tumor. Tumor recurrence occurred in three of eight patients and was associated with death. The remaining five children were 2–6 years post CRS and HIPEC disease free [34]. These results are partially concordant with our experience showing one patient with granulosa cell tumor 37.1 months after CRS and HIPEC alive and one patient with yolk sac tumor 8 months postoperatively death. There is no data about the treatment of PSM of a clear cell carcinoma of the tube with CRS and HIPEC.

4.7. Gastric neuroendocrine tumor

The largest study about PSM arising from neuroendocrine tumors was published by Elias et al., in 2014 and illustrated the performance of CRS and HIPEC. Amongst mainly neuroendocrine tumor from ileal or appendiceal origin (71%), one patient was reported with gastric origin, who was finally treated with CRS only. The authors could not conclude a benefit for CSR and HIPEC versus CRS alone and would favor CRS due to the perioperative morbidity of the HIPEC procedure [7].

4.8. Cancer of unknown primary syndrome

The diagnosis of CUP-syndrome after CRS and HIPEC is extremely rare due to the fact that the histological results of the operative specimen often reveals an ovarian or appendiceal cancer, which was invisible to preoperative examinations. Consequential, there is no data exceeding case reports about PSM of CUP-syndrome.

4.9. Malignant peripheral nerve sheath tumors

There is no data published about a single case of PSM arising from malignant peripheral nerve sheath tumors. These tumors are likely high-grade tumors with an aggressive metastatic pattern. We reported one patient who died after 10 months due to tumor progression.

4.10. Strengths and weaknesses of this study

This study suffers from the classic biases of retrospective studies on rare tumors. Nevertheless, it has the mission of updating the current situation, while improving the lack of data by adding this case series. This should encourage us to support a prospective registry within the rare peritoneal tumors network (RENAPE) to improve a better definition for indications for CRS and HIPEC for these unusual indications.

5. Conclusion

The difficulties in deciding of whether to perform CRS and HIPEC for PSM arising from unusual malignancies are remaining. The decision must be based on an interdisciplinary board which considers patient's age, general condition, comorbidities, the probability of achieving complete cytoreduction, the existence of a chemosensitive tumor or one with slow biologic progression, primary tumor origin, and tumor burden as measured by the peritoneal cancer index. Perioperative morbidity are acceptable in specialized PSM centers. We need more data to achieve the goal of a better definition of indications in rare PSM. The prospective registration in the rare peritoneal tumor registries (the French Network for Rare Peritoneal Malignancies [RENAPE] in France, and/or the Peritoneal Surface Oncology Group International [PSOGI] internationally) could lead to achieve this goal.

Ethical approval

The study was approved by the ethics committee of the Charité, Universitätsmedizin – Berlin, Germany (EA1/009/16).

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Author contribution

A.B. study design, data collection, data analysis, writing, final approval for publication C.Z., W.R. data collection, data analysis, review & revision of article and final approval for publication.

J.P., B.R. interpretation of data, review & revision of article and final approval for publication.

Conflicts of interest

The authors have no conflict of interest to disclose.

Guarantor

22.04.2017 Andreas Brandl M.D.

Consent

The manuscript is not a case report and patients are not identifiable.

Registration of research studies

Our study UIN is: researchregistry1938.

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