Evaluation and management of toxicity of cytoreductive surgery/hyperthermic intraperitoneal chemotherapy: the initial experience of a single centre study

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Background. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a treatment modality for peritoneal surface malignancies with efficacy reported in many trials. Discrepancies, however, in the indication criteria, the extent of the surgical procedure, HIPEC regimens and toxicity evaluation represent a problem when comparing this method with other therapeutic modalities.
Methods. We describe the initial experience with CRS/HIPEC using different chemotherapy regimens (oxaliplatin, cisplatin, mitomycin C and doxorubicin) at the Comprehensive Oncology Centre Olomouc.
Results. A perioperative mortality of 2% and perioperative morbidity of 11%, according to Clavien-Dindo were observed. Interestingly, all these patients underwent HIPEC with oxaliplatin 460 mg/m^2. The median duration of admission to hospital was 6 days in the intensive care unit (range 2–28 days) and 7 days in the surgical ward (range 1-21 days). Hospital admission did not exceed 2 weeks in 75% of patients. These results are consistent with the published results of large centres performing this treatment modality mainly due to pre-operative preparation of patients and pre-treatment and post-treatment management of HIPEC/CRS toxicity. Evaluation of the efficacy in terms of time to progression and overall survival (OS) is limited by the short follow up period.
Conclusion. CRS/HIPEC performed is a safe method with low perioperative mortality.

Key words: cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, oxaliplatin, mitomycin C, cisplatin, toxicity, adverse events, morbidity

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INTRODUCTION

Surgery, radiation and pharmacological therapy represent the three principal components of the multimodality curative treatment of cancer. Cytoreductive surgery (CRS)/ hyperthermic intraperitoneal chemotherapy (HIPEC), a therapeutic method consisting of radical surgery, regional application of cytotoxic agents and hyperthermia, is unique in combining all of these three fundamental approaches in the treatment of peritoneal malignancies. In an era of targeted therapy, CRS/HIPEC represents an alternative concept to molecular targeting, i.e. anatomical targeting of anticancer drugs, increasing the efficacy by potential synergisms with surgical cytoreduction and with the effect of hyperthermia. The options for the treatment of peritoneal carcinomatosis were limited until the advent of CRS/HIPEC. Peritoneal carcinomatosis is considered the terminal stage of a disease. The efficacy of systemic chemotherapy is limited by poor vascularisation of the peritoneum[1], the presence of tumour hypertension, which prevents the influx of cytotoxic drugs into the tumour tissue[2], and also by the fact that most tumors presenting with peritoneal carcinomatosis are only moderately sensitive to cytotoxic drugs. The incidence of peritoneal malignancies is not negligible. The incidence ranges from 0.2-3 cases per million people per year, for rare tumours such as mesothelioma, to 4 to 7.2 cases per 100 000 people per year for secondary peritoneal malignancies such as colorectal cancer or ovarian cancer[3].

CRS/HIPEC combines extensive surgical procedure with administration of heated (41-43 °C) high dose chemotherapy. The surgical procedure includes peritoneal surface stripping, omental resection, multiple visceral resections (such as splenectomy, appendectomy, and bowel resection) and lymphadenectomy of regional basins. Mitomycin C, cisplatin, oxaliplatin, doxorubicin and paclitaxel are the cytotoxic agents most commonly used in HIPEC protocols. The duration of the surgery is around 10 h. Nevertheless, low mortality from 0.9 to 3.2% and acceptable morbidity of 12-33% is reported when appropriate procedure and selection of patients is performed in tertiary centres[4]. There is no unified classification system of treatment toxicity. Different authors use several classification systems including Clavien-Dindo or Common Terminology Criteria of Adverse Events (CTCAE) v3.0. The reported serious toxicity differs according to the in-

dividual classification system from 11% to 60% (ref.[4-6]) and declines within 4 months after CRS/HIPEC (ref.[7]).

The efficacy of CRS/HIPEC in the treatment of peritoneal malignancies has been demonstrated in a number of prospective trials. CRS/HIPEC have been reported to prolong the median OS to 5 years, - i.e. by 50% compared with conventional surgery in the treatment of pseudomyxoma peritonei. The median OS of patients with mesothelioma peritonei has been reported to increase from 12 months to 34-92 months[8,9]. The results of the randomized phase 3 trial, comparing CRS with CRS/HIPEC in the treatment of inoperable ovarian cancer stage FIGO III, revealed the prolongation of median OS by 11.8 months in favour of CRS + HIPEC (ref.[10]). The efficacy of CRS/HIPEC has also been demonstrated in the treatment of peritoneal carcinomatosis of colorectal origin, a disease entity with a dismal prognosis. CRS/HIPEC has increased the median OS by 12 months compared with standard systemic chemotherapy[11]. There are several ongoing randomized trials evaluating the efficacy of CRS/HIPEC in the treatment of peritoneal carcinomatosis of gastric primary.

In spite of these encouraging results, CRS/ HIPEC has yet not become the standard of care. There is a lack of a unified system for adverse events classification and evaluation of peritoneal surface involvement. Moreover, there is a difference in the extent of the surgical procedure, the method of the lavage as well as in the HIPEC regimens. The choice of the appropriate cytotoxic agents or drug combination is crucial. The cytotoxic agents should not lead to local intraperitoneal toxicity. Agents which are systemically metabolized into an active form are also not suitable. There is an important synergism between the drug and hyperthermia. Heat influences chemotherapy cytotoxicity and the pharmacokinetics in terms of influx and efflux of the agent into the tissue.

We present the initial experience and preliminary results of CRS/HIPEC performed in the Comprehensive Oncology Centre Olomouc with evaluation and management of CRS/HIPEC toxicity.

PATIENTS AND METHODS

We retrospectively evaluated a cohort of 44 patients who underwent CRS/ HIPEC between 1 January 2016 and 1 January 2018 in the Comprehensive Oncology Centre Olomouc. The clinical and pathologic parameters of all the patients, such as gender, age, site of the primary, extent of the disease, extent of the peritoneal involvement (evaluated with peritoneal cancer index; PCI), extent and completeness of the surgical procedure (evaluated with the CCS score), previous surgical and systemic treatment, postoperative systemic treatment and time to progression of the disease (progression-free survival; PFS) were retrieved. PFS was defined as the time from the date of the CRS/HIPEC procedure to the date of progression of the disease. The date of progression was based on clinical and imaging examination. Tumour markers (CA 125, CEA, CA 19-9, and CA 72-4) were examined in 3-month intervals. Computed Tomography scan of the thorax, abdominal cavity and pelvis were performed in 6-month intervals. The Kaplan-Meier method was used to calculate median PFS with the help of software SAS EG 5.

The adverse events, toxicity and safety of the treatment have been evaluated according to the surgical classification Clavien-Dindo (postoperative morbidity), length of hospital admission, stay in the intensive care unit and in the surgical ward. Perioperative mortality was defined as the ratio of the deceased patients, within 30 days of the procedure to the total number of the patients who underwent CRS/HIPEC.

All patients were discussed by a multidisciplinary team.

The indication criteria were as follows:
1/ disease disseminating to the peritoneum
2/ no more effective treatment option available
3/ performance status of patients PS 0-1 according to the WHO classification

The contraindications were:
1/ the presence of visceral metastases, e.g. liver metastases, pulmonary metastases; or the presence of bone metastases
2/ the performance status of patients PS 2 and less according to the WHO classification
3/ surgical contraindications including involvement of large veins of arteries, metastases of small intestine serosa and invasion of the visceral organs or the abdominal wall
4/ comorbidities contraindicating large surgical procedures

Eligible patients for CRS/HIPEC signed an informed consent with the procedure. Regarding the safety of the

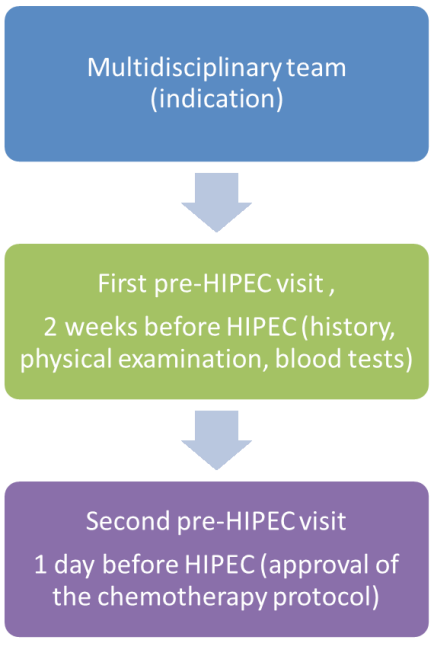

Fig. 1. Scheme of pre-HIPEC preparation of patients.

Table 1. Subgroups of patients according to the primary tumor.

Primary	n	Recurrent disease / Primary treatment	PCI (range)	CCS0	CCS1	CCS2
Ovarian cancer	17	7/10	5 (2-39)	10	3	4
Colorectal cancer	9	8/1	10 (1-25)	6	0	3
Pseudomyxoma peritonei	8	1/7	15 (6-34)	6	1	1
Mesothelioma	9	0/9	20 (3-31)	5	2	2
Endometrial cancer	1	1/0	6	0	0	1

n – number of patients, PCI – Peritoneal cancer index, CCS – cytoreduction score defined as macroscopically complete surgery (CCS0); optimal residual disease ≤2.5 mm in any region (CCS-1); or largely incomplete surgery with residual disease >2.5 mm (CCS-2).

procedure, patients are followed in several pre HIPEC and post HIPEC visits (Fig. 1).

Special attention was paid to nutritional status, risk of infection, medication especially regarding corticosteroids and oral anticoagulant use which may affect postoperative complications such as bleeding, delayed surgical wounds healing, pressure lesions, systemic infections, respiratory failure and increased hospitalization duration and increased mortality rate[12-14].

The first visit took place 2 weeks before CRS/HIPEC with a review of the patient's history, changes in medication, physical examination and complete blood test. The second visit followed one day before CRS/HIPEC with actual blood tests and a physical examination. The HIPEC regimen protocol is only approved in case of no contraindications. The post-CRS/ HIPEC visit to assess additional toxicity and manage adverse events followed 4 to 6 weeks after the procedure. The patients are followed further in 3 month intervals.

Table 2. HIPEC regimens used in COC Olomouc.

Primary	HIPEC regimen	n
Colorectal cancer	oxaliplatin 460 mg/m^2	7
	mitomycin C 30 mg//m^2	2
Mesothelioma peritonei	cisplatin 50 mg/m^2	9
	doxorubicin 15 mg/m^2	
Ovarian cancer	cisplatin 75 mg/m^2	17
	mitomycin C 30 mg/m^2	1
Pseudomyxoma peritonei	Oxaliplatin 460 mg/m^2	7
	mitomycin C 30 mg/m^2	1
Endometrial cancer	cisplatin 75 mg/m^2	1

n – number of patients.

RESULTS

Forty-four patients, 32 females and 12 males, were included in the retrospective analysis. All patients underwent the close method of CRS/HIPEC procedure. The cohort consisted of 17 patients with ovarian cancer, 9 patients with colorectal cancer, 9 patients with peritoneal mesothelioma, 8 patients with pseudomyxoma peritonei and 1 patient with endometrial cancer. The median age of the patients was 61 years (range 36 to 76 years).

The subgroup of 17 patients with ovarian cancer included 7 patients with the second or third recurrence of the disease. Ten patients had prior surgery for ovarian cancer. The median PCI was 5 (range 2-39). Cisplatin (75 mg/m^2) was administered in 16 patients and mitomycin C (30 mg/m^2) was administered in one patient with platinum-resistant disease. Ten patients had complete cytoreduction CCS0, 3 patients CCS1 and 4 patients CCS2 (Tables 1 and 2).

Only one patient out of 9 in the subgroup with colorectal cancer had no prior treatment. All the other patients had recurrent disease and had prior surgical or systemic treatment. The median PCI was 10 (range 1-25). Oxaliplatin (460mg/m^2) was administered to 7 patients and mitomycin C (30 mg/m^2) was used with 2 patients. Six patients underwent complete cytoreduction CCS0. It was impossible to accomplish a complete cytoreduction with 3 patients; the score of the cytoreduction was CCS 2.

With one exception, all the patients in the subgroup with pseudomyxoma peritonei underwent CRS/HIPEC as the primary treatment. Only one patient had a recurrent disease. The median PCI was 15 (range 6-34). Oxaliplatin (460 mg/m^2) was administered in 8 patients, and mitomycin C (30 mg/m^2) was administered in one patient. Complete cytoreduction of CCS 0 was achieved in 6 cases, one patient had minimal residual disease CCS1, and one patient had incomplete cytoreduction of CCS 2.

All the patients with mesothelioma peritonei were treatment-naive. A definitive histology confirmed sarcomatoid mesothelioma in one patient while other patients had epithelial peritoneal mesothelioma. The median PCI was 20 (range 3-31). All the patients were treated with cisplatin (50 mg/m^2) and doxorubicin (15 mg/m^2). Optimal cytoreduction of CCS-0 was achieved with 5 patients, cytoreduction of CCS-1 with 2 patients, and CCS-2 was accomplished ~~in~~ with 2 patients.

Preliminary results of PFS in the subgroups of patients

The median PFS has not been reached in the subgroup of 17 patients with ovarian cancer. The median of the follow up was 7 months (range 1–19 months; Fig. 2). In the subgroup of patients with colorectal cancer, the median PFS was 6 months (95%CI: 3–6.3 months; Fig. 3). No patient with pseudomyxoma peritonei has progressed during the median follow up of 7 months (range 1-16 months). One patient with mesothelioma peritonei had a disease

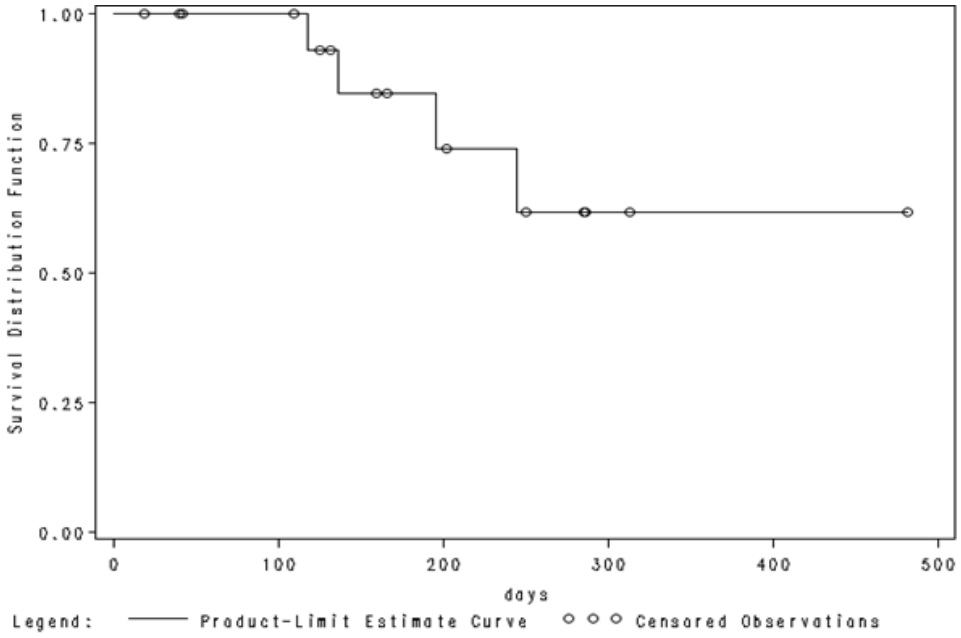

Fig. 2. Progression-free survival of patients with ovarian cancer.

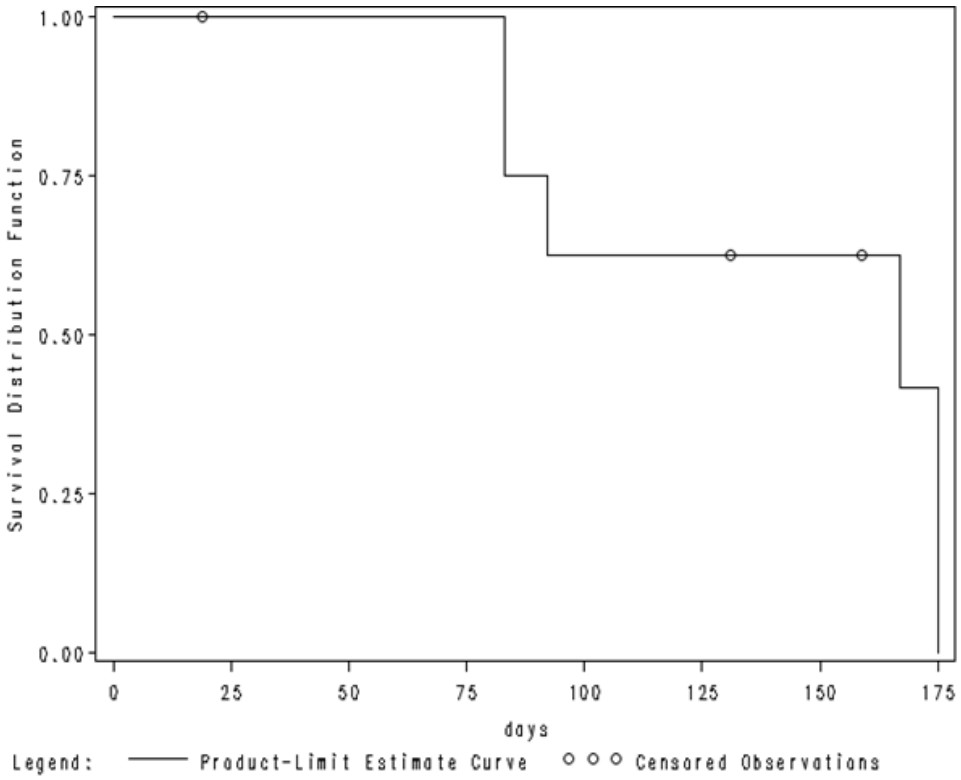

Fig. 3. Progression-free survival of patients with colorectal cancer.

progression, and the median follow up in this subgroup was 10 months (range 1–22 months). One patient with endometrial cancer was free of the disease 9 months after CRS/ HIPEC.

Adverse events, toxicity and safety of the treatment

Perioperative mortality was 2% (1/44) due to acute liver necrosis in one patient who received HIPEC oxaliplatin during the first week after surgery. Serious perioperative morbidity grade 3 and 4, according to the Clavien-Dindo classification, was 11% (5/44). Serious complications occurred in 4 patients with colorectal cancer and 1 patient with pseudomyxoma peritonei. All these patients underwent HIPEC with oxaliplatin 460 mg/m2. The patients were re-operated for suspected abdominal bleeding and inflammatory complications.

We observed postoperative non-surgical bleeding in the peritoneal cavity in our set with oxaliplatin HIPEC administration. We have not found any surgical source, eg. bleeding from vessels or from visceral organs as liver or spleen. This was a kind of diffuse bleeding from the soft tissues, from the retroperitoneum and abdominal wall after peritonectomy even if we have used a very precise surgical technique with the use of advanced thermocoagulation.

The median duration of admission to hospital was 6 days in the intensive care unit (range 2–28 days) and 7 days in the surgical ward (range 1–21 days). The hospital admission did not exceed 2 weeks in 75% of the patients.

DISCUSSION

The results of the present cohort of patients show a low perioperative mortality and acceptable morbidity associated with CRS/HIPEC with the proposed management of pre-HIPEC and post-HIPEC visits. No prolonged admission to either the intensive care unit or general surgical ward was reported. Most patients were discharged within 14 days of the procedure with the possibility of sequential adjuvant systemic treatment. The results of perioperative mortality of 2% and postoperative morbidity of 11% are consistent with the published results of high volume centres[4-6]. The results reflect the experience of the centre in terms of the "learning curve" and correct patient selection by the multidisciplinary team[15]. The perioperative mortality and morbidity are influenced by the extent of the surgical procedure, HIPEC regimens used as well as by the performance status of the patient, age, nutritional status, previous antitumor treatment, comorbidities and current medication. Increased morbidity is associated with performance status >1, age > 60 years and hypoalbuminemia. Additional complications occur in obese patients[15]. We believe that the scheme of pre-HIPEC and post-HIPEC visits with intervention to minimize the complications also contributed to the low morbidity and mortality numbers in our cohort. Serious morbidity was mainly reported in patients with colorectal cancer who had a recurrent disease and were mostly heavily pre-treated. In patients with colorectal cancer, the median PCI was 10 and complete cytoreduction was accomplished only in 50%. The HIPEC regimen utilized was oxaliplatin at a dose of 460 mg/m^2 administered in 30 min. Oxaliplatin is one of the most commonly used cytotoxic agents in HIPEC regimens. Oxapliplatin efficacy and toxicity have been evaluated in several retrospective trials. Some authors report the superiority of oxaliplatin above mitomycin C in terms of prolonged OS (ref.[16]), mostly in tumours with an unfavorable histology and more extensive involvement of peritoneum[17]. The present results differ from previously published retrospective data that did not report an increased rate of oxaliplatin toxicity compared to other cytotoxic agents[18-20] but are consistent with the results of the large randomized trial Prodige 7 (ref.[21]). This trial did not show greater efficacy of HIPEC with oxaliplatin in terms of prolonged OS or PFS compared to cytoreductive surgery alone, but increased risk of postoperative complications. The potential benefit of oxaliplatin was only observed in patients with low PCI from 11 to 15, and in this subgroup of patients the median OS was prolonged compared to surgery alone[21].

The evaluation of time to progression is limited by the short duration of the follow up in the present cohort. The cohort is also very heterogeneous even when split into subgroups of patients according the primary site. The heterogeneity with regard to the prior treatment of the patients and recurrence of the disease is mainly pronounced in the subgroup of patients with ovarian cancer and colorectal cancer. There is also heterogeneity in the HIPEC regimens and completeness of surgery. Only one patient had progression of the disease in the subgroups with mesothelioma and pseudomyxoma peritonei in the follow up of 7 to 10 months. These results are consistent with the published data that consider CRS/HIPEC as a standard therapeutic modality in this setting. In the case of pseudomyxoma peritonei, CRS/HIPEC has a prolonged median PFS to 8.2 years and median OS to 16.3 years[22]. In case of mesothelioma peritonei, conventional surgery and systemic chemotherapy resulted in a median OS of 1 year whereas CRS/HIPEC led to a median OS of 2.8 to 7.8 years[23].

The results of a prospective randomized trial of ovarian cancer, comparing CRS versus CRS/HIPEC, confirm CRS/HIPEC as a standard treatment modality in ovarian cancer stage FIGO III. This trial reported a median PFS of 14.2 months in a patient treated with CRS/ HIPEC versus 10 months in patients treated with CRS alone. The median OS was prolonged by 11 months[10]. The present cohort included 7 patients with recurrent ovarian cancer. In case of recurrent ovarian cancer, a much shorter PFS is expected. The PFS in a randomized phase 3 trial of recurrent ovarian cancer and maintenance therapy with PARP inhibitors reached only 5.5 months in the placebo group[24]. In the subgroup of patients with ovarian cancer the median PFS was not reached after a follow up of 7 months.

The prognosis of carcinomatosis of colorectal origin is dismal, with the reported median OS ranging between 5–12 months[25]. CRS/HIPEC initially brought some encouraging results which were presented by Verwaal et al.[26]. In the randomized trial, CRS/HIPEC prolonged OS by 5 months compared to systemic treatment of the peritoneal carcinomatosis. Similar results were reported by Elias et al.[27] in the patients treated with CRS/HIPEC the median OS was 63 months. These results were not confirmed, however, by prospective randomized trial PRODIGE 7 presented by Quenet et al.[21]. The trial compared CRS versus CRS/HIPEC. Patients who underwent CRS/HIPEC with oxapliplatin had more postoperative complications. The key role of cytoreductive surgery was emphasized, however, in this study. The median PFS in the subgroup of patients with colorectal cancer in the present cohort reached only 6.2 months. As mentioned previously, however, this subgroup consisted of heavily pre-treated

patients, and only 50% of the patients had complete cytoreduction of CCS0.

This initial experience and preliminary results confirm the safety of the combined treatment modality of CRS/HIPEC although the results are limited by the size and heterogeneity of the cohort. More complications were seen in HIPEC with oxaliplatin in the present cohort. These results are consistent with the recently published data from a prospective randomized trial of colorectal cancer and differ from previous retrospective trials. A larger cohort of patients is needed to compare the toxicity of the individual HIPEC regimens.

CONCLUSION

Correct indication of the patients by multidisciplinary teams is essential. Close follow up with pre-HIPEC and post-HIPEC visits with early interventions may contribute to low morbidity and mortality numbers. The performance status of the patients, previous treatments and the possibility of performing complete cytoreduction of CCS0-1 needs to be taken into consideration. The present preliminary results need to be assessed with caution with regard to the short duration of the follow up and heterogeneity of the cohort. However, these results support the benefit of CRS/HIPEC in the treatment of patients with pseudomyxoma peritonei, peritoneal mesothelioma and ovarian cancer.

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