

REVIEW ARTICLE

Management of peritoneal surface malignancy: a review of the recent literature

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Summary

Peritoneal carcinomatosis (PC) is a condition that has been associated with poor outcomes and up until recently was considered a terminal condition. However, recent data suggest that cytoreductive surgery (CRS) and the administration of hyperthermic intraperitoneal chemo-

therapy (HIPEC) is an effective therapeutic approach. This paper is a review of the recent literature regarding this issue.

Key words: colon cancer, HIPEC, mesothelioma, ovarian cancer, peritoneal carcinomatosis, pseudomyxoma

Introduction

The management of PC has proven to be a challenge for both medical and surgical oncologists. In the past, the presence of diffuse implants in the peritoneal cavity denoted terminal-stage disease, however current therapeutic approaches are in a position to improve patient outcome. If left untreated, the median overall survival with PC is 3-6 months [1]. CRS followed by HIPEC has proven to be a very effective treatment modality against several forms of PC [2].

Patient selection

A most important parameter to be assessed in the implementation of CRS & HIPEC is which patients may benefit from the procedure. So far CRS & HIPEC have been performed on patients with either primary peritoneal malignancy, such as peritoneal mesothelioma, or PC stemming from the appendix, ovaries, colon and rectum, stomach, pancreas and sarcoma.

When evaluating the fitness of a patient for CRS & HIPEC, the physician should take into account the tumor biology and the extent of the disease, whether there are alternative treatment options with lower morbidity and mortality and

equivalent outcomes, as well as the patient's age and comorbidities, which may compromise the postoperative course.

Cytoreductive surgery

CRS should not be confused with debulking surgery, which is surgery aimed to reduce the disease burden. Instead, cytoreduction is a series of peritonectomy procedures and visceral resections, as they have been described by Sugarbaker [3], aiming for the minimum possible residual disease, with optimal cytoreduction achieved when residual tumor is ≈ 0 . Our team has recently described a series of guidelines on performing diaphragmatic peritonectomy [4].

Rationale of HIPEC

Conventional treatment of PC includes surgery and systemic chemotherapy. However, surgery leaves at least microscopic disease behind and systemic chemotherapy is generally not effective due to poor drug penetration, relative resistance and systemic toxicity [5]. The administration of chemotherapy into the peritoneal cavity, not only ensures a better tissue exposure to the drug, but also minimizes systemic toxicity, as the

macromolecules do not enter systemic vascular circulation [6].

Regional treatment needs to fulfill three requirements in order to be effective:

- sufficient residence time (duration of drug contact with the residual disease)
- sufficient coverage with the administered solution (peritoneal contact area) and
- sufficient penetration of the drug into the tumor nodules [7].

Tumor microenvironment and microcirculation allow for a better drug permeability into the neoplastic tissue vs the adjacent normal anatomic structures [8].

Drug delivery at a temperature of 39 to 43°C increases cytotoxic activity, as increased temperature enhances the responsiveness of the tumor cells to the antineoplastic agents (“thermal chemosensitization”)[9]. Most cytotoxic agents used for HIPEC exhibit a significant enhancement of their pharmacokinetic properties when administered under hyperthermic conditions [10,11], thus improving the peritoneal–plasma barrier penetration and drug exposure time.

Peritoneal carcinomatosis index (PCI)

PCI is a valuable tool for the preoperative and intraoperative evaluation of disease extent [12]. The peritoneal cavity is divided in 13 regions and a lesion size score is recorded for each one, adding up to the final score, which can be used as a prognostic indicator for the disease course.

Preoperative and intraoperative assessment of the PCI appears to be concordant, even when evaluated by junior surgeons, with a slight increase in the score after CRS, proving it is a reliable tool for measuring the extent of PC [13].

Completeness of cytoreduction score (CC-score)

The completeness of cytoreduction score is the most powerful prognostic indicator for disease course, as it correlates significantly with overall survival after CRS & HIPEC [14,15]. A CC-0 equals to no visible disease, CC-1 is residual tumor < 0.25cm, CC-2 is 0.25 to 2.5cm and CC-3 is > 2.5cm [16,17]. Complete cytoreduction is considered to be achieved when the CC score is 0 or 1 [18].

Clinical application of CRS & HIPEC

Pseudomyxoma peritonei

Pseudomyxoma peritonei is a form of PC characterized by abnormal quantity of extracellu-

lar mucinous material and represents one of the most classic indications for CRS & HIPEC. Its clinicopathological features influence greatly the disease course. It is classified as disseminated peritoneal adenocarcinoma (DPAM), which is a low grade lesion, peritoneal mucinous carcinomatosis (PMCA), which is high grade, and an intermediate group (IG).

In a recent series from the Netherlands by Kuijpers et al., CRS & HIPEC were performed on 300 pseudomyxoma patients, achieving a median progression free survival (PFS) of 53 months, a median overall survival (OS) of 130 months, a 3-year overall survival rate of 77% and a 5-year overall survival rate of 65% [19].

A retrospective analysis of 48 patients with pseudomyxoma peritonei, 6 of which were treated with CRS & HIPEC, reported that HIPEC did not offer significantly to OS time, however age and pathologic type were prognostic factors [20].

Low grade appendiceal mucinous neoplasm is a precursor lesion of pseudomyxoma peritonei. Its management with minimal access cytoreductive surgery (MACRS) & HIPEC proved to be a safe alternative to the open procedure [21].

In a recent series of 80 patients with pseudomyxoma peritonei who underwent CRS & HIPEC, the median OS was 144 months and median PFS 88 months. Completeness of cytoreduction was the only significant variable influencing the outcome [22].

In another recent series of 39 patients, the 5-year overall survival rate was 89% and the 10-year overall survival rate 35%. The median OS was 37 months, while the median PFS was 4 months. The pathologic subtype was an independent prognostic factor and the implementation of HIPEC was significantly associated with postoperative recurrence time [23].

Previous patient series with pseudomyxoma peritonei are presented in Table 1.

Mesothelioma peritonei

Mesothelioma peritonei, or diffuse malignant peritoneal mesothelioma (DMPM), is a locally aggressive tumor with poor prognosis, associated most commonly with exposure to asbestos. The implementation of CRS & HIPEC has improved survival.

In a recent series of 42 patients affected by DMPM who underwent CRS & HIPEC, achieving a complete cytoreduction (CC-0, CC-1) in 90.4% of the patients, median OS was 65 months, while 1-year and 5-year overall survival rates were 63%

Table 1. Series of pseudomyxoma peritonei patients

First author, year [ref.no.]	Patients,N	Management	Morbidity %	Mortality %	3-year survival	5-year survival	10-year survival
Sugarbaker, 1999 [67]	385	CRS + perioperative HIPEC	27	2.7		CC-1, DPAM: 86% CC-1, PMCA + IG: 50% CC>1: 20%	CC>1: 0%
Witkamp, 2001 [68]	46	CRS + HIPEC	39	8.7	81%		
Elias, 2003 [69]	36	CRS + early postoperative or intra-operative IP chemotherapy	44	13.8		OS: 66% DFS: 55% DPAM: 74% IG, PMCA: 54%	
Deraco, 2004 [70]	33	CRS + HIPEC	grade II: 15 grade III: 18	3		OS: 97% PFS: 43% locoregional PFS: 59%	

CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy, CC: completeness of cytoreduction score, DPAM: disseminated pseudomyxoma peritoneal adenocarcinoma, PMCA: peritoneal mucinous carcinomatosis, IG: intermediate group, OS: overall survival, PFS: progression free survival

and 44% respectively [24].

A prospective study of 65 MPM patients identified as significant prognostic factors tumor histology, disease burden and the ability to achieve adequate cytoreduction in patients undergoing CRS & HIPEC. Median PFS and median OS were 13.9 and 46.2 months, respectively [25].

In another series, among 26 patients who underwent CRS & HIPEC for MPM, 8 had to be treated again with HIPEC, at approximately the same time other patients needed to receive systemic chemotherapy. Patients who underwent repeat HIPEC had an increased median survival (80 months), vs those on whom HIPEC was performed once. Positive prognostic factors were a low PCI and a low CC score [26].

In a series of 27 DMPM patients presented by Baratti et al. who underwent complete CRS & HIPEC, it was reported that the median OS and DFS were 62.3 and 25.1 months, respectively, with patients surviving more than 7 years (43.6%), appearing to be cured [27].

GLUT-1 expression by the tumor, as detected with immunohistochemistry, appeared to be a poor prognostic factor in a 28 DMPM patient series [28].

A multicentric study of 211 patients associated with more extensive tumor resection, low histologic grade and HIPEC with cisplatin (vs mitomycin) revealed a prolonged survival [29].

Schaub et al., having studied 104 patients who underwent CRS & HIPEC for MPM, produced a nomogram as a tool to assess patients who would benefit the most from the procedure, identifying histological type, preoperative PCI and preoperative serum CA-125 levels as having the greatest

impact on OS [30].

Bijelic et al., in a phase II study, came to the conclusion that adjuvant bidirectional chemotherapy with intraperitoneal pemetrexed combined with intravenous cisplatin is a safe therapeutic option for DMPM, with acceptable toxicity and morbidity rates [31].

Epithelial ovarian cancer

Several issues have raised as to the implementation of CRS & HIPEC in the treatment of PC from epithelial ovarian cancer (EOC), regarding mainly the patient selection and the optimal timing for the procedure.

While so far age over than 65 years was considered a major contraindication [32], two recent studies by Votanopoulos et al. [33] and Spiliotis et al. [34] demonstrated that HIPEC can be safely performed in patients older than 70 years, with acceptable postoperative morbidity and mortality.

Prognostic and predictive factors for optimal HIPEC in recurrent EOC are age < 65 years, Karnofski performance status > 80, interval from initial diagnosis > 12 months, PCI < 20, CC-0 or CC-1, absence of retroperitoneal lymph nodes and platinum - sensitive disease [35].

CRS & HIPEC have been performed at several time points in the disease course. However, it has been proven that maximum efficacy is achieved either after neoadjuvant chemotherapy without previous resection (interval CRS & HIPEC) or after initial cytoreduction and a full course of adjuvant chemotherapy in patients with clinically complete response (consolidation CRS & HIPEC) [15,36]. A recent study of 42 patients suggested that CRS &

HIPEC are most effective when applied as upfront and first-recurrence treatment, however it is recognized that these results warrant further evaluation in the context of a clinical trial [37].

The extent of cytoreduction is one of the most crucial prognostic factors, improving greatly OS in all disease stages, when a complete cytoreduction (CC-0 or CC-1) is achieved [38].

Vergote et al. demonstrated in a randomized trial including stage IIIC and IV EOC patients that neoadjuvant chemotherapy followed by interval debulking surgery and primary debulking followed by chemotherapy have similar outcomes in terms of survival, indicating complete resection of macroscopic disease as the most important prognostic factor, whenever surgery is performed [39].

A recent case-control study by Fagotti et al. compared survival data in 30 platinum sensitive EOC patients undergoing secondary CRS & HIPEC vs 37 patients who did not undergo HIPEC. Statistically significant results were reported in favor of the HIPEC group regarding the rates of secondary recurrence, the duration of secondary response and mortality [40].

In a recent series of 70 EOC patients, divided in two groups (first recurrence after surgery and adjuvant chemotherapy, 6 months after chemotherapy vs multiple relapses), survival was similar in the two groups after CRS & HIPEC [41].

A recent study of 566 EOC patients after CRS & HIPEC demonstrated similar survival rates for

both advanced and recurrent disease, also between chemosensitive and chemoresistant disease [42]. Survival was similar in another recent study in both advanced and recurrent disease [43].

The CHIPOR study is a phase III randomized trial in progress, evaluating the efficacy of HIPEC with cisplatin in patients with a first EOC recurrence, 6 months after first-line treatment [44].

A recent phase III trial on 120 EOC patients by Spiliotis et al.[45] demonstrated a survival benefit in the HIPEC group. Moreover, it was shown that in the HIPEC group, the mean survival was not different between platinum resistant patients vs platinum sensitive disease, while in the non-HIPEC group, there was a statistically significant difference between platinum sensitive vs platinum resistant disease.

Recent patient series are presented in Table 2.

Colorectal carcinomatosis

Approximately 25,000 colorectal cancer patients worldwide are suitable candidates for CRS & HIPEC yearly. It has been proven that HIPEC improves survival significantly compared with palliative chemotherapy [46,47].

All recent prospective and case-control studies all report the survival benefit that CRS & HIPEC adds [48-53].

Clinical trials concerning colorectal cancer and HIPEC are in progress. The one from the American Society of Peritoneal Surface Malignan-

Table 2. Series of epithelial ovarian cancer patients

First author, year [ref. no.]	Patients, N	Stage	Optimal CR %	Median OS	3-year OS %	5-year OS %	Median DFS	5-year DFS %	Morbidity %	Mortality %
Furet, 2013 [71]	17	Recurrent	94	8,9 y			11.9 m		58.8	0
Chan, 2012 (review) [72]	1167	Advanced		14-64 m		35-70	13-56 m		0-40 major	0-5
		Recurrent		23-49 m		12-54	13-24 m		0-49 major	0-10
Bakrin, 2012 [73]	246	Recurrent, Persistent	92.2	48.9 m					11.6	0.37
Deraco, 2012 [74]	56	Recurrent	96.4	25.7 m		23	10.8 m	7%	26.3	5.3
Tentes, 2012 [75]	43	Advanced	69.8			54			51.2	4.7
Spiliotis, 2011 [76]	24 (CRS & HIPEC) vs. 24 (CRS)	Recurrent	83 vs 66	19.4 m vs 11.2 m (SS)	50 vs. 18				40 vs 20	0 vs 0
Spiliotis, 2014 [45]	60 (CRS & HIPEC) vs 60 (CRS)	Recurrent		26.7 m vs 13.4 m (SS)	75 vs 18 (SS)					

m: month, y: year, CR: cytoreduction, OS: overall survival, DFS: disease free survival, SS: statistical significance

cy (phase III) has initial promising results and the COMBATAC trial (phase II) from Germany, which will explore the efficacy of HIPEC combined with systemic chemotherapy [54]. PRODIGE 7 is an ongoing phase III trial in France, aimed to assess if HIPEC adds a survival benefit after CRS for colorectal carcinomatosis [44].

Second look laparotomy has proved very useful in identifying patients at high risk for PC of colorectal origin and the subsequent HIPEC administration [55,56]. Patients at high risk for PC are those who have a positive peritoneal lavage, who have had a mucinous T3 carcinoma or a T4 adenocarcinoma, if intraoperative tumor rupture occurred, if invasion of adjacent structures was present, N2 status or patients with positive or dubious surgical margins. Elias et al. performed second look surgery and HIPEC in asymptomatic high risk patients one year after the initial operation, to find that 56% of them had indeed developed PC. After second look surgery and HIPEC, the 5-year OS was 90% and the 5-year DFS was 44%. The authors also noted that the presence of PC at second look surgery is prognostic of recurrence [56].

The implementation of CRS & HIPEC in patients with metastatic ovarian disease of colorectal or appendiceal origin demonstrated similar survival rates in patients both with and without ovarian metastases, denoting that despite the disease being extensive, it is still responsive to this treatment approach [57].

Results of phase II trials are presented in Table 3.

Gastric cancer

The efficacy of CRS & HIPEC in the treatment of peritoneal dissemination of gastric cancer has been proven not only in prospective studies, but also in the setting of a phase III randomized trial, demonstrating that HIPEC adds a significant sur-

vival benefit [58]. With good patient selection and complete cytoreduction, a 5-year survival of 23% can be achieved [59].

A meta-analysis of the efficacy of intraperitoneal chemotherapy demonstrated an increased survival over the first 3 years post treatment [60].

Recent series present a survival benefit that needs to be evaluated in larger cohorts [61,62], also prophylactic HIPEC has been identified to improve outcome [63].

GASTRICHIP is a phase III trial in progress, aimed to assess the 5-year survival in gastric cancer patients who undergo D2 resection and HIPEC vs D2 resection alone [64].

A new prospect in the treatment of inoperable gastric cancer involves the treatment with bidirectional chemotherapy (intraperitoneal and systemic). Patients initially receive 3-4 cycles of neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) and this leads to downstaging in 30% of the patients, in 50% of whom complete cytoreduction can be achieved. The treatment is completed with the administration of adjuvant intraperitoneal and systemic chemotherapy (AIPS) [65].

Morbidity, mortality and quality of life after CRS & HIPEC

It is still unclear whether increased morbidity and mortality is related to the extent of CRS or HIPEC. Major surgery with visceral resections and peritonectomy procedures is itself associated with high morbidity.

Most common complications include ileus, anastomotic leakage, bleeding, wound infection, fistula formation, pleural effusion and thrombocytopenia [35].

Zhu et al., in a review article, reported a morbidity rate ranging from 14 to 56.5% and a mortality rate ranging from 0 to 4.2% [66].

Regarding quality of life, despite the ini-

Table 3. Phase II trials in colorectal PC treated with CRS & HIPEC

First author, year [ref. no.]	Patients, N	Follow – up (months)	Median survival (months)	2-year survival %	5-year survival %
Pestiau, 2000 [77]	44	40	24	-	30
Elias, 2001 [78]	64	52	36	60	27
Pilati, 2003 [79]	34	15	18	31	-
Shen, 2004 [80]	37	15	28	55	34
Glehen, 2004 [81]	23	60	33	54	21
Verwaal, 2005 [82]	59	-	43	-	43
Elias, 2006 [83]	30	55	60	73	48

tial drop in physical, emotional, functional and well-being scores after surgery, these return to baseline levels at 3, 6 and 12 months postoperatively. Most patients reported a return to baseline or better level of functioning within 3 months postoperatively [66].

Conclusion

CRS and HIPEC are safe therapeutic approaches, which, when applied to carefully selected PC patients, greatly improve survival of this, otherwise considered, terminal condition.

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