Curr Colorectal Cancer Rep (2017) 13:144–153
DOI 10.1007/s11888-017-0361-x

Current Management of Peritoneal Carcinomatosis From Colorectal Cancer: the Role of Cytoreductive Surgery and Hyperthermic Peritoneal Chemoperfusion

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Published online: 8 April 2017

Abstract Peritoneal carcinomatosis (PC) from colorectal cancer (CRC) is a disease with a poor prognosis, often thought to be a terminal illness with no hope except for palliative treatment. New therapeutic modalities combining cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have shown favorable outcomes and may provide a significant survival benefit in a selected group of patients. The main rational for CRS is to remove all visible tumor burden to allow for the chemotherapeutic agent (HIPEC) to eradicate any microscopic residual disease. The Amsterdam statement formulated at the 9th International Congress on Peritoneal Surface Malignancies supports the use of CRS with HIPEC as a standard of care for selected patients with small-to-moderate volume PC from CRC. Selecting appropriate patients who would benefit from CRS/HIPEC is paramount to derive the maximum oncological outcomes while minimizing the risks of postoperative complications and mortality. In this paper, we will review the role for CRS/HIPEC in the management of PC from CRC.

Keywords Peritoneal carcinomatosis · Colorectal cancer · Cytoreductive surgery · Hyperthermic chemoperfusion

This article is part of the Topical Collection on *Surgery and Surgical Innovations in Colorectal Cancer*

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Introduction

Globally, colorectal cancer (CRC) is the third leading cause of cancer, totaling 1.6 million incident cases in 2013, and the fourth leading cause of cancer-related mortality, accounting for 771, 000 deaths [1]. Peritoneal carcinomatosis (PC) is present in about 4–15% of patients with CRC at initial diagnosis and in up to 50% in recurrent disease following curative resection [2–7]. Patients with T4 disease, advanced nodal stage, and right-sided tumors have a higher risk for synchronous PC [6]. Adding to these factors, patients who undergo emergency or non-radical resection of the primary tumor are at a higher risk of a metachronous presentation of PC [7].

Peritoneal carcinomatosis was thought for a long time to be a terminal disease with limited surgical options and only amenable to palliative treatment. Earlier studies showed that the median survival of patients with peritoneal carcinomatosis was from 5.2 to 7 months [3, 6, 8]. Due to these dismal results, new therapeutic modalities emerged, including cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). The aim of this treatment strategy is to provide locoregional control and improved long-term survival. CRS with HIPEC has been used with variable success to treat pseudomyxoma peritonei, appendiceal mucinous neoplasias, peritoneal mesothelioma, PC from gastric, colorectal, and ovarian cancer, and other primary peritoneal surface malignancies [9–12].

The aim of this review is to discuss the pathophysiology of PC, the rationale of using CRS with HIPEC for the treatment of PC, the surgical technique, and the chemotherapeutic agents used. In addition, we will present the current treatment approaches for PC from colorectal cancer and the clinical and oncological outcomes of these therapies.

Pathophysiology of Peritoneal Carcinomatosis From GI Malignancies

PC is thought to be a locoregional disease with two main mechanisms that result in peritoneal spread of the primary tumor: (1) transmural tumor invasion that results in the exfoliation of free cells, which directly spread to the peritoneum; (2) visceral perforation or surgical trauma that causes cell spillage from the bowel lumen or the dissected vasculature that harbor tumor cells in transit [13].

Peritoneal spread results from a cascade of events that start by the loss of cell-cell adhesion molecules [14, 15]. This is followed by anoikis resistance, which refers to cell resistance to apoptosis and usually occurs when a normal cell loses cell matrix contact [16]. Thereby, tumor cells migrate and adhere to the peritoneal surface through integrin and cadherin proteins. Then, using proteolytic enzymes such as matrix metallopeptidase, the tumor cells digest the extracellular matrix, facilitating invasion, colonization, and finally, homing to the peritoneum [17].

The distribution of peritoneal disease is nonrandom and is concentrated usually in specific areas such as the pelvis, the subphrenic and paracolic spaces, as well as in Morrison's pouch, which are gravity-dependent areas. PC also concentrates at the omentum and diaphragmatic peritoneum as they constitute the absorptive surface for peritoneal fluid. On the other hand, the small intestine serosa is spared in the early stages of PC due to the peristaltic motility preventing tumor cell adhesion. Collectively, peristaltic movement of the bowel, fluid absorption, gravity, and tumor characteristics determine the pattern of tumor spread in the peritoneum known as neoplastic redistribution [18, 19].

Rationale for Cytoreduction and HIPEC

The presence of localized disease within the peritoneal cavity with the absence of distant metastasis makes CRS with HIPEC an attractive approach. The main rationale of CRS is to remove the bulk of the disease in order to allow for the chemotherapeutic agents to treat any remaining small volume or microscopic residual tumor. While the additional contribution of HIPEC to prolonged survival after surgery is not known, it is well established that the best perfusion strategies cannot penetrate more than few millimeters into the tumors. Thus, decreasing the bulk of the disease to microscopic or subcentimetric is thought to allow better penetration of cytotoxic drugs into the remaining tumor cells [13]. Based on the Norton-Simon hypothesis, tumor response to chemotherapy and cell death is proportional to the growth rate of the tumor [20, 21]. Since smaller tumors tend to grow faster until they overcome their blood supply, reducing the size of the tumors will stimulate the remaining cells to proliferate and thereby become potentially more sensitive to chemotherapy [22, 23]. Additionally, extensively debulking the tumors might potentially remove resistant clones and lead to a decrease in the chance of tumor-resistant development. With smaller residual disease, chemotherapy should be more effective in treating the disease, thus reducing the time for the cells to divide and to develop drug-resistant clones [18].

The rationale behind the use of intraperitoneal chemotherapy is to intensify the dose of chemotherapy delivered to the tumor while limiting the systemic toxicity of the drug. The blood and the peritoneal cavities are separated by a semipermeable membrane with a specific peritoneal-plasma partition that allows non-lipophilic and high molecular weight chemotherapeutic agents to accumulate in the peritoneal cavity, limiting their entry to the circulation [24–26]. In addition, hyperthermia potentiates the effects of chemotherapeutic agents independently of the cell cycle phase of the tumor cell, leading to higher tumoricidial effects with short exposure [27–29]. The timing of the peritoneal perfusion is also important. It is thought that intraoperative perfusion is more effective than the postoperative approach. Intraoperative treatment allows the placement of the chemotherapeutic agent in an adhesion-free space and minimizes the exfoliation of cancerous cells from surgery. On the other hand, postoperative drug instillation may be hindered by intra-abdominal adhesions and might be complicated by the presence of an intra-abdominal catheter [13, 30, 31]. More data are still needed for a better understanding of the mechanism of action of different chemotherapy agents, their effect on oncological outcomes, and the role of hyperthermia in the treatment of peritoneal malignancies.

Surgical Technique

The aim of CRS is to remove all visible disease with a target of complete cytoreduction (no visible tumor) to allow HIPEC to have an optimal effect [18]. The oncological principles of peritonectomy and CRS were first described by Sugarbaker. This includes the removal of the parietal and visceral peritoneal area affected by tumor deposits with multivisceral resection of organs that have significant tumor burden [32]. Usually, a splenectomy, cholecystectomy, appendectectomy, adnexectomy, and small bowel resection are needed depending on the location of the tumor implants. The primary colorectal tumor should be removed with a wide portion of the mesocolon or mesorectum and adequate lymphadenectomy. Because the risk of anastomotic leaks is higher after HIPEC, if rectal resection is performed, the authors recommend creating a diverting loop ileostomy or proceeding with an end colostomy if the likelihood of pelvic recurrence is high. Organ resections can be coupled with in situ destruction of tumor implants if they involve vital organs that cannot be resected. In addition, it is important to perform a complete lysis of adhesions and to open all intra-abdominal spaces by

taking down all ligamentous barriers in order to allow optimal circulation of the chemotherapeutic perfusate to facilitate adequate exposure of all residual disease to the drug.

The completeness of cytoreduction is graded by the surgeon as CC-0 (no visible disease), CC-1 (<2.5 mm residual disease, CC-2 (2.5–25 mm), and CC-3 (>25 mm residual disease), or by using the R score (R0 = complete resection, R1 = no gross disease with microscopic positive margins, R2 = macroscopic residual disease [R2a ≤ 5 mm, R2b = 6–20 mm, R2c ≥ 20 mm]; Table 1) [33, 34].

There are open and closed techniques to perform HIPEC. The open technique consists of placing a plastic sheet over the abdomen. The surgeon will access the abdomen though a slit in the plastic cover and manipulate the viscera to provide homogenous spatial distribution of the chemotherapeutic drug [33]. The closed technique, endorsed by the authors, consists of closing the abdomen temporarily with a running suture after placing inflow and outflow catheters for circulation of the chemotherapeutic drug. This technique improves penetration of the therapeutic drug due to increased intra-abdominal pressure and enhances safety for the surgical team as it will minimize contact with the drug [35, 36]. Two inflow catheters are placed under the left and right costal arch lying underneath the diaphragm. An additional inflow catheter can be placed at the level of the right iliac fossa lying along the mesenteric root. The outflow drain is placed in the pelvis entering through the left iliac fossa. A 3 L volume of crystalloid perfusate is established at a flow rate of 800 to 1000 ml/min with an inflow temperature above 42 °C using a special hyperthermia pump. This device pumps the solution into the peritoneal cavity, withdraws, reheats, and recirculates it back to the body for a period of time specified by the surgeon, usually 90 min. The chemotherapeutic drug is added at specific concentration and allowed to perfuse for a variable time period depending on the drug used. Thereafter, the skin is opened, the catheters removed, and the anastomoses are created. Finally, the ostomies are formed if needed and the fascia is closed in the usual fashion. The patient is transferred to the intensive care unit for monitoring [37].

Chemotherapy Agents

Agents appropriate for HIPEC should be directly cytotoxic and therefore cell cycle nonspecific. Moreover, they should have no severe direct local toxicity, have low systemic toxicity, have known efficacy against the tumor type treated, and have a synergistic effect with heat [18]. Different regiments of single or combination chemotherapies have been used in HIPEC procedures including mitomycin-C +/− doxorubicin or +/− cysplatin, oxaliplatin, and cisplatin + doxorubicin [38]. At the Fifth International Workshop on Peritoneal Surface Malignancy, there was an agreement that cisplatin and mitomycin-C can be used in routine clinical practice as single agents [38].

Table 1 Completeness of cytoreduction (CC) score [33]

	Classification	Residual disease
Complete	CC-0	None
	CC-1	<2.5 mm
Incomplete	CC-2	2.5 mm–2.5 cm
	CC-3	>2.5 cm

Many centers, including ours, use mitomycin-C for the treatment of PC from CRC. To standardize HIPEC delivery, the American Society of Peritoneal Surface Malignancies proposed mitomycin-C as the drug of choice using the closed technique. The dose suggested was 40 mg of mitomycin-C with 30 mg being delivered at time 0 and 10 mg at 60 min with a total duration of 90 min. The drug is to be delivered using 3 L of perfusate at an inflow temperature of 42 °C [39••]. Mitomycin-C is an alkylating antineoplastic antibiotic isolated from Streptomyces bacterial species. It cross-links DNA and thereby causes the inhibition of DNA synthesis [40]. It has adventitious pharmacokinetic properties with a high intraperitoneal-to-plasma drug AUC ratio, and it can penetrate tumors as thick as 2–5 mm and its activity is enhanced by hyperthermia [41]. The only randomized trial comparing systemic chemotherapy +/− palliative surgery to CRS with HIPEC used mitomycin-C as the chemotherapeutic agent and found improved survival with the CRS with HIPEC [42]. While the additional benefit of HIPEC to CRS cannot be answered by this trial, the question may be addressed when the results of the PRODIGE 7 trial are published as it compares CRS to CRS with HIPEC [43].

Perioperative Outcomes of CRS and HIPEC

While minimally invasive surgery has been adopted in metastatic CRC over the last decades with favorable perioperative outcomes, the extent of the disease in PC prevents such an approach and calls for the ultimate maximally invasive surgical procedure, which is CRS [44]. In the past, this approach has drawn criticism due to its high morbidity and mortality with limited evidence of its benefit.

In a systemic review of 24 series of CRS with perioperative intraperitoneal chemotherapy, Chua et al. found that the rate of major complications was 0–53% across all studies and was 12–52% in high-volume centers [45]. Postoperative complications were related to surgery and chemotherapy. The most common were ileus (0–86%), abscess (0–37%), hematological toxicity (0–28%), fistula (0–23%), sepsis (0–10%), anastomotic leak (0–9%), deep venous thrombosis/pulmonary embolism (0–9%), and renal failure (0–7%). The rate of mortality was 0–17% across all studies and 0.9–5.8% in tertiary high-volume centers. The most common causes of mortality

were sepsis and multi-organ failure [45]. A more recent report using the American NSQIP database from 2005 to 2001 cited an overall morbidity of 33% and mortality of 2% in a cohort of 694 patients [46•]. Similarly, in a multi-institutional series of 2298 patients, the rates of major operative complications and treatment-related mortality were 24 and 2%, respectively [47].

Predictors of major morbidity are performance status, peritoneal cancer index (PCI) score, extent of cytoreduction, number of anastomoses, number of peritonectomies and resections, operative duration, and dose of chemotherapy [48–52, 53•]. Several studies have shown that this procedure has a learning curve that needs to be overcome in order to improve postoperative outcomes [53•, 54]. We previously reported that 180 cases are needed to minimize severe morbidity in the institutional experience of a high-volume CRS/HIPEC program [53•]. Mentorship by an experienced surgeon can decrease the number of cases required to become proficient and thereby optimize postoperative outcomes [55].

While this procedure may pose significant morbidity and mortality, these outcomes are comparable to other major surgical procedures and may be justified as it is the last and only resort for cure in patients with PC from CRC. Careful selection is needed to optimize the outcomes following such a procedure [45, 46•].

Oncologic Outcomes of Systemic Chemotherapy in PC for CRC

There is a paucity of prospective data on the effect of systemic therapy alone in patients with PC. In the earliest periods where fluorouracil was used alone, the survival was dismal with a median not exceeding 7 months [3, 6, 8, 56, 57]. In a more recent pooled analysis of the North Central Cancer Treatment Group phase III trials N9741 and N9841, where patients with PC from CRC were treated with more contemporary chemotherapy, including oxaliplatin- and irinotican-based regimens, the median overall survival of 364 patients with PC from CRC was 12.7 months. The use of oxaliplatin, fluorouracil, and leucovorin was superior to irinotican, leucovorin, and fluorouracil [58]. The National Comprehensive Cancer Network guidelines recommend the use of combinations of cytotoxic chemotherapy and/or biological agents for the treatment of nonresectable metastatic CRC [59]. While these results were superior to those in the earliest studies where monotherapy was used, the prognosis is still so dismal that alternative therapeutic modalities were investigated such as CRS and HIPEC.

Oncologic Outcomes of CRS and HIPEC in PC for CRC

Several expert groups and surgical societies have now endorsed the use of CRS/HIPEC in selected patients with PC from CRC. The Amsterdam statement formulated at the 9th International Congress on Peritoneal Surface Malignancies supports using CRS with HIPEC as the standard of care for selected patients with small-to-moderate volume PC from CRC [60]. Likewise, the Society of Surgical Oncology released a consensus statement that "systemic therapy alone is no longer appropriate for patients with limited peritoneal dissemination from a primary or recurrent colon cancer," recommending the referral of patients with PC to a surgical oncologist experienced in CRS with HIPEC [61]. The literature supporting this recommendation is based on several hundred patients of numerous multicenter and single-center series, a few case-matched control studies, and one randomized controlled trial (Table 2).

In 2004, Glehen reported the outcomes of 506 patients with PC from CRC treated with CRS with perioperative intraperitoneal chemotherapy at 28 institutions [5]. With a median follow-up of 53 months, the overall median survival was 19.2 months in all patients, 32.4 months in patients with complete CRS, and 8.4 months for patients with incomplete CRS. Positive predictors of survival were complete CRS, limited disease extent, age less than 65 years, treatment by second procedure, and the use of adjuvant therapy.

In 2010, Elias et al. published a large multicenter study including 523 patients with PC from CRC from 23 centers [62]. With a median follow-up of 45 months, the overall median survival was 30.1 months and the 5-year overall survival was 27%. Similar to previous studies, favorable predictors of survival were limited PC extent, complete CRS, no lymph node invasion, and the use of adjuvant therapy. Notably, 16–24% of patients in these studies were treated with early postoperative intraperitoneal chemotherapy (EPIC) instead of HIPEC [62].

Weber et al. reviewed 14 single-center studies and found that the median survival ranged from 12.8 to 38.4 months. The 5-year overall survival varied from 11 to 36%. One study reported a median survival of 60.1 months and a 5-year overall survival of 48% as it only included patients with complete CRS or residual disease less than 2 mm [63, 64].

Elias et al. compared 48 patients treated with palliative chemotherapy to 48 patients who underwent CRS with HIPEC and found that the median survival of the latter group was 62.7 months compared to 23.9 months for the standard chemotherapy group [65]. Franko et al. found the median survival of CRS with HIPEC patients ($n = 67$) was 34.7 months compared to 16.8 months for control patients receiving only palliative systemic therapy ($n = 38$) [66]. Similarly, Chua et al. showed that the use of CRS with HIPEC was associated with a median survival of 38 months compared to 9 months for palliative treatment [67].

Verwaal et al. randomized 105 patients to systemic chemotherapy with fluorocuracil-leucovorin with or

Table 2 Oncological outcomes following CRS with HIPEC reported by selected relevant studies

Author, year	Therapy	*n*	5-year survival (%)	Median survival (months)
Randomized trial				
Verwaal et al. 2003/2008 [42, 68••]	HIPEC	54	45[a]	22.3
	Control	51	–	12.6
Multicenter studies				
Glehen et al. 2004 [5]	HIPEC EPIC	271 123	27	19.2
	HIPEC + EPIC	112		
Elias et al. 2010 [62]	HIPEC EPIC	443 84	–[b]	30.1
	HIPEC + EPIC	9		
Case–control studies				
Elias et al. 2009 [65]	HIPEC	48	51	62.7
	Control	48	13	23.9
Franko et al. 2010 [66]	HIPEC	67	–	34.7
	Control	38	–	16.8
Chua et al. 2011 [67]	HIPEC/EPIC	110	–	38
	Control	184	–	9

[a] Patients with R1 resection

[b] Three-year survival 48%

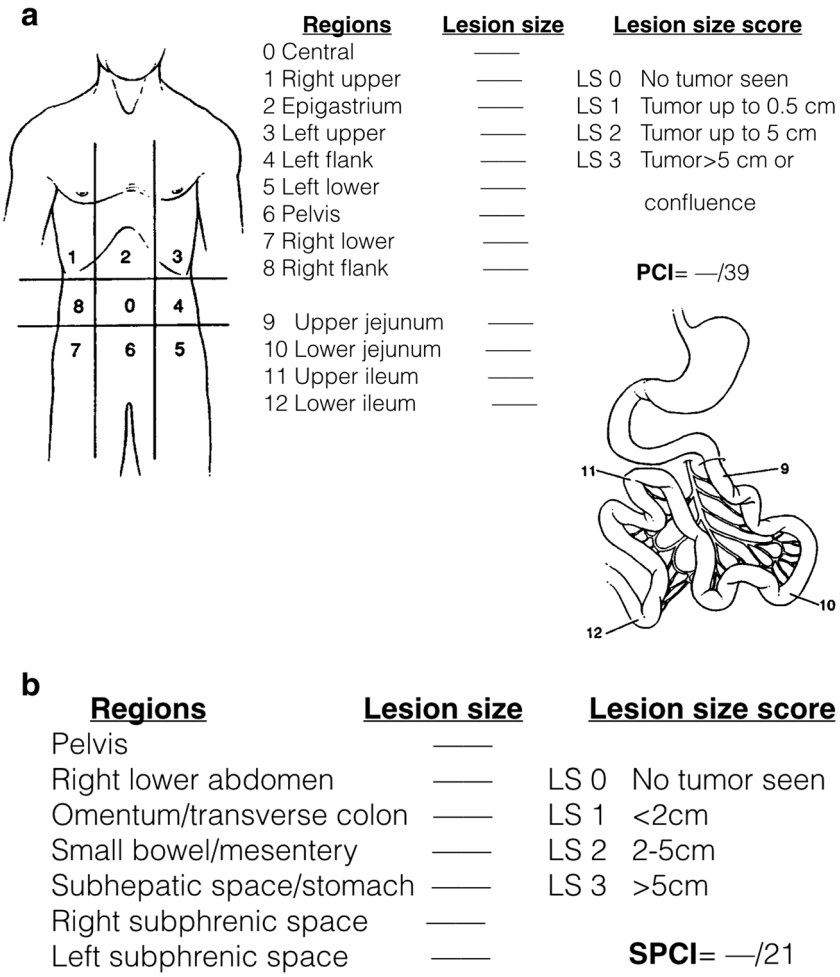

Fig. 1 Different systems to quantify the extent of peritoneal disease. **a** Peritoneal Carcinomatosis Index (PCI) score. Reproduced from Sugarbaker [33], with kind permission from Springer. **b** Simplified Peritoneal Carcinomatosis Index (SPCI) score [73]

without palliative surgery or to CRS with HIPEC using mitomycin-C. The primary tumor was colonic in 66.7% of the cases, rectal in 11.8% and appendiceal in 21.6%. With a median follow-up of 21.6 months, they found that the median survival was improved to 22.3 months with CRS with HIPEC compared to 12.6 months with the standard therapy. Subgroup analysis did not find any effect of the site of the primary tumor on survival. The extent of the disease and the completeness of CRS were associated with survival [42]. In a subsequent study with an 8-year follow-up, Verwaal et al. showed that patients without residual macroscopic tumors after CRS had a median survival of 48 months and a 5-year survival rate of 45% [68••].

Collectively, these data are encouraging as they show that CRS with HIPEC can provide prolonged survival from a disease that was considered to be incurable. Patients with low disease burden amenable for complete cytoreduction benefit the most from this treatment modality in combination with systemic chemotherapy.

Current Management of CRC with PC

A multidisciplinary approach is paramount for appropriate patient selection and management of patients with PC from CRC. Careful patient selection for CRS/HIPEC enables better oncological outcomes while minimizing the risks of postoperative complications and mortality. This treatment modality consists of a long operative procedure that could be associated with substantial morbidity and mortality [52]. Therefore, only patients who are medically fit should be considered for CRS/HIPEC. Reuter et al. showed that patients with an Eastern Cooperative Oncology Groups (ECOG) status ≥2 have a complication rate of 89% compared to 26% for patients with an ECOG status <2 [52].

Concurrently, one should take into account preoperative factors that predict a favorable oncologic outcome. First, a thorough staging work-up with cross-sectional imaging should be performed since patients with extraperitoneal disease or bulky retroperitoneal disease are not eligible for CRS with HIPEC. Patients with hepatic metastasis have worse

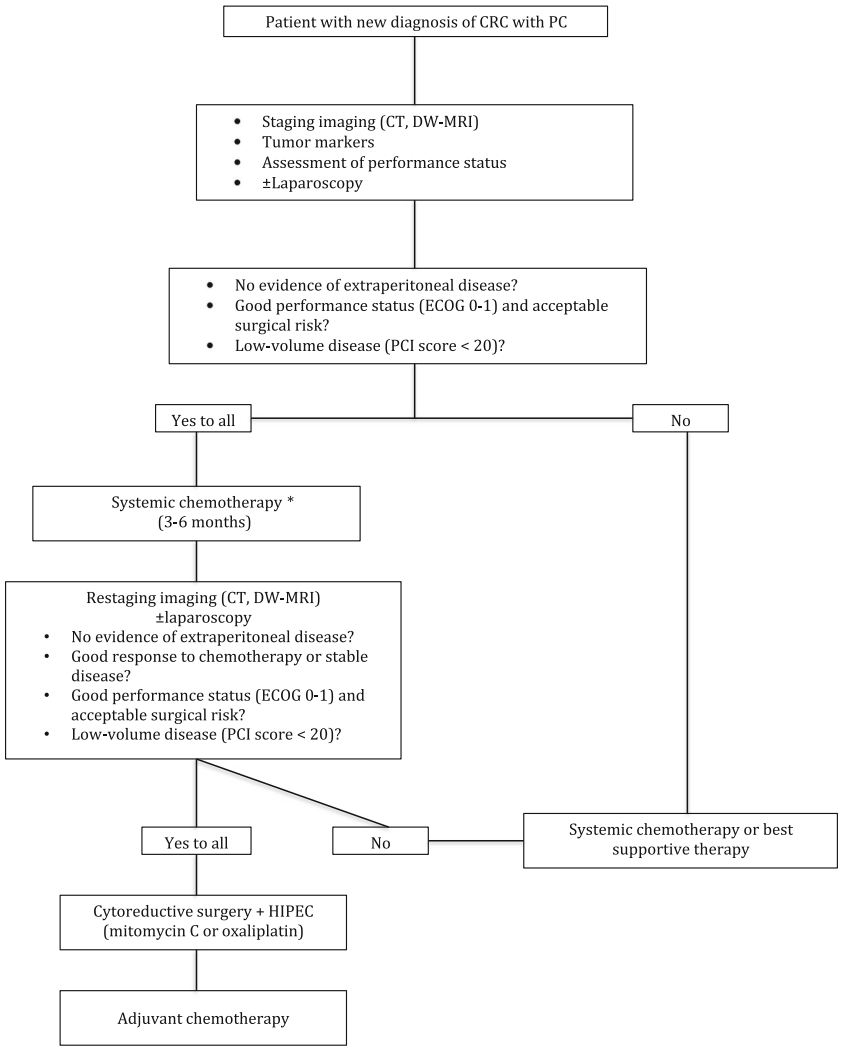

Fig. 2 Management algorithm for colon cancer with peritoneal carcinomatosis. * Systemic chemotherapy treatment may vary based on patient's health, previously received chemotherapy regimens, Kras mutation status, and/or tumor characteristics. Abbreviations: *CRC*, colorectal cancer; *CT*, computerized tomography; *DW-MRI*, diffusion-weighted magnetic resonance imaging; *ECOG*, Eastern Cooperative Oncology Groups performance status; *HIPEC*, hyperthermic intraperitoneal chemotherapy; *PC*, peritoneal carcinomatosis; *PCI*, Peritoneal Cancer Index score

oncological outcomes and should not be routinely considered [69]. There is some controversy regarding the best imaging technique to use to adequately stage and assess tumor burden in patients with PC [70]. Our group considers that a helical CT scan with IV contrast may be sufficient in patients with bulky peritoneal disease. However in patients with small peritoneal implants, diffusion-weighted magnetic resonance imaging (DW-MRI) may be a more sensitive study. Moreover, DW-MRI may be a superior technique for early detection of recurrence [70]. Several serum tumor markers have been reported to be elevated in patients with peritoneal malignancies of gastrointestinal etiology (CEA, CA 19.9, CA 125) [71]. Although routinely obtained as part of pretreatment or preoperative work-up and to assess treatment response, these markers are not relevant in patient selection for CRS/HIPEC.

In addition, only patients with disease amenable to complete cytoreduction (CC0/1 or R0/1) should be considered since incomplete cytoreduction (CC 2/3 or R2) is associated with worse survival [5, 69]. Therefore, assessment of the disease burden should be performed intraoperatively and should be scored. Different systems are used to quantify the extent of peritoneal disease (Fig. 1). The PCI system was first developed by Sugarbaker and scores the disease burden from 0 to 36 based on the size of the tumor and its distribution along 13 regions [72]. This scoring system can be used to determine a favorable group of patients. Sugarbaker showed that the 5-year survival was 50% for patients with PC from colon cancer and PCI ≤10, 20% for PCI of 11–20, and 0% for PCI >20 [33]. Therefore, he recommended that PC from CRC with PCI >20 should be treated with palliative intent only. Glehen et al. showed that patients with PC from CRC and a PCI <13 had significantly better survival outcomes with 5-year survival rates of 33% compared to 11% for patients with PCI ≥13 [5]. The Netherlands Cancer Institute developed the Simplified PCI (SPCI) which quantifies the tumor burden in seven regions with a maximum score of 21 [73]. Patients with six or seven regions affected or with an SPCI >12 had limited benefit from CRS with HIPEC [73, 74].

In our practice, we applied a simple algorithm of selection and management of patients with PC from CRC (Fig. 2). Patients with PC with CRC could be acceptable candidates for CRS/HIPEC if they present with absent extraperitoneal metastases, good performance status (ECOG 0–1), and a low volume of disease (PCI score <20) that is amenable to complete cytoreduction based on preoperative cross-sectional imaging (CT scan or DW-MRI). We initially offer these patients 3 to 6 months of systemic chemotherapy (usually 5-fluoracil + oxaliplatin or irinotecan with or without bevacizumab or cetuximab). Systemic chemotherapy treatment may vary based on patient's health, previously received chemotherapy regimens, Kras mutation status, and or tumor characteristics. The data regarding the benefit of neoadjuvant systemic chemotherapy versus upfront CRS/HIPEC for newly diagnosed PC from CRC is inconclusive [75]. However, we believe that securing systemic chemotherapy upfront could be a useful tool to assess tumor response and biology to further select patients who will benefit from CRS/HIPEC. At the completion of this treatment, new staging cross-sectional imaging is performed. If the patient has stable disease or a good response without distant metastases, has good performance, and tumor burden is still amenable to complete cytoreduction, we proceed with CRS/HIPEC. After recovery from surgery, we recommend adjuvant systemic chemotherapy. Often diagnostic laparoscopy is necessary to assess peritoneal staging and resectability. If patients have a rapid progression of disease while on the initial systemic chemotherapy course (usually with poorly differentiated and aggressive tumors) or have deterioration of their performance status, then systemic chemotherapy or best supportive therapy is recommended. All our patients are discussed by a multidisciplinary tumor board of physicians, and treatments are tailored for each individual patient based on his or her overall health, previous treatments received, and tumor histology. Given the potential morbidity associated with this procedure, thorough discussion with patients and family is recommended to set clear expectations of potential benefits and complications associated with CRS and HIPEC.

Conclusions

CRS with HIPEC is a promising therapeutic modality that can offer improved long-term survival to selected patients with PC from CRC. While previous studies show encouraging results, more robust trials and standardized selection criteria, unified drug delivery, and centralization of the procedure in centers of excellence are important to ascertain the benefit of this procedure.

Acknowledgements The authors would like to thank Dave Primm for his help in editing this manuscript.

Compliance with Ethical Standards

Conflict of Interest Ibrahim Nassour and Patricio M. Polanco declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Funding Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award No. UL1TR001105. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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