

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer: survival outcomes and patient selection

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Background: Chemotherapy hyperthermic intraperitoneal chemotherapy (HIPEC) is playing an ever increasing role in the management of colorectal cancer (CRC) with peritoneal metastases (PM) as results approach those of surgical resection of liver metastases. Selection criteria for treatment type, sequence and timing of currently available therapies remain ill-defined.

Methods: We review the current published literature analyzing outcomes by treatments with surgery, systemic chemotherapy, cytoreductive surgery (CRS) and HIPEC, and ongoing clinical trials. A clinical pathway that incorporates all currently available therapies, determining the timing and sequence of such therapies was constructed.

Results: Most of the literature on outcome data comes from studies reporting the results of CRS and HIPEC with large series showing a median survival of 32-47 months. Meanwhile, the vast majority of patients, over 90% in the United States, are being treated with palliative systemic therapies following the NCCN guidelines.

Conclusions: Cooperation between medical and surgical oncologists represents an unmet need in oncology when it comes to patients with CRC with PM. The presented clinical pathway constitutes a feasible and much needed first step to start this cooperation.

Keywords: Cytoreductive surgery (CRS); hyperthermic intraperitoneal chemotherapy (HIPEC); peritoneal carcinomatosis; colorectal cancer (CRC)

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Introduction

Peritoneal metastases (PM) are a frequent manifestation in the natural history of colorectal cancer (CRC) and are associated with limited survival (1). About 8% of patients at the time of primary resection, and up to 25% of patients with recurrent CRC will develop metastatic disease confined to the peritoneal surfaces (2). When it comes to treatment of patients with CRC with PM (CRC-PM), there appears to be a dichotomy that unfortunately continues to grow deeper roots: more than 90% of patients will be treated with a combination of palliative cytotoxic chemotherapy and a biological agent and about 5% will be treated with

a combined modality that incorporates cytoreductive surgery (CRS) to remove all visible metastatic disease to the peritoneal cavity and hyperthermic intraperitoneal chemotherapy (HIPEC) to eradicate microscopic residual disease. When it comes to published outcomes from these treatment modalities, the exact opposite can be found: the vast majority of the literature reflects outcomes from CRS and HIPEC and very few studies report on the outcome of patients treated with systemic therapies. Some of the cited reasons for the low inclusion of CRC-PM patients into clinical trials include: (I) mixing all patients with stages IV A and B; (II) relative low incidence (less than 20%)

of PM; (III) PM are usually associated with other sites of metastases; and (IV) patients with low tumor burden are difficult to be evaluated with RECIST criteria (3). When it comes to selection criteria for treatment type and sequence of therapeutic modalities at the time of diagnosis of PM of colorectal origin, the selection criteria for either treatment strategy remain ill-defined. In addition, there is no established non-surgical process to rationally select patients for management, either for inclusion/stratification in clinical trials or as a component of standard-of-care (4). Consequently, precise pre-treatment stratification represents an unmet need in oncology.

The aim of this study is to review outcome data from both treatment modalities and to present a clinical pathway that incorporates all currently available therapies, determines the sequence and duration of these therapies from the time of diagnosis of PM from CRC and establishes selection criteria based on the existing evidence and published outcomes.

Materials and methods

We conducted a comprehensive literature search of PubMed using the words CRC with PM and focused on manuscripts from 2004 to 2015 that included data on selection criteria and outcomes from either of the two treatment modalities (systemic therapies or CRS and HIPEC) as well as any publications that incorporated in a predetermined fashion the timing and sequence of such therapies. We also included manuscripts that focused on trying to determine a different combination of the available therapies and some of the ongoing clinical trials. Based on an analysis of existing evidence, we constructed a clinical pathway that starts at the time of diagnosis of PM of colorectal origin with precise non-surgical pretreatment stratification and that incorporates all currently available therapies, determining the sequence and timing of such therapies.

Results

Outcome of patients treated with systemic therapies

Even though many prospective randomized trials have been conducted in patients with unresectable, metastatic CRC, very few of them have included patients with metastatic disease that involves the peritoneum. Analysis of four studies from both sides of the Atlantic (5-7) demonstrates that few patients with PM of colorectal origin are included

in these trials and that the vast majority of these patients will also have other sites of hematogenous metastases.

First, Franko and colleagues (5) reported a pooled analysis of two large phase III trials from the North Central Cancer Treatment Group (NCCTG) that included 2,101 patients with CRC-PM treated only with systemic chemotherapy. Of these 2,101 patients, 1,646 patients participated in the N9741 trial that evaluated first-line chemotherapy for metastatic CRC. The remaining participated in the N9841 trial that evaluated the role of second-line chemotherapy (n=455). Over 80% of these patients had metastatic disease via the hematogenous route and just 17% of the total group had PM in addition to liver and/or lung metastases. Forty-four patients, 2.1%, had metastatic disease confined to the peritoneal surfaces.

Evaluation of their outcome demonstrated that patients with PM had higher risk of death owing to all causes than patients without PM (median OS, 12.7 *vs.* 17.6 months; HR, 1.32; 95% CI, 1.15-1.50; $P<0.001$). This unfavorable prognostic influence of PM, persisted even after adjusting for age, performance status, liver metastases, and other factors (OS: HR, 1.3; $P<0.001$).

Two similar studies, CAIRO and CAIRO 2, conducted by the Dutch Colorectal Cancer Group (DCCG) (6) were reported by Klaver and colleagues. In the CAIRO study (7), 820 patients were randomized between sequential treatment (first-line: capecitabine, second-line: irinotecan, and third-line: oxaliplatin plus capecitabine, arm A) and combination treatment (first-line: irinotecan plus capecitabine, second-line: oxaliplatin plus capecitabine, arm B). In the CAIRO2 study (8), 755 patients were randomized between capecitabine, oxaliplatin, and bevacizumab (CB regimen), and the same regimen plus weekly cetuximab (CBC regimen).

An analysis of the type of patients enrolled in these two phase III studies showed similar results as the North American studies, with over 90% of the patients having no evidence of metastatic disease involving the peritoneal surfaces. In the CAIRO study only 34 patients (4%) had PM and of these 34 patients only 4 had isolated PM. In the CAIRO2 study, only 47 patients (6%) had PM and 5 of them had isolated PM.

An analysis of the outcome on both studies showed that the presence of PM was associated with a decreased survival when compared to those patients without PM. Median OS in the CAIRO study were 10.4 months versus 17.3 months for patients with and without PM ($P<0.001$). Similar results were found on CAIRO2, with median OS of 15.2 versus

Table 1 Survival outcome of patients with CRC-PM undergoing CRS + HIPEC

Author	Year	N	Overall survival (mo)	Five-year survival (%)
Glehen (10)	2004	377	32	40
da Silva (11)	2006	70	33	32
Shen (12)	2008	121	34	26
Chua (13)	2009	54	33	NR
Franko (14)	2010	67	34	26
Elias (15)	2010	523	32	30
Elias (16)	2011	146	41	42
Ung (17)	2013	211	47	42
Chua (9)	2013	722	33	43
Esquivel (4)	2014	705	41	NR

CRC-PM, colorectal cancer with peritoneal metastases; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

20.7 months ($P < 0.001$). Interestingly, the median number of treatment cycles between patients with or without PM did not differ in both studies. However, the occurrence of major toxicity was more frequent in patients with PM treated with sequential chemotherapy in the CAIRO study as compared to patients without PM but this was not reflected in reasons to discontinue treatment. No difference in major toxicity was observed in the CAIRO2 study.

The authors concluded that these findings demonstrate a decreased efficacy of current standard chemotherapy with or without biological agents in patients with PM of colorectal origin when compared to those patients without PM. In addition, they concluded that this difference cannot be explained by undertreatment or increased susceptibility to toxicity, but rather that there most exist a different biological behavior of tumors that spread to the peritoneal cavity that conveys a relative resistance to treatment.

On another report, Chua and colleagues reviewed the therapeutic options of 2,492 patients with metastatic colon cancer from 19 studies between 1995 and 2009. He reported a survival of only 12.5 months [5-24] for patients having undergone palliative surgery and/or systemic chemotherapy versus a survival of 33 months [20-63] for patients that underwent a more comprehensive treatment strategy with a complete CRS and HIPEC (9).

Outcome of patients treated with CRS and HIPEC

Table 1 includes a summary of recent publications from centers around the world that include at least 50 patients on

their studies, treated with CRS and HIPEC. It is interesting to see that median survival of almost 3 years is very common with a few studies reporting median survivals of 40 plus months, with median 5-year survivals of about 30%. The common denominator for a good long term result includes achieving a complete cytoreduction and avoiding surgery in patients with large tumor burden and poorly differentiated/signet ring cell histologies.

Prodige 7

Prodige 7 is a prospective randomized multicenter phase III trial by the French group where patients with CRC and limited peritoneal dissemination were taken to the operating room. The study was designed to evaluate what is the added benefit of HIPEC to a complete CRS (18). If a complete CRS was achieved, the patients were randomized in the operating room to receive HIPEC or not. This study finished accrual at the end of 2013 and we are anxiously awaiting the results. In this study, HIPEC was delivered with oxaliplatin (460 mg/m^2) in 2 L/m^2 of dextrose 5% over 30 minutes at a minimal temperature of $42 \text{ }^\circ\text{C}$. One hour before the HIPEC, 20 mg/m^2 of leucovorin and 400 mg/m^2 of 5-fluorouracil were given intravenously.

Outcomes after complete cytoreductive surgery (CRS) and systemic therapy only

Recently, Desoigneux *et al.* (19) reported a very interesting manuscript. They recognize that although the efficacy of

surgery in patients with CRC-PM has been demonstrated, the evidence to support the role of HIPEC is less certain. To address this issue, they reported the overall survival (OS), progression-free survival (PFS) and morbidity on fifty consecutively included patients treated for CRC-PM with complete CRS and systemic chemotherapy only.

The median peritoneal cancer index (PCI) was 8 (range, 1-24). Twenty three patients had liver or lung metastases (LLM). Twenty two patients had synchronous metastases. Median follow-up was 62.5 months (95% CI, 45.4-81.3) and median survival was 32.4 months (21.5-41.7). Three- and 5-year OS were 45.5% (0.31-0.59) and 29.64% (0.17-0.44) respectively. Presence of LLMs with PM was significantly associated with poorer prognosis, with survival at 5 years of 13.95% (95% CI, 2.9-33.6) *vs.* 43.87% (22.2-63.7) when no LLM were present ($P=0.018$). Median PFS was 9.5 months (95% CI, 6.2-11.1).

They concluded that with an equivalent PCI range and despite one of the highest rates of LLM in the literature, their survival data of CRS + systemic chemotherapy only compare well with results reported after additional HIPEC. The therapy was well tolerated with acceptable morbidity without any mortality.

Clinical pathway

Figure 1 represents a clinical pathway for the suggested management of patients with CRC-PM from the time of diagnosis of their PM. The pathway incorporates all currently available therapies and stratifies patients by the Peritoneal Surface Disease Severity Score (PSDSS).

Discussion

Individualized, sometimes even personalized, based on genomic profile analyses, multidisciplinary care is the hallmark of cancer care in 2015. Unfortunately, due to reasons that are hard to decipher, this is not the case for patients with CRC with PM. The vast majority of them, over 90% in the United States, are being treated in a generic and mono-disciplinary fashion by medical oncologists with the strategy of continuing combinations of cytotoxic chemotherapy with biological/targeted agents until (I) disease progression; (II) intolerable side effects; or (III) death. The 2015 NCCN guidelines (21) include recommendations for a multidisciplinary evaluation of patients with CRC metastatic to the liver and/or lung, including the evaluation by a thoracic and/or liver surgeon

but if the patients have PM, the recommendations switch to generic and mono-disciplinary, including only palliative systemic therapy. This strategy has proven beneficial to many patients with unresectable metastatic CRC with outcomes that over the last 20 years have gone from a median survival of 12 to now 30 months. This strategy is also the result of prospective randomized trials that include multiple institutions with large number of patients. However, the majority of these patients have liver and/or lung metastases and very few of the patients entered into these clinical trials will have PM. Some of the reasons for these low numbers include the fact that PM are difficult to be characterized with current imaging modalities and the fact that many patients with CRC-PM also have other sites of metastatic disease. Consequently, the outcome of patients with isolated PM treated with modern systemic therapies remains unknown for the most part and the strategy of treatment is extrapolated from a different group of patients: patients with multiple sites of metastases that are not candidates for surgery.

As shown on *Table 1*, multiple studies demonstrate a very favorable median survival when CRS and HIPEC are incorporated into the treatment algorithm of these patients. However, these studies are retrospective studies and include highly selected patients with most of them having received many cycles of systemic therapy. In addition, the question of how much does HIPEC contribute to a complete cytoreduction is being asked with an increased frequency but remains unanswered. Also, the selection criteria for CRS and HIPEC continue to be ill-defined. This might be in part because selection criteria are a process in evolution. Traditionally, we have focused on selection criteria that could help us identify those patients that could have a complete cytoreduction. Over the next years, we realized that not all patients with a complete cytoreduction derived long term benefit (22). We started adding the role of tumor burden and histology as well as clinical symptoms in the PSDSS. This score demonstrated that the outcome of patients with CRC-PM undergoing a complete CRS and HIPEC is much more complex than achieving a complete cytoreduction.

The French trial (Prodige 7) was designed to evaluate what is the added benefit of HIPEC to a complete CRS. The participation of multiple institutions with varying degrees of experience and the fact that the timing of incorporation of systemic therapies and the agents used were not mandated to participate on the trial, will make this trial in my estimate, a negative study that will fail to

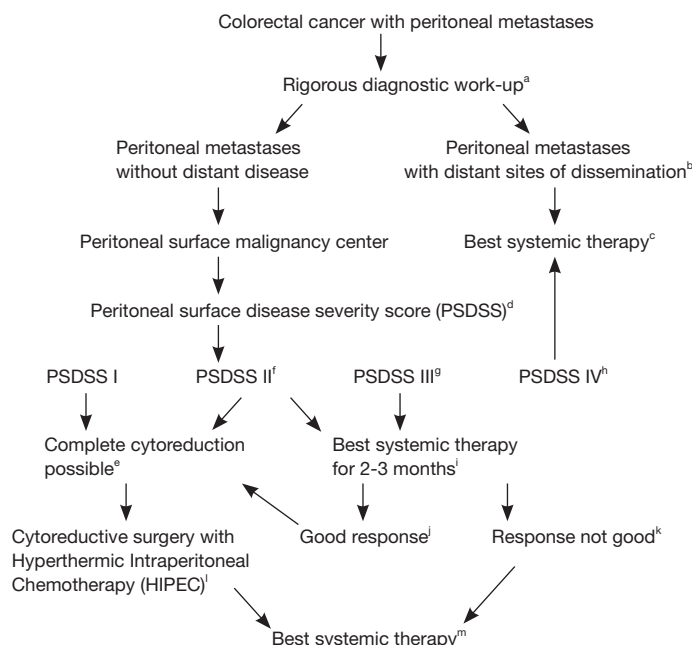


Figure 1 Clinical pathway for the management of peritoneal surface malignancies of colorectal origin. ^a, this should include a recent colonoscopy. A CT scan of the chest, abdomen and pelvis with maximum oral and intravenous contrast. A PET scan should be done in those patients in whom there is evidence or suggestion of hematogenous dissemination on the CT scan. K-ras status should be determined in all patients. ^b, patients with peritoneal metastases and LLM should be referred to a medical oncologist for systemic therapy. Patients with 3 or fewer small, liver metastases (20) can be considered for cytoreductive surgery and HIPEC if they had a good response to the first 3 months of systemic therapy. ^c, best systemic therapy includes a combination of cytotoxic chemotherapy and biological agents. Cetuximab or panitumumab should be considered in those patients that could potentially become surgical candidates and are K-ras wild type. ^d, the Peritoneal Surface Disease Severity Score (PSDSS) (Table 2) was introduced in an attempt to stratify patients with colorectal cancer with peritoneal metastases according to four tiers of estimated disease severity based on a 3-point scale that includes: (I) symptoms; (II) extent of peritoneal dissemination; and (III) primary tumor histology. ^e, variables associated with increased chances of having a complete cytoreduction: complete cytoreduction means that no macroscopic residual disease was left after the operative procedure. The following are clinical and radiographic variables that are usually associated with increase chances of achieving a complete removal of all tumor greater than 2.5 mm; ECOG performance status 2 or less; no evidence of extra-abdominal disease; up to 3 small, resectable parenchymal hepatic metastases; no evidence of biliary obstruction; no evidence of ureteral obstruction; no evidence of intestinal obstruction at more than one site; small bowel involvement: no evidence of gross disease in the mesentery with several segmental sites of partial obstruction; small volume disease in the gastro-hepatic ligament. ^f, PSDSS II patients that have a low CT-PCI (PCI <10) and are good candidates for a complete cytoreduction can go directly to surgery and have systemic therapy after. ^g, PSDSS III have a very low chance of having an upfront complete cytoreduction and therefore should have best systemic therapy first. Re-staging and re-evaluation should be done after 2 or 3 months of systemic therapy. ^h, PSDSS IV patients do not have a good long term outcome even when achieving a complete cytoreduction. These patients should have best systemic therapy first and should have cytoreductive surgery and HIPEC under a clinical protocol. ⁱ, best systemic therapy includes a combination of cytotoxic chemotherapy and biological agents. Consider cetuximab or panitumumab in those patients that are K-ras wild type. If using bevacizumab, it appears to be prudent to hold the bevacizumab after cycle #5 and use only the cytotoxic agents for cycle #6. ^j, the three parameters evaluated to judge the response to the “neo-adjuvant” systemic therapy include: (I) performance status; (II) CEA; and (III) imaging studies. Improvement of at least one of these parameters with the other two remaining unchanged should be the minimum requirement to consider a response as good. Patients with PSDSS II and III, who had a good response, should be evaluated for cytoreductive surgery and HIPEC. ^k, worsening of any of these three parameters while receiving systemic therapy should be considered as not having a good response. In this situation, systemic therapy should be continued and changing the cytotoxic and/or biological regimen should be considered. ^l, American Society of Peritoneal Surface Malignancies Standardized HIPEC delivery in patients with colorectal cancer with peritoneal dissemination. (I) HIPEC method: closed; (II) drug: mitomycin C; (III) dosage: 40 mg; (IV) timing of drug delivery: 30 mg at time zero; 10 mg at 60 minutes; (V) volume of perfusate: three liters; (VI) inflow temperature: 42 degrees celsius; (VII) duration of perfusion: 90 minutes. ^m, patients with a PSDSS I that had cytoreductive surgery and HIPEC should receive standard best systemic therapy. Patients with a PSDSS of II or III that had a poor response to their first 3 months of systemic therapy and then have a good response after changing systemic agents should be considered for cytoreductive surgery and HIPEC. HIPEC, hyperthermic intraperitoneal chemotherapy.

Table 2 Peritoneal Surface Disease Severity Score (PSDSS) of colorectal cancer with peritoneal metastases

Variables	Score
Clinical	
No symptoms	0
Mild symptoms	1
Severe symptoms	6
CT-PCI	
PCI <10 (low)	1
PCI 10-20 (medium)	3
PCI >20 (high)	7
Histology	
G1, G2 N- L- V-	1
G2 N+ and/or L+ and/or V+	3
G3 signet ring	9

Score: 2-3, stage I; 4-7, stage II; 8-10, stage III; >10, stage IV. Clinical symptoms: mild symptoms, weight loss <10% of body weight, mild abdominal pain, some ascites; severe symptoms, weight loss >10% of body weight, unremitting pain, bowel obstruction, symptomatic ascites. PCI: by imaging (CT, PET, MRI) or exploration (laparoscopy or evaluation at time of first operation (in synchronous peritoneal carcinomatosis). PCI, peritoneal cancer index; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; N, lymph nodes; L, lymphovascular invasion; V, vascular invasion.

demonstrate the role of HIPEC. In addition, it is possible that patients that randomized to the no HIPEC arm, might receive another surgery with HIPEC after they recur. Having said that, a very important contribution will be that it will show the value of having surgery to remove the PM and receiving systemic chemotherapy. Therefore, this will be a landmark study highlighting the importance of a multidisciplinary management of patients with CRC-PM.

In 2015, much of our efforts should be directed at trying to establish precise-pretreatment stratifying parameters that will help us evaluate the role of all currently available therapies and will assist in identifying relative and absolute prognostic indicators that can be the basis of prospective trials. A very important study would be to evaluate the role of systemic therapies in patients with isolated CRC-PM and stratified by the PSDSS. This study is being carried out in the United States every day in many patients but nobody is keeping track of it. There is no reason why medical and

surgical oncologists should not be able to work together and offer a true multidisciplinary evaluation to all patients with PM (23). Entering these patients into prospective registries is a necessary first step that can happen today.

Our future goal should be to increase the resectability of patients with CRC-PM by improving selection criteria and early referrals but also by using systemic therapies in a neo-adjuvant setting. Better outcomes will be tied to therapies that help to maintain the complete surgical response and whether that includes HIPEC and/or more systemic therapies will have to be determined in due time.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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