

Peritoneal metastases of colorectal origin treated by cytoreduction and HIPEC: An overview

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Abstract

Colorectal peritoneal carcinomatosis was considered a terminal condition with a merely palliative treatment that included only supportive care, palliative surgery and the best systemic chemotherapy. Since the birth of a new approach, cytoreductive surgery with peritonectomy procedures together with hyperthermic intraperitoneal chemotherapy and/or early postoperative intraperitoneal chemotherapy to treat peritoneal carcinomatosis, many research groups contributed with promising results using this procedure being up to date this strategy the only one that has shown curative benefits on colorectal peritoneal carcinomatosis achieving reported overall survival rates up to 64 mo and five-year survival rates up to 51%. The aim of this paper is to expose an updated overview of the therapeutic possibilities of these procedures in colorectal peritoneal metastases in the same way that our Unit of Oncologic Surgery has performed since 1997 with more than four hundred procedures.

Key words: Carcinomatosis peritoneal; Colon cancer; Intraperitoneal chemotherapy; Cytoreduction; Peritonectomy

Core tip: The carcinomatosis peritoneal from colon origin has turned from a terminal condition to a curative scenery. The cytoreduction and peritonectomy procedures with hyperthermic intraperitoneal chemotherapy have achieved 50% in 5 years overall survival, with a low morbidity that is not higher than other major surgical procedures.

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INTRODUCTION

Colorectal cancer (CRC) is considered the third most common cancer. One of the major aspects related to treatment failure is the appearance of peritoneal metastases (PM), which are thought to be present in about 40% of patients with CRC at some time during the natural history of this disease^[1]. The occurrence of PM may be a result of the growth of the primary tumor allowing the exfoliation of malignant cells intraperitoneally when the serosa is exceeded or be the consequence of a surgical manipulation when lymphatics or blood vessels are transected.

In the past, colorectal peritoneal carcinomatosis was considered a terminal condition with a merely palliative treatment that included only supportive care, palliative surgery and the best systemic chemotherapy, achieving

survival rates not exceeding seven months according to the multicenter study EVOCAPE^[2] with 5-FU and Leucovorin, reaching up to 23.4 mo survival with modern chemotherapy like Oxaliplatin and Irinotecan^[3]. Fortunately, in the 80's decade, a renewed interest in malignant diseases with peritoneal extension and the introduction of the concept of initial loco-regional disease resulted in the birth of a new approach. Thus, Elias *et al*^[4] described and popularized several procedures, including cytoreductive surgery (CRS) (with peritonectomy procedures) together with hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy (EPIC), to treat peritoneal carcinomatosis^[5]. Many research groups contributed with promising results using complete cytoreduction of macroscopic disease combined with HIPEC in order to treat microscopic disease. Although preliminary data were viewed with great scepticism, to date, this strategy is the only one that has shown curative benefits on colorectal peritoneal carcinomatosis achieving reported overall survival rates up to 46 mo^[6] and five-year survival rates up to 51%^[3].

The aim of this paper is to expose an updated overview of the therapeutic possibilities of these procedures in colorectal PM.

PATIENT SELECTION

The importance of a good general health status must be emphasized. The candidates for these procedures should be younger than 70 years with physiological age of less than 65 years, but it is a relative condition. Severe cardio-respiratory disease, renal failure, untreated malignant neoplasm or World Health Organization (WHO) index > 2 are considered major contraindications to CRS + HIPEC^[7]. Furthermore, all patients included to CRS with curative intention shouldn't present tumour progression while on chemotherapy. The key to a successful outcome is an appropriate selection of patients in order to achieve complete cytoreduction, since this is an essential prognostic factor^[8]. To this respect, it has been demonstrated that patients with incomplete cytoreduction and residual tumor ≥ 2.5 mm don't achieve more than 6 mo survival^[9,10].

In that sense, preoperative evaluation should include complete colonoscopy and CT scan of the chest and abdomen, focused the attention on radiologic manifestations of PM such as: ascites, peritoneal nodules or masses, peritoneal thickening and enhancement or mesenteric effacement. In those cases in which any extra-peritoneal or extra-abdominal disease is suspected, positron emission tomography (PET) may be useful to evaluate the extension of the disease.

From a preoperative point of view, some authors have related certain preoperative clinical and radiological variables with the possibility of achieving complete cytoreduction. Among them, it is worth to remark, the absence of extra-abdominal disease, not more than 3 small-size and resectable liver metastases, no high volume

of disease in the gastrohepatic ligament, no evidence of multiple enteric, ureteric or biliary obstruction, as well as no evidence of gross involvement of mesentery or several segments of intestine which cause intestinal obstruction^[11].

The extension of the peritoneal disease represents one of the major prognosis factors for survival and, thus, could represent another criteria for patient selection. To quantify it, several index have been proposed, but presently, the most widely used is the Peritoneal Cancer Index (PCI) described by Sugarbaker. In relation to this index, some authors have considered that a PCI higher than 10 lead to a worse prognosis and a score greater than 20 as a possible contraindication to CRS and HIPEC, as the 5-year survival rate in patients with PCI > 19 is 7%^[10]. To evaluate more accurately PCI, diagnostic laparoscopy may be useful as reported by Valle *et al*^[12] who performed staging laparoscopy in 97 patients, achieving good correlation between the PCI subsequently assessed at the time of laparotomy. However, this is a challenging evaluation procedure, especially in those patients previously operated on, due to the risk of iatrogenic injury during the exploration.

In addition to the PCI, recently, a new preoperative severity index of peritoneal carcinomatosis called "Peritoneal Surface Disease Severity Score" (PSDSS) has been described. This score, which includes the PCI and other variables such as clinical symptomatology and histopathology of the primary tumor, consists on four grades, showing that the stages III and IV have a negative impact on survival (Table 1)^[13].

The presence of multiple liver metastases represents a relative contraindication as several studies have shown that there is no negative impact on survival rates when liver metastases are inferior to 3, chemo-sensitive, and can be fully resected at the time of surgery^[14]. In this study, 3 year-overall and disease-free survivals were 41.5% and 26% respectively. In the same line, other authors have observed similar findings in similar scenarios, especially when PCI is low^[15]. On the contrary, the presence of extra-abdominal metastases and massive retroperitoneal lymphatic involvement, mainly in cases of non-responsive to systemic chemotherapy, should be considered absolute contraindications. Nevertheless, some authors have proposed that extrahepatic disease might not be a contraindication to attempt an R-0 resection if the number of sites of metastases is less than five^[16].

CYTOREDUCTIVE SURGERY WITH PERITONECTOMY AND PERIOPERATIVE INTRAPERITONEAL CHEMOTHERAPY PROCEDURES

Maximum CRS aims to remove all macroscopic disease using extensive visceral resections and peritonectomy procedures as described by Sugarbaker^[5]. When tumour fully invades the visceral surface of different organs,

Table 1 Peritoneal Surface Disease Severity Score

Symptomatology	PCI	Histology
No symptoms (0)	< 10 (1)	Well differentiated or moderately differentiated + N0 (1)
Moderate symptoms (1)	10-20 (3)	Moderately differentiated + N1 or N2 (3)
Severe symptoms (6)	> 20 (7)	Poorly differentiated or ring seal (9)

(0): Score. Moderate symptoms is defined as weight loss of < 10%, moderate abdominal pain, ascites asymptomatic. Severe symptomatology is defined as weight loss of > 10%, pain that continues, intestinal obstruction, symptomatic ascites. PCI: Peritoneal Cancer Index (0-39). Histology of the primary tumor. N regional lymph node metastasis. Grade I: Summation result = (2-3); Grade II: (4-7); Grade III: 8-10; Grade IV: > 10.

resection may be necessary. One of the major technical limitations found by an oncological surgeon is the whole involvement of the small bowel as prevents to perform a complete tumour cytoreduction.

The realization of CRS along with HIPEC improves the outcomes in a single surgical act. However, to achieve this goal, an optimal debulking without macroscopic tumor residue (CC-0 resection) or with a tumor residue less than 2.5 mm (CC-1 resection) must be accomplished, since complete cytoreduction has been shown the most important prognostic factor for survival^[17,18]. Other major prognostic factors associated with worse outcomes are: grades 2 and 3 *vs* grade 1 histopathologic grade, PCI > 20, lymph node-positive primary tumors and volume of preoperative PM^[17-19].

Intuitively, minimally invasive approach for therapeutic purpose might appear not to be useful in this setting, nevertheless, in carefully selected patients, totally laparoscopic CRS and HIPEC has been performed successfully. In that way, Esquivel *et al.*^[20] have reported success rates up to 95% with acceptable morbidity in patients with a PCI < 10^[21,22]. Although others authors have also remarked this possibility, these data are preliminary and must be taken cautiously.

Intraperitoneal administration of cytostatic drugs presents pharmacokinetic advantages because of the plasma-peritoneum barrier that allows the administration of loco-regional high doses of chemotherapy with minimal systemic effects. This characteristic may also lead to a positive effect on recurrence and survival rates^[4]. Perioperative administration lead to an extensive intrabdominal diffusion without any of limitations related to postoperative adhesions. Furthermore, hyperthermia has shown greater cytotoxic capacity. Therefore, in *in vitro* tests at 42.5 °C, certain cytostatic drugs such as Oxaliplatin, Mitomycin C, Doxorubicin, Irinotecan or Cisplatin, have demonstrated to increase their cytotoxicity and penetration, and thus, their antitumor effects^[23]. However, at present, the use of HIPEC is only indicated in cases achieving complete cytoreduction since the penetration of intraperitoneal chemotherapy is limited to several millimetres. On the other side, the administration of EPIC

is related to a higher morbidity as Elias *et al.*^[24] showed in randomized trial as the use of this variety of chemotherapy has been introduced in different treatment protocols^[25].

New chemotherapy drugs such as bevacizumab, an humanized monoclonal antibody that produces angiogenesis inhibition by inhibiting vascular endothelial growth factor A (VEGF-A), are being tested at the moment in animal models and might be useful as perioperative chemotherapeutic agent in the next future^[26,27].

SURVIVAL OUTCOMES AND MORBIMORTALITY OF CYTOREDUCTIVE SURGERY AND HIPEC

The results contributed by many authors, although mainly in a retrospective way, demonstrate that degree of cytoreduction is the most determining factor for survival. All comparative trials report a median survival superior to 2 years for patients treated with complete CRS (CC-0) or with residual tumor less than 2.5 mm (CC-1), reaching some of them survival rates above 50% at 5 years^[3,28]. Dutch randomized phase III trial conducted by Verwaal *et al.*^[9,29] first published in 2003 and latest updated in 2008, compared CRS and HIPEC (Mitomycin C) with intravenous chemotherapy and palliative surgery as sole treatment in patients suffering from colorectal peritoneal carcinomatosis. This trial showed significant differences in terms of overall survival (22.2 mo *vs* 12.6 mo), and a 5-year survival up to 45% in favour of the patients treated with CRS and HIPEC. These data forced to stop the trial for ethical issues. In addition, another similar study conducted by Elias *et al.*^[3] that compared latest systemic chemotherapy to CRS and HIPEC showed a significantly better outcomes in favour of the combined procedure, reaching a median survival of 63 mo and 51% at 5 years overall survival, being these, the best outcomes reported to date using CRS and HIPEC in colorectal PM.

To date, only one systematic review and meta-analysis has been published regarding CRS + HIPEC in colorectal PM. In that study, de Cuba *et al.*^[30] concluded that when liver metastases are presented in addition to isolated PM, there is a trend towards a lower overall survival after curative resection. Furthermore, these authors also support that CRS + HIPEC is superior to modern systemic chemotherapy in increasing overall survival.

Since 2003, numerous studies reporting the outcomes of CRS and HIPEC have been published. Table 2 summarizes the characteristics of most of them.

On the other hand, since CRS and HIPEC were described, these procedures have been criticized due to a high morbidity. This fact could be true at the beginning; however, currently the morbidity, when this surgery is performed in experienced units, is not superior to that which presents any major gastrointestinal surgery. In that sense, the combination of CRS and HIPEC is a complex procedure that exposes the patient to an acceptable mor-

Table 2 Survival outcomes of patients underwent cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Ref.	Type of study	Year	n	Overall survival (mo)	Five-year survival	Overall morbidity ¹	Perioperative mortality
Verwaal <i>et al</i> ^[9]	RCT	2003	39	22	NR	NR	NR
Glehen <i>et al</i> ^[31]	RMS	2004	377	32	40%	22.9%	4%
da Silva <i>et al</i> ^[17]	RS	2006	70	33	32%	NR	NR
Kianmanesh <i>et al</i> ^[15]	RS	2007	30	38	44%	39%	2.3%
Bijelic <i>et al</i> ^[32]	RS	2008	49	33	20%	NR	NR
Shen <i>et al</i> ^[33]	RS	2008	121	34	26%	42%	5.5%
Yan <i>et al</i> ^[34]	RS	2008	50	29	NR	NR	NR
Elias <i>et al</i> ^[3]	CRS	2009	48	63	51%	NR	NR
Chua <i>et al</i> ^[19]	RS	2009	54	33	NR	NR	NR
Franko <i>et al</i> ^[28]	CRS	2010	67	34.7	26%	NR	NR
Elias <i>et al</i> ^[10]	RMS	2010	523	32	30%	31%	3%
Quenet <i>et al</i> ^[35]	PS	2011	146	41	41.8%	47.2%	4.1%
Ung <i>et al</i> ^[6]	RS	2013	211	46.8	42%	NR	NR

¹Morbidity data comes from different classifications and grades, so major morbidity might be lower in most cases. RCT: Randomized clinical trial; RMS: Retrospective multicenter study; RS: Retrospective Study; CRS: Comparative Retrospective Study; PS: Prospective Study; NR: Not reported.

bidity and mortality (Table 2). To this respect, main high-grade morbidity of these patients is related to surgery and presented in form of anastomotic leak, intraperitoneal sepsis or abscesses, and hematologic and renal toxicities related with HIPEC. Multivariate analyses including in different studies show the extension of disease, number of anastomosis, duration of intervention and incomplete cytoreductive surgery as independent risk factors for morbidity^[10].

RECOMMENDATIONS FOR THE MANAGEMENT OF PATIENTS DIAGNOSED FOR COLORECTAL PERITONEAL CARCINOMATOSIS

All surgeons or oncologists diagnosing a colorectal peritoneal carcinomatosis, before, during or after surgery; especially in young patients with limited disease, should consider the evaluation of the case for a multidisciplinary team in a specialized unit in order to offer the realization of this therapeutic approach with curative intent. An exploratory laparotomy without a description of the extent of the disease should be a prohibited action. In this sense, when a peritoneal carcinomatosis is discovered intraoperatively, it is recommended that the surgeon describe in detail the extension and allocation of PM according to the PCI. This conduct will allow the correct evaluation of these patients in specialized units, avoiding inappropriate transfers, resource consumptions and discomfort to the patient. Likewise, a very detailed description of the PM extent will prevent an unnecessary laparotomy in those cases in which a complete cytoreduction is not possible^[11].

In the same way, the realization of CRS without HIPEC should be avoided since this conduct limits the possibility of receiving a combined treatment with curative intent and better outcome. Resection of peritoneum without HIPEC allows free tumor cells to implant and

grow all over the abdominal cavity, which impairs future treatment options and increase the risk of morbidity^[11]. From this point of view, there are a group of patients that although undergoing complete resection without HIPEC, are at high-risk of developing colorectal peritoneal carcinomatosis. Thus, resected minimal synchronous macroscopic PM, synchronous ovarian metastases and perforated primary tumors could benefit of second-look surgery with CRS and HIPEC as it seems to be that up to 55% of asymptomatic patients may present PM at one year^[36].

Finally, an emergency surgeon that incidentally is faced with a colorectal peritoneal carcinomatosis should avoid unnecessary surgical dissection and solve the urgent situation (obstruction and/or perforation and/or abdominal sepsis) using the minimum necessary surgical gesture.

CONCLUSION

At present, CRS and HIPEC procedures represent a therapy with curative intent in selected patients with colorectal peritoneal carcinomatosis. The finding of a peritoneal carcinomatosis requires surgeons and oncologists to not ignore this treatment option and to refer such patients to experienced units in the treatment of peritoneal surface malignancies, in order to limit morbidity and increase their survival.

It is clear that there are many unknowns pending to be solved in the next few years such as different modes, time, dose, temperature and drugs for HIPEC to decrease local recurrence after CC-0 resections. Furthermore, at this moment, several trials are evaluating the role of second-look surgery with CRS + HIPEC as well as the possibility of prophylactic HIPEC when primary colorectal cancer shows synchronous PM or is a high risk patient to develop carcinomatosis^[36]. These novel strategies might be incorporated in the future therapeutic protocols of colorectal PM.

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