Cytoreductive Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Metastasis from Colorectal Cancer

Hideaki Yano, MD, PhD, FRCS¹

¹Consultant General and Colorectal Surgeon, University Hospital Southampton, Southampton, Hampshire, United Kingdom

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Address for correspondence Hideaki Yano, MD, PhD, FRCS, Consultant General and Colorectal Surgeon, University Hospital Southampton, Tremona Road, Southampton, Hampshire, SO16 6YD, UK (e-mail: hideaki.yano@uhs.nhs.uk; yano-tky@umin.ac.jp).

Abstract

Peritoneal metastasis from colorectal cancer (PM-CRC) is used to be considered a systemic and fatal condition; however, it has been growingly accepted that PM-CRC can still be local disease rather than systemic disease as analogous to liver or lung metastasis.

Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is now considered an optimal treatment for PM-CRC with accumulating evidence. There is a good reason that CRS + HIPEC, widely accepted as a standard of care for pseudomyxoma peritonei (PMP), could be a viable option for PM-CRC given a similarity between PM-CRC and PMP.

Recent years have also seen that modern systemic chemotherapy with or without molecular targeted agents can be effective for PM-CRC. It is possible that neoadjuvant or adjuvant chemotherapy combined with CRS + HIPEC could further improve outcomes.

Keywords

- HIPEC
- PCI
- cytoreductive
- carcinomatosis

Patient selection, utilizing modern images and increasingly laparoscopy, is crucial. Particularly, diagnostic laparoscopy is likely to play a significant role in predicting the likelihood of achieving complete cytoreduction and assessing the peritoneal cancer index score.

It is well established that in a certain number of patients with colorectal liver or lung metastasis, cure can be achieved by metastasectomy. Likewise, some cases with peritoneal metastasis from colorectal cancer (PM-CRC) may present as local spread rather than systemic spread and may be amenable to cure by surgical resection.

It can be safely said that the treatment that has the most evidence and is therefore believed to be optimal for PM-CRC is cytoreductive surgery (CRS) in the form of peritonectomy combined with hyperthermic intraperitoneal chemotherapy (HIPEC).¹

CRS + HIPEC has already been established as a standard of care for pseudomyxoma peritonei (PMP)² and is now considered the most reliable treatment for PM-CRC considering the similarity between PMP and PM-CRC.

Conventional Treatment of Synchronous Colorectal Peritoneal Metastasis

According to the Japanese national colorectal cancer registry that accumulated 25,612 cases between 2000 and 2004, the incidence of peritoneal metastasis at the time of diagnosis/surgery (synchronous peritoneal metastasis) was 4.5%, second most to liver metastasis (10.9%), followed by lung metastasis (2.4%).³

The majority of colorectal cancers with synchronous peritoneal metastasis presents with symptoms, such as bleeding or obstruction. Therefore, resection of primary cancers is justified unless the patients are too unfit or there are anatomical limitations, for example, (a) ascending or transverse colon cancer where the primary tumors or metastatic nodes massively invade the duodenum or pancreas,

(b) rectosigmoid or rectal cancers that massively invade the bladder or prostate, etc.

Possible clinical scenarios would be following: (a) peritoneal involvement was suspected on preoperative computed tomography (CT) or positron emission tomography (PET) scans and extensive peritoneal involvement was confirmed on surgery where the primary tumor was removed to palliate symptoms (bleeding, obstruction, etc.) unless too unfit or extensive local spread, otherwise only bypass or stoma was fashioned; or (b) mild-to-moderate peritoneal involvement was established unexpectedly only on surgery where both primary and peritoneal tumors were removed (R1) or only primary tumors were removed (R2). And then systemic chemotherapy would be given postoperatively (as adjuvant if R1) wherever possible.

Potential problems in those scenarios in relation to CRS + HIPEC would be following: (a) systemic chemotherapy is considered to be less effective for peritoneal metastasis than for liver or lung metastasis; (b) the rate of “curative” resection, and the possibility of achieving cure, is extremely low and could be improved by CRS + HIPEC; (c) it is possible that the resection of primary tumors in the presence of macroscopic peritoneal deposits could induce the implantation of tumor cells onto the newly-created raw surfaces; and (d) the increasing use of laparoscopic or robotic surgery could be detrimental to the diagnosis and treatment of peritoneal metastasis because of misdiagnosis of small peritoneal nodules or inadequate dissection as a result of its limited operative views.

Therefore, new treatment strategies could be more judicious that include (a) delayed and scheduled CRS + HIPEC where the primary tumor is deliberately left in situ with either stenting or stoma formation and definitive CRS + HIPEC is performed after 3 to 6 months of systemic $\pm$ intraperitoneal chemotherapy; (b) upfront HIPEC where HIPEC is given at the time of surgery provided R1 surgery is achieved; or (c) second-look HIPEC where a second-look laparotomy is performed after 6 to 12 months of initial surgery where CRS + HIPEC is performed if peritoneal disease is found or otherwise HIPEC only.

Conventional Treatment of Metachronous Colorectal Peritoneal Metastasis

Among all the differences between peritoneal and other distant metastases, recurrence is the difficulty of radiological imaging studies. By utilizing CT, magnetic resonance imaging (MRI), and PET, the diagnosis can be made fairly easily and, moreover, even its surgical resectability can now be predicted quite accurately in liver or lung metastasis, which strikes a sharp contrast to peritoneal metastasis. As a result, metachronous PM-CRC tends to be detected at a later stage.

To achieve early discovery and early intervention, the identification of high-risk patients who will be likely to develop peritoneal recurrence and the proactive use of diagnostic laparoscopy are crucial with a caveat that it might be controversial whether early discovery will actually lead to better survival as is the case with liver or lung metastasis.

Systemic Chemotherapy

Although various novel agents have been introduced and have proven to be effective for the management of metastatic colorectal cancer, evidence is lacking in the efficacy of modern chemotherapy regimens including FOLFOX and FOLFIRI in combination with molecular-targeted agents such as cetuximab, panitumumab, and bevacizumab in patients with PM-CRC. None of the large-scale clinical trials that evaluated modern systemic chemotherapy have reported response or survival specific to patients with PM-CRC. It is likely that because such trials recruit only patients with evaluable lesions where reliable measurements of tumor size are available on X-ray, CT, or MRI, patients with PM-CRC are usually excluded. Hence, limited evidence is available on the response and survival associated with systemic chemotherapy for patients with PM-CRC.

PM-CRC has generally been considered to carry poorer prognosis compared with liver or lung metastasis. Franko et al analyzed 2,095 patients with metastatic colorectal cancer who were recruited in a large-scale clinical trial. They found the median survival time of 12.7 months in patients with PM-CRC that was significantly shorter than 17.6 months in patients without PM-CRC.⁴

Surgical Treatment

A surgical approach combining CRS and HIPEC is gaining acceptance in the oncologic community as a treatment option for patients with PM-CRC. This treatment was first described by Spratt et al in 1980⁵ before being further developed by Paul Sugarbaker of the Washington Cancer Institute in the 1990s.⁶

This procedure involves stripping of the diseased peritoneum (peritonectomy) with multiple visceral resections, performed with an aim of achieving macroscopic tumor removal. Then, prior to any intestinal anastomosis, a heated chemotherapeutic agent is administered and perfused in the abdomen for a certain period of time to chemically sterilize all peritoneal surfaces (usually mitomycin C or oxaliplatin for 30–60 minutes at the temperature of 41–43°C). HIPEC allows a high local concentration of a cytotoxic drug with minimal systemic adverse effect thereby aiming to achieve microscopic tumor removal. Hyperthermia has been demonstrated to have a synergistic effect with chemotherapy and thus to enhance the cytotoxicity of the drug.⁷

To reiterate, the rationale behind CRS + HIPEC for PM-CRC revolves around (a) the analogy between PM-CRC and PMP and (b) the higher surgical curability of colorectal cancer in general than any other gastrointestinal malignancies.

Factors that preclude CRS + HIPEC generally include gross involvement of (a) small bowel and its mesentery; (b) retroperitoneum, particularly ureters; and (c) hepatoduodenal ligament and porta hepatis.

In recent years, there has been accumulating evidence of the efficacy and safety of CRS + HIPEC for PM-CRC. In summary, it is increasingly known that (a) CRS + HIPEC can confer 5-year survival of 30 to 40% in selected patients,

Table 1 CRS + HIPEC for colorectal peritoneal metastasis

Principal investigators	Reference no.	Countries	Year of publication	Period of accrual	Number of patients	Median survival time (months)	1-year survival (%)	2-year survival (%)	3-year survival (%)	5-year survival (%)
Zoetmulder	8	The Netherlands	2003	1998–2001	39	22	70	45	–	–
Verwaal	9	The Netherlands	2005	1995–2003	59	43	94	–	56	43
Msika	10	France	2007	1996–2006	30	38	–	72	–	44
Bartlett	11	USA	2008	2001–2007	36	–	85	–	45	–
Levine	12	USA	2008	1992–2005	30	41	–	–	62	36
Elias	13	France	2009	1998–2003	48	63	–	81	–	51
Morris	14	Australia	2009	1997–2008	54	33	87	70	44	–
Elías	15	French multicenter	2010	1990–2007	439	33	85	60	45	29
Cavaliere	16	Italian multicenter	2011	1995–2007	124	25	83	50	–	–

Abbreviations: CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

(b) better survival is achieved in patients with less peritoneal involvement, (c) CRS + HIPEC is associated with 12% of morbidity and with < 1% of mortality in experienced teams, and (d) favorable outcomes continue to be reported globally.¹

Recent major studies reporting outcomes of CRS + HIPEC are summarized in ► **Table 1**. The median survival of patients undergoing CRS + HIPEC was 33 (range, 22–63) months. The median 1-, 2-, 3-, and 5-year survival rates were 85% (range, 70–94%), 65% (range, 45–81%), 46% (range, 44–62%), and 40% (range, 29–51%), respectively.^{8–16} In highly selected patients with limited PM-CRC, the median survival may be as high as

63 months and 5-year survival as high as 51% as reported by Elias et al.¹³

Much has been learnt from these clinical trials, with the development of staging systems in the form of preoperative/intraoperative scoring to aid selection to improve outcomes. Completeness of cytoreduction and the extent of PM-CRC are universally the most important prognostic factors. Peritoneal cancer index (PCI, range, 0–39) is the most widely spread scoring system (► **Fig. 1**) to describe the extent of PM-CRC, which not only predicts the likelihood of complete cytoreduction but is also a strong prognosticator in patients with a

Fig. 1 Peritoneal cancer index (PCI).

complete cytoreduction. The 5-year survival ranged from 44% in patients with a low PCI (< 6), 22% in patients with a PCI^{7–12} to 7% in patients with a high PCI (> 19).¹⁵ Currently, a PCI > 20 should be considered as a contraindication for CRS + HIPEC.

The combination of major surgery and HIPEC in patients with PM-CRC carries significant morbidity (16–65%) and mortality (0–16%).¹⁷ Perioperative complications include intraabdominal hemorrhage, anastomotic leak or fistula, respiratory failure, venous thromboembolism and hematological toxicity associated with HIPEC occurs in 8 to 31%.¹⁸ A learning curve exists in this major operation, and according to the most recent reports the mortality is $< 1\%$ in experienced hands.

With the accumulating evidence including a randomized controlled trial,⁸ a few multi-institutional registries,¹⁹ and innumerable case series, the efficacy of CRS + HIPEC for PM-CRC is described in several national guidelines. The Netherlands, France, Germany, Spain, the United Kingdom, Norway, Korea, and Italy have all clearly stated that selected patients should be treated at experienced centers. The National Institute of Care and Excellence (NICE), UK, states in its guidance (Interventional Procedures Guidance, IPG 331) that current evidence on the efficacy of CRS followed by HIPEC for peritoneal carcinomatosis shows some improvement in survival for selected patients with colorectal metastases, but evidence is limited for other types of cancer. It also states that the evidence on safety shows significant risks of morbidity and mortality that need to be balanced against the perceived benefit for each patient and that, therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.²⁰

Multimodal Treatment

It is logically reasonable to try to combine the novel chemotherapy and the aggressive surgery, namely CRS + HIPEC. In the recent COMBATAC trial, after the primary cancers are removed by laparotomy or laparoscopy, the patients are given 3 to 6 months of chemotherapy and undergo CRS + HIPEC followed by postoperative chemotherapy.²¹

Second-Look HIPEC

A further emerging concept is “second-look” at 6 to 12 months for patients at high risk of PM-CRC based on perforated primary tumors (T4), resected Krukenberg ovarian metastases or resected localized peritoneal disease at the primary operation. Forty-one high-risk patients had systemic chemotherapy and underwent second-look laparotomy at 6 to 12 months after primary surgery.²² Low-volume resectable peritoneal metastases were present in 23 patients (56%), who subsequently underwent CRS + HIPEC; and no macroscopic disease was present in the remaining 18 patients (44%), who underwent HIPEC alone.²²

These promising results led to the prospective multicenter trial ProphyloCHIP, in which patients at high risk of PM-CRC after resection of primary tumor and who are receiving standard oxaliplatin-based adjuvant chemotherapy will be randomized to surveillance alone or systematic exploratory

laparotomy plus HIPEC. The primary outcome measure is the 3-year disease-free survival and the secondary outcome measures are the 3- and 5-year overall survivals.

Prophylactic/Adjuvant/Upfront HIPEC

Prophylactic/adjuvant/upfront HIPEC may be appropriate for some of the patients who are at high risk of PM-CRC after initial surgery. At institutions where HIPEC is available at the time of primary colorectal cancer resection, the primary resection is augmented intraoperatively by complete CRS. Not only the bowel resection, but also greater and lesser omentectomy and oophorectomy in women are required. Prior to the intestinal reconstruction, HIPEC is administered. After HIPEC, the bowel anastomosis is performed and the abdomen is closed. These patients then receive intensive adjuvant chemotherapy.²³

It is thought that the intraoperative chemotherapy combined with a primary colon cancer resection is of very low morbidity and carries no mortality. Patients who might benefit from upfront HIPEC include those with a tumor perforation (T4), a positive peritoneal cytology, adjacent organ involvement or fistula formation, and rupture of the primary cancer during the resection.

A couple of trials is ongoing in the Netherlands, Spain, and Italy.

Conclusion

Recent results suggest that judicious selection of patients (e.g., PCI < 20) for CRS + HIPEC is crucial and CRS + HIPEC is likely to be superior to the current best systemic chemotherapy. Integrated treatment strategy combining systemic chemotherapy and CRS + HIPEC appears to be most effective.

As we await the results of ongoing trials, we must continue to commit to future trials that will contribute to the body of evidence to support CRS + HIPEC. A neoadjuvant trial by the German group to investigate the role of preoperative systemic chemotherapy prior to CRS + HIPEC will allow us to determine if neoadjuvant chemotherapy may facilitate CRS by downstaging the peritoneal disease burden and thereby improving survival. In addition, the role of prophylactic HIPEC for patients at high risk of PM-CRC requires to be elucidated.

Conflict of Interest

None.

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