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Hyperthermic Intraperitoneal Chemotherapy (HIPEC) and Cytoreductive Surgery (CRS) for Colorectal Cancer: Potential for Individualized Care, Review of Current Treatment Trends, Recent Advancements, and a Look into the Future

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Abstract

Purpose of Review Peritoneal metastases (PM) secondary to colorectal cancer is associated with a poor prognosis. However, cytoreductive surgery with hyperthermia intraperitoneal chemotherapy (CRS/HIPEC) has risen to a more accepted roll in the treatment of peritoneal metastatic disease for various cancers; colorectal cancer is no exception. This review aims to discuss the recent updates and findings for treatment of peritoneal disease secondary to colorectal cancer, especially with respect to individualized patient factors that affect outcomes.

Recent Findings There are many new studies showing the validity of cytoreductive surgery CRS/HIPEC in a select group of patients with PM. Many studies show that lower peritoneal cancer index score, use of various chemotherapeutic regimens, histology, preoperative health status, adequate nutrition, and other factors all benefit survival/treatment of this unique patient group.

Summary Current evidence supports an aggressive multidisciplinary approach to peritoneal disease secondary to colorectal cancer. Standardized treatment practice, highly selective patient criteria, low PCI score, and early recognition of patients at risk for PM show survival benefits and better outcomes for patients with a disease process that was once only treated with palliative interventions.

Keywords Colon neoplasms · Rectal cancer · Colorectal cancer · Peritoneal carcinomatosis · Peritoneal metastasis · Cytoreductive surgery · Peritoneal surgery · Hyperthermic intraperitoneal chemotherapy · HIPEC · Peritoneal infusions · Patient selection · Combined modality therapy

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Introduction

Peritoneal carcinomatosis (PC) has historically had a poor prognosis with survival rarely exceeding a few months [1]. Previously, treatment had been focused solely on palliation, but with the advent of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in the 1980s and 1990s, disease survival has improved significantly. The goal of CRS/HIPEC is to achieve an R-0 resection and remove all evidence of gross disease from the peritoneal cavity. Once this has been completed, hyperthermic chemotherapy is instilled into the abdomen to treat microscopic disease that was not addressed by the debulking surgery. In order to continue to improve results, there has been a growing focus on patient-specific factors that influence outcomes. Preoperative factors, such as age, sex, and co-morbidities, as well as tumor-specific factors like colon vs rectal cancer, cancer histology,

and extent of intraperitoneal disease can significantly influence outcomes. Intra-operative factors like completeness of cytoreduction and postoperative factors such as use of chemotherapy and what type of chemotherapy is employed also play a role and should be considered when selecting therapy. The aim of this literature review is to discuss the current state of CRS/HIPEC surgery with a focus on individual patient factors that influence outcomes.

Methods

We performed a systematic literature search encompassing both PubMed and Web of Science with the following search parameters ***TOPIC*****:** (“*Hyperthermic Intraperitoneal Chemotherapy*” *OR HIPEC*) *AND* ***TOPIC*****:** (“*cytoreductive surgery*” *OR* “*cytoreduction*”) *AND* ***TOPIC*****:** (“*colorectal cancer*” *OR* “*colorectal neoplasms*” *OR* “*peritoneal neoplasms*” *OR* “*peritoneal carcinomatosis*” *OR* “*mucinous adenocarcinomas*”) *AND* ***TOPIC*****:**(“*systematic review*” *OR* “*systematic reviews*” *OR* “*meta-analysis*” *OR* “*meta-analyses*” *OR* “*clinical trial*” *OR* “*clinical trials*”) and (*Hyperthermic Intraperitoneal Chemotherapy* [*two*] *OR* “*HIPEC*” *OR* “*hyperthermia*, *induced*” [*MeSH*]) *AND* (*cytoreductive surgery* [*tw*] *OR* “*Cytoreduction Surgical Procedures*”[*Mesh*] *OR* “*CRS*”) *AND* (*colorectal cancer* [*tw*] *OR* “*colorectal neoplasms*” [*Mesh*] *OR* “*peritoneal neoplasms*” [*MeSH Terms*] *OR peritoneal carcinomatosis* [*Text Word*] *OR* “*adenocarcinoma*, *mucinous*” [*MeSH Terms*] *OR mucinous adenocarcinomas* [*Text Word*]) respectively. This resulted in 1400 possible papers that matched the initial search criteria. Next, we focused our search from the initial 1400 papers to the year 2013 and beyond which narrowed the results down to 908 papers. The search was further narrowed by only selecting papers that contained in the title or keywords section the words colon, rectal, or colorectal. Using those search criteria, the results became 267 papers in total. Next, the 267 abstracts were individually read and any pure literature reviews, non-English papers, and papers not pertaining to colon/rectal PC were excluded. This left us with 153 sources. This was a combination of meta-analysis’s, primary papers, systematic reviews to use to create our systematic literature review on Hyperthermic Intraperitoneal Chemotherapy (HIPEC) and Cytoreductive Surgery (CRS) for Colorectal Cancer: Potential for Individualized Care.

Systemic Therapy

Systemic chemotherapy has a role to play for PM related to CRC, though there are only a few randomized control trials available that evaluate the timing and exact role of systemic chemotherapy with CRS/HIPEC, and they have been contradictory. Some have found that timing (either preoperative, perioperative, or postoperative) of systemic chemotherapy does not have a significant difference in overall survival and progression-free survival. However, many of the patients in the adjunct group never made it to their systemic treatment secondary to postoperative complications. Therefore, certain patients may benefit from preoperative systemic treatment vs postoperative chemotherapy. Other studies have found that pre-, peri-, or postoperative chemotherapy did not impact survival outcomes. [2–6]. Still another study found that preoperative chemotherapy is best for outcomes after CRS/HIPEC. In this study, median survival was 38 months in the adjunct group, whereas median survival was not reached in the preoperative group ($p < 0.01$). The 3-year overall survival rates were 50% and 89% in the pre- and postoperative groups, respectively, and preoperative chemotherapy was independently associated with improved survival [7]. Other additional modalities/adjuncts have been studied as well. One study found that CRS/HIPEC with complete cytoreduction and neoadjuvant therapy containing bevacizumab increased overall survival vs just CRS/HIPEC and nonadjunct chemotherapy. Others have found that administration of bevacizumab prior to complete cytoreduction and HIPEC for colorectal carcinomatosis was associated with twofold increased morbidity. Thus, the oncologic benefit of bevacizumab before HIPEC warrants further investigation [8–10]. In addition, some studies have looked at CRS/HIPEC vs CRS plus systemic chemotherapy vs other modalities. These studies found CRS with systemic chemotherapy to be a reasonable option with increased outcomes if CRS/HIPEC were not available at that institution. However, most of the data available found CRS/HIPEC to be the superior modality for selected patients [11–13]. Given the variability in the existing data, the ideal timing of systemic chemotherapy is not uniform and should be decided in a case-by-case scenario with a multidisciplinary team to individualize the care of each unique patient. More prospective studies are needed to evaluate the roll, timing, and regimen of systemic chemotherapy for CRC patients with PM.

Patient Selection

For colorectal cancer with peritoneal metastases, prognosis both preoperatively and postoperatively is a highly discussed topic with patients and within multiple disciplinary teams. The need for appropriate patient selection is a necessity for institutions preforming CRS/HIPEC. Preoperative workup with imaging, multidisciplinary team coordination, and proper patient selection is vital for successful outcomes [14]. Many studies on prognostic indicators related to patient selection have been performed. Common prognostic indicators are age, sex, primary site, lymph node (LN) status, peritoneal

cancer index (PCI) score, completeness of cytoreduction score (CC score), number of visceral resections required, systemic chemotherapy, and progression-free survival (PFS). Most of the research points to the PCI and lymph node status as the strongest predictors of overall survival [2, 15–20]. The higher the PCI, the greater the chance of not obtaining an R-0 resection, thus decreasing overall survival, while a lower PCI is associated with increased survival, with a PCI of < 11–12 being associated with better outcomes. Additionally, the greater number of visceral resections needed to obtain adequate debulking is associated with decreased overall survival [4, 15, 16, 21–23]. Finally, data shows that the histology of the primary tumor is also a major role player in overall survival (signet ring cell type, mucinous, appendiceal, poorly differentiated) [24]. The absence of signet ring cells and mucinous component type with the presence of microsatellite sequence instability are favorable prognostic factors with disease-free survival increasing from 12.4 to 24.9 months while the presence of signet ring cells show a decrease in survival from 45.8 to 12.1 and a mucinous component has been associated with a decreased survival from 51.9 to 35.1 months [25, 26].

With many prognostic indicators showing changes in survival, researchers have developed scoring systems to improve patient selection and guide treatment. There are multiple scoring systems, both preoperative and postoperative in nature, such as mCOREP, COMPASS, PSDS/PSDSS, and CEA/PCI ratio. These scoring systems attempt to provide individualized prognostic indicators for survival, morbidity/mortality [27•, 28•, 29–31]. It is also well documented that intra-operative PCI, histologic type, evidence of systemic metastasis, and quality of cytoreduction are important prognostic factors for patient survival [32–34]. Multiple studies have evaluated the above-mentioned scoring systems and found that the mCOREP, or the modified version of the COREP score, was superior to COMPASS. The mCOREP or COMPASS score may allow for more individualized care and prevent patients from undergoing unnecessary treatment [27, 35, 36]. The American Society of Peritoneal Surface Malignancies (ASPSM) published work that showed that the PSDS could also be utilized preoperatively to appropriately stratify patients into treatment groups/clinical trials based on projected survival, further demonstrating that preoperative and postoperative scoring systems help select the appropriate treatment for patients based on their unique characteristics [29].

Extraperitoneal disease secondary to metastatic colorectal cancer and PM have previously been a contraindication for CRS/HIPEC. However, recent data has shown that this may not need to be the case. Studies have shown that liver metastasis is no longer a hard contraindication for CRS/HIPEC in patients with synchronous disease. In fact, combined parenchyma-preserving liver resection, cytoreductive surgery, and IPC in patients with LM and PC from CRC can be performed safely and results in promising overall survival with comparable morbidity to CRS/HIPEC alone [37–42]. On the other hand, other studies have found that simultaneous LR and CRS-HIPEC were associated with increased operative time, length of hospital stay, reoperation, and postoperative morbidity, and worse outcomes compared to CRS-HIPEC alone. There are some institutions who are pushing for two-stage operations for patients with synchronous disease [43–45]. Thus, it may be beneficial to resect the liver metastasis in colorectal patients with peritoneal metastatic disease along with hepatic metastasis but not simultaneously due to the increased risk. More studies are therefore needed to investigate a one-stage vs two-stage approach to this patient population.

There is also growing evidence that PM secondary to rectal cancer should not be a hard contraindication to CRS/HIPEC. Patients with peritoneal metastasis may also benefit from CRS/HIPEC with similar outcomes to that of colon cancer patients with PC [46, 47]. However, there is an alternative data showing that PC associated with rectal cancer may not share the same survival benefits from CRS/HIPEC [48].

Recent data from the literature suggests that treating PM patients at the earliest stage possible will greatly affect the overall outcome for patients. Patients identified to be at high risk for developing PM, or found intra-operatively to have PM, benefit from CRS/HIPEC or HIPEC either at the initial operation or early after discovery. There is also evidence supporting increased survival with routine second-look surgery in patients with PM discovered at the initial oncologic operation that ended up undergoing CRS/HIPEC [49, 50•, 51•, 52–55].

HIPEC Model and Treatment Modalities

HIPEC has slowly become the standard of care for treatment of PM in a select group of patients. However, there are multiple treatment regimens with different chemotherapy formulations that have been described in the literature. Examples of the most commonly used regimens are mitomycin C, oxaliplatin, cisplatin, doxorubicin, 5-fluorouracil, or a combination of these drugs [56, 57].

The open abdomen technique is the classic method, but many surgeons have turned to closed abdomen technique as it decreases the exposure to operative personnel as well as preventing heat loss. Studies have looked at open vs closed and have concluded no difference except for better intra-abdominal temperatures during perfusion for the closed technique [58]. However, adhesions during the perfusion process have been hypothesized to decrease the efficacy of the closed abdomen perfusion process. Thus, some recommend adding laparoscopic techniques to enhance the perfusion process by breaking down intra-abdominal adhesions [59]. Researchers have looked at CRS/HIPEC vs cytoreductive surgery with hyperthermic intraperitoneal chemotherapy plus early

postoperative intraperitoneal chemotherapy (CRS/HIPEC +EPIC). Studies have shown no difference in OS and RFS but the EPIC group did have more grade III/IV complications and concluded that HIPEC alone may be the preferred treatment for colorectal patients [60, 61].

Most trials and studies have used mitomycin C alone or in combination with other agents during the intraperitoneal perfusion process, though some groups have used oxaliplatin with similar survival outcomes [62]. Oxaliplatin use has been limited to date due to electrolyte abnormalities and the side effect of renal insufficiency. Some suggest the use Dianeal (Dianeal PD4 dextrose 1.36%) carrier solution vs glucose carrier with good data to show a decrease in the electrolyte abnormalities [63]. Glockzin et al. found that oxaliplatin in combination with intravenous 5-FU and folic acid did not increase morbidity and mortality [64]. In addition, others have found that intraperitoneal oxaliplatin reduced the chemoperfusion time vs intraperitoneal MMC without adversely influencing the complication rate, toxicity, or short-term survival [65, 66]. Irinotecan has also been looked at, and recently collected data suggests that the morbidity and toxicity rates of irinotecan-based and oxaliplatin-based HIPEC are comparable [67]. Other research has shown no clear benefit in RFS and OS for HIPEC with oxaliplatin or MMC in patients with PC from CRC [68]. However, others have found that in selected patients with low burden of disease and favorable histology's, mitomycin C may be a better agent for HIPEC versus oxaliplatin [69]. A meta-analysis from 2017 found that CRS/HIPEC showed benefit for patients with PC, but the difference in the chemotherapy regimens used was not associated with OS and disease-free survival (DFS) after CRS and HIPEC [70]. Given the data for use of HIPEC, HIPEC is clearly beneficial when combined with cytoreductive surgery, but the wealth of differing data, techniques, and standard of practice muddies the water on the exact combination of hyperthermia, drug, and duration of intraperitoneal chemotherapy. A more standardized approach with prospective studies is warranted. More studies like the COMBATAC trial are needed to decide the most effect treatment regimen [71].

The chemotherapy used during HIPEC has a specific set of side effects, such as neutropenia for mitomycin C and renal insufficiency for cisplatin. Thus, research into adjunct therapies to decrease or eliminate these side effects is of high importance in order to improve morbidity and mortality. One study found that amifostine may be of benefit if given during intraperitoneal administration [72]. As discussed earlier, the use of mitomycin C is widespread and common. One of its feared side effects is neutropenia. In one study, there was an increased chance of neutropenia that was directly related to the plasma levels of mitomycin C during perfusion. As this can be monitored intra-operatively, these patients can be placed on neutropenic surveillance earlier than other patients who had lower intra-operative chemotherapy levels [73]. In addition, sarcopenic patients appear to be more sensitive to mitomycin C than other patients with PC, especially when it comes to postoperative neutropenia. Thus, these patients may need a dose-base protocol or more aggressive treatment strategy with white blood cell growth factors [74]. In support of this, it appears that neutropenia may be associated with the MMC dosage at T30 after the start of HIPEC. A threshold of 572 μg/L gives a predictive sensitivity of 86% and a specificity of 80%. These results may influence the management of patients undergoing MMC-HIPEC and place high-risk patients under neutropenic monitoring while the other patients can undergo standard hematological monitoring [73].

A Look into the Future

As we look toward the future of CRS/HIPEC for the treatment of peritoneal metastatic disease secondary to colorectal cancer, we must look at advancements in the diagnosis and treatment of the disease in order to make treating PC more efficient and cost-effective. We must also develop modalities to increase the chance for cure and survival. To increase the chance of an R-0 resection, multiple groups have looked at utilizing fluorescence imaging to advance treatment of PC. Groups found that indocyanine green could improve the cytoreduction and thus outcomes for patients undergoing CRS of CRC. By injecting indocyanine green 24 h prior to CRS that they could correctly identify cancerous lesions with a sensitivity of 72.4% and correctly identify non-cancerous lesions with a specificity of 60%. In addition, the use of molecular-guided fluorescence has been shown to be efficacious in identifying peritoneal disease during surgery [75–78]. Mouse studies have also shown that use of hand-held cathepsin-based fluorescent imaging systems shows promise for detecting nearly/barely visible peritoneal tumors [79].

As imaging modalities continue to improve, there has been increased use of FDG-PET-CT scan in the use of aiding physicians quantifying the burden of disease. Preoperative FDG-PET-CT detected the presence of colorectal PC in 96% of patients suffering from PC with no mucinous histology and in 60% of patients suffering from PC with mucinous histology. However, despite a high detection rate, this imaging modality typically underestimated the amount of disease involvement. FDG-PET-CT scan was also found to have a false-positive rate of 11%. They related these false positives to previous mesh placement or other foreign bodies in patients. Knowing these details about a patient can prevent patients with false positives being excluded from treatment [80, 81]. Another study looked at FDG-PET-CT and found that the sensitivity and specificity of FDG-PET/CT for PC detection were 85% and 88% respectively. The most scored quadrant by FDG-PET/CT corresponded to the most scored quadrant at surgery at a rate 77.3%. Thus, this study group concluded that

FDG-PET/CT may represent a useful tool for evaluating response to neoadjuvant chemotherapy in patients with PC of CRC origin [82]. These studies show that new modalities such as FDG-PET and fluorescence imaging are on the horizon in the treatment of peritoneal disease.

An exciting new technology that could be used on a large scale for drug screening and personalized treatment is the utilization of organoids as preclinical models for HIPEC treatment. Organoids are an ex vivo form of normal or cancer stem cells in a tridimensional matrix. These matrices can then be developed into fully differentiated "mini organs." The mini organs can mimic similar architecture and function of various organs in the body. Organoids are relevant models to study the chemosensitivity of peritoneal metastases from CRCs. Such models could be used for large-scale drug screening strategies or personalized medicine for colorectal carcinoma [83••].

As our understanding of CRC and PM increases, one can begin to imagine a patient-tailored regimen becoming the standard of care. Biomarkers are beginning to be heavily investigated, showing promise for a future where they are used not only for selecting the appropriate patients but also the appropriate therapeutic regimen. Examples of tumor markers of high interest in peritoneal disease are integrin alpha2beta1, CD44, and MUC16, as well as L1CAM, EpCAM, MUC1, sLe(x) and Le(x), chemokine receptors, Betaig-H3, and uPAR [84]. Sluiter et al. found that in a recent study that selects patients with PM secondary to CRC, VCAN expression (in addition to a good PCI and lymph node status) had improved survival compared to patients with tumors expressing VEGF [85, 86]. In addition, other biomarkers such as bloom syndrome protein (BLM), circulating tumor cells (CTC), and EGFR have been studied. Low BLM levels and CTC negative patients revealed a statistically significant improved survival compared to elevated BLM and CTC positive patients after HIPEC [87, 88]. These and other future biomarkers could be used for prognostic scoring and personalized treatment for individuals with PM from CRC.

Neoplastic epithelium presence on histopathology is another exciting topic of the study. Research on this marker has found that patients who are lacking neoplastic epithelium on final pathology have a more favorable survival outcome versus the patients with neoplastic epithelium present on final pathology. This has the potential to be a future biomarker for preoperative patient selection and post CRS/HIPEC surveillance, as these patients are at greater risk of recurrence [89]. Finally, MOC31PE immunotoxin has been shown to destroy cells expressing tumor-associated epithelial cell adhesion molecule, which is highly expressed in colorectal cancer. CRS/HIPEC may offer long-term survival to patients with peritoneal metastasis from colorectal cancer (PM-CRC) but many patients experience recurrences that could possibly be prevented or treated with MOC31PE, which is now undergoing clinical trials. The phase I trial showed negligible systemic absorption of the drug while drug concentrations recovered from peritoneal fluid samples were in the cytotoxic range. MOC31PE that recovered from peritoneal cavity retained its cytotoxicity [90•]. MOC31PE and similar drugs could be the future of treatment for PC, though more studies are needed.

Quality of Life after CRS/HIPEC

Another key consideration when selecting patients for potential CRS/HIPEC surgery is their quality of life (QOL). Despite multiple studies about acceptable morbidity and mortality, it is also important to consider the effect of such an extensive surgery has on patients' QOL. Numerous studies have shown that despite initial low-grade complications, recurrence, and initial lower QOL scores, most patients return to baseline QOL within 3 months to 2 years after surgery [91–94]. However, one study in our review did show lower QOL scores in patients after CRS/HIPEC who had higher PCI score, longer duration of surgery, and the presence of a stoma [95]. This supports the notion that patient selection preoperatively also affects postoperative, morbidity, mortality, and QOL. One of the larger impacts on patient QOL is that many patients who undergo CRS/HIPEC require some form of nutritional support during their postoperative care. A few studies have examined the effect that varying levels of nutritional support have on QOL. One study found that placing a feeding tube at the initial operation had no difference in recovery or complications in the feeding tube placement group vs TPN group and the feeding tube group actually had an increased length of stay and readmission rate [96]. Most of the literature, though, supports the idea that most patients, even if they experience initial struggles in recovery, can have a quality of life that is near baseline as they get farther away from surgery. This data puts forth that despite CRS/HIPEC being a high-risk, reward procedure, most patients make it back to baseline quality of life within an acceptable time frame.

Conclusion

Current evidence supports a multidisciplinary approach to peritoneal metastatic disease secondary to colorectal cancer. Standardized treatment practice, highly selective patient criteria, low PCI score, and early recognition of patients at risk for PM show survival benefits and better outcomes for patients with a disease process that was once only treated with palliative interventions. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy is the standard of care for patients with resectable disease. All patients with peritoneal carcinomatosis as a result of metastatic colorectal cancer should be referred to institutions that preform CRS/HIPEC for further evaluation and consideration of this treatment

modality. Research into PC and CRS/HIPEC is ongoing and shows promise of improved diagnostic modalities, evolving surgical techniques, and more potent and tailored chemotherapy all of which demonstrate data for improved survival, morbidity, mortality, and quality of life for select patients.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- • Of importance
- •• Of major importance

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