

Surgical management and hyperthermic intraperitoneal chemotherapy for locally advanced colorectal cancer

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Abstract: Locally advanced colorectal cancers (CRC) pose several management challenges, including local recurrence and the development of peritoneal metastases (PM). These recurrences are associated with a poor prognosis and onerous complications. In selected patients with PM, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) have shown to confer survival benefit. However, its effectiveness depends on the disease extent and this combined treatment is associated with significant morbidity. Additionally, early detection of PM is difficult even with state-of-the-art imaging techniques. Due to the high-risk of developing PM, locally advanced CRC are currently being investigated in several trials, including adjuvant HIPEC in an attempt to reduce the risk of PM. This review article sets out to examine the current data available on this topic, in an attempt to determine the suitability and effectiveness of HIPEC in the management of locally advanced CRC.

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

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Introduction

Locally advanced colorectal cancers (CRC) comprise of 10–20% of all CRC (1,2), and pose several management challenges to the surgeon. These tumours extend through the serosa of the bowel, and present with perforation, obstruction and/or invasion of adjacent organs or structures. They are classified as T4 lesions by the American Joint Committee on Cancer staging schema (3). In addition to their presentation, the locally advanced CRC are often associated with local recurrence and the development of peritoneal metastases (PM). These recurrences are difficult to treat and hence synonymous with poor prognoses and difficult to manage complications.

Hyperthermic intraperitoneal chemotherapy (HIPEC), in combination with cytoreductive surgery has increasingly

been recognised as an effective treatment option in selected CRC patients with recurrent disease confined to the peritoneum (4–8). As a result, given the proof of concept of HIPEC as an effective treatment strategy for peritoneal disease, locally advanced CRC are currently being investigated in several adjuvant HIPEC trials (9–11) in an attempt to reduce the risk of PM and local recurrence. This review article sets out to examine the current literature regarding the use of HIPEC for locally advanced CRC.

Colorectal PM

The development of PM is associated with a poor prognosis, with median survival of about 6 months if untreated, and between 6–15 months if treated with palliative systemic therapy (12). This survival outcome

is significantly worse compared to palliative treatment for non-peritoneal recurrences. In addition, the quality-of-life (QOL) of patients with PM is often considerably reduced because of ascites, and bowel, ureteric and biliary obstruction caused by the peritoneal disease. In selected patients with metastatic disease confined to the peritoneum, cytoreductive surgery (CRS) and HIPEC have been shown to confer survival benefit. A large number of phase II studies and one randomized controlled trial have been published on CRS-HIPEC for CRC, demonstrating an improved survival in comparison with systemic chemotherapy only (4-7). However, the effectiveness of CRS-HIPEC depends largely on the amount of disease, the extent of cytoreduction and type of chemotherapy (13-15). With complete cytoreduction and HIPEC, 5-year survival rates of 40–51% have been reported (14). Moreover, survival is appreciably lower if macroscopic disease remains. Additionally, CRS-HIPEC is associated with substantial morbidity (16,17).

It is clear that there are significant disadvantages in treating PM at a late stage, however it is recognized that early detection of peritoneal disease is difficult, even with current state-of-the-art imaging techniques. As a result, the majority of patients with PM present with extensive disease, and are often only offered palliative treatment. Therein lies the need for effective prophylactic treatment to prevent the development of PM in high-risk patients.

Patients at high-risk of developing PM

Important risk factors for metachronous PM typically include more than just T4 disease. Other prognostic features include the presence of tumour perforation, mucinous and signet ring cell histology, nodal stage, right-sidedness and positive resection margins (18). As can be appreciated in the following paragraphs, the definition of high-risk CRC varies in each study, but typically always includes T4 locally advanced tumours.

Case-control studies

To date, there have been 2 prospective case-control studies done to evaluate the feasibility and utility of HIPEC in reducing PM in high-risk CRC patients (19,20). Both reported improved 5-year overall survival rates in the patients who received prophylactic HIPEC at the time of primary surgery. In the study by Sammartino *et al.* (19),

high-risk cases were defined by T4, perforation and mucinous histology. Prophylactic HIPEC was with oxaliplatin. PM and local recurrence developed significantly less often in the patients who received prophylactic HIPEC compared to controls (4% *vs.* 28%) ($P < 0.03$). Patients in the prophylactic HIPEC group also survived longer (median overall survival 59.5 *vs.* 52 months). Despite similar morbidity, Kaplan-Meier survival curves disclosed significantly longer disease-free and overall survival in the prophylactic HIPEC, than in the control group ($P < 0.05$ and $P < 0.04$).

In the paper by Baratti *et al.* (20), high-risk cases were defined as T4, synchronous krukenburg tumours and minimal peritoneal disease. Prophylactic HIPEC was with cisplatin and mitomycin-C, and correlated to lower PM cumulative incidence [hazard ratio (HR) 0.04, 95% CI, 0.01–0.31; $P = 0.002$], and better overall survival (HR 0.25, 95% CI, 0.07–0.89; $P = 0.039$) and progression-free survival (HR 0.31, 95% CI, 0.11–0.85; $P = 0.028$). Reported morbidities from HIPEC were minimal in both papers, and there were no reported mortalities. Our institution is currently completing a feasibility study on prophylactic HIPEC for high risk colorectal cancers, and the preliminary results have also shown that prophylactic HIPEC is feasible with minimal morbidity, and does not delay time to adjuvant systemic therapy.

A French HIPEC group attempted to determine the utility of HIPEC in high-risk patients by performing a systemic re-look surgery and HIPEC with oxaliplatin, at 1 year post primary surgery for high-risk CRC patients (21). The 41 patients included in the study were all asymptomatic, with negative cross-sectional imaging and tumour markers, during their 1-year follow-up after primary surgery. In these 41 patients, the investigators found an astounding rate of occult PM of 56%. This study suitably illustrates the reality of PM in advanced CRC and the difficulty in detecting PM at an early stage, while highlighting the potential utility of prophylactic HIPEC.

A minimally invasive approach has also been described by Chouillard *et al.* as a safe and feasible tool to administer adjuvant HIPEC in patients whose primaries pose a high risk of peritoneal recurrence (22). In this study, 16 colorectal patients with either: (I) T4 or N2 and above primaries; (II) positive peritoneal cytology; (III) localised satellite nodules; (IV) perforated or obstructed primary tumor were enrolled. Staged laparoscopic HIPEC was performed at a mean interval of 5 weeks (range, 0–8 weeks) from the primary

surgery. There was no conversion to open HIPEC and major morbidity occurred in 19% (n=4) of patients.

Randomised controlled trials

There are several randomised studies, designed to explore the utility of HIPEC for locally advanced CRC patients. Currently, only the Dutch COLOPEC trial has been completed and published (9), while the French PROPHYLOCHIP trial is completed but has only been presented and not yet published (10), and two other studies by the Italian and Chinese groups are still open for recruitment (23,24).

COLOPEC was the first published study, carried out in nine specialised HIPEC hospitals in the Netherlands. The study included 204 patients, with T4 or perforated colon cancers, who were randomly assigned (1:1) before curative resection of the primary tumour to adjuvant HIPEC followed by adjuvant systemic chemotherapy or to adjuvant systemic chemotherapy alone. Adjuvant HIPEC was with oxaliplatin, and was either performed simultaneously (9%) or within five to eight weeks (91%) after the primary tumour resection. All patients without evidence of recurrent disease at 18 months were subjected to a diagnostic laparoscopy, and the primary end points were PM-free survival at 18 months.

Within the HIPEC group, 19 (19%) patients were diagnosed with PM: 9 (47%) during surgical exploration preceding intentional adjuvant HIPEC, 8 (42%) during routine follow-up, and 2 (11%) during the 18-month diagnostic laparoscopy. In the non-HIPEC group, 23 (23%) patients were diagnosed with PM: 7 (30%) during laparoscopy at 18-months and the remaining 16 during regular follow-up, before 18 months. In the intention-to-treat analysis, there was no difference in PM-free survival at 18 months [80.9% (95% CI, 73.3–88.5%) for the HIPEC group *vs.* 76.2% (68.0–84.4%) for the non-HIPEC group, log-rank one-sided P=0.28]. The complication rate for the patients who received adjuvant HIPEC was 14%. The authors concluded that adjuvant HIPEC with oxaliplatin for patients with T4 or perforated colon cancer did not result in improved 18 months PM-free survival.

The main criticism of the COLOPEC study is the high proportion (91%) of patients who received adjuvant HIPEC at the delayed setting (5 to 8 weeks post primary tumour resection), during which adhesions may have limited the distribution and effectiveness of HIPEC. In addition, 9 (9%) of the 100 patients in the HIPEC group had PM detected

before the HIPEC could be given.

The PROPHYLOCHIP trial also did not show any benefit of adjuvant HIPEC with oxaliplatin in patients with minimal resected PM, Krunkenburg tumours, or a perforated primary tumour compared with surveillance (3-year disease-free survival 51% *vs.* 44%, P=0.75) (10).

The results of these two trials question the effectiveness of the 30-min HIPEC protocol with oxaliplatin, and may be due to the limited exposure to the chemotherapy, resulting in an inadequate antitumor effect. In addition, the time at which the adjuvant HIPEC is delivered is also crucial, and ideally during the time of primary resection.

The PROMENADE, APEC and HIPECT4 trials investigating adjuvant HIPEC for locally advanced CRC are currently recruiting patients, with the latter using mitomycin-C, and will certainly shed more light on this matter.

Colorectal local recurrences

The role of CRS and HIPEC in the management of locally recurrent colorectal cancer is a matter of debate. While some consider local and peritoneal recurrences as a single entity, both representing indications for CRS & HIPEC (25); others frown upon the use of HIPEC in isolated local recurrences (26,27). Dumont *et al.* in an attempt to differentiate the two compared the clinico-pathological characteristic of patients with local *vs.* peritoneal recurrence following CRS & HIPEC and found the former to have a higher likelihood of organ involvement and lymph node metastases and an increased mortality (27). Limited data in this area precludes us from making any firm conclusions, suggesting the need for future prospective studies to differentiate the two during the selection of patients for CRS and HIPEC.

In light of PRODIGE-7

The most recent debate regarding HIPEC for CRC, surfaced after the much awaited PRODIGE-7 trial was presented in 2018 (13). This trial was designed to investigate the role of HIPEC in metachronous PM, but did not show a survival benefit of the addition of HIPEC to cytoreductive surgery. Despite the results, and bearing in mind that this trial has not been published to date, CRS and HIPEC are still used worldwide, largely because the results cannot be extrapolated to mitomycin-C as the chemotherapy drug, nor to the up-front application in the adjuvant setting.

Conclusions

The challenge of managing locally advanced CRC remain, but might be lessened by the use of HIPEC in the adjuvant setting. Despite the negative trials, HIPEC continues to hold promise of reducing these difficulties and is continuously being evaluated in several trials, and may prove more effective if used for locally advanced CRC with additional high-risk features.

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Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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