Purpose: Colorectal cancer (CRC) has potential to spread within the peritoneal cavity, and this transcoelomic dissemination is termed “peritoneal metastases” (PM). Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a radical strategy to treat selected CRC patients with PM. Studies suggest that identification of CRC patients at high risk of PM may lead to earlier treatment strategies and improve survival in this subset of patients. The aim of this article was to summarise the current evidence regarding CRC patients at high risk of PM.

Methods: A retrospective review of articles on CRC patients with high risk of PM published up to December 2014 in PubMed, Medline, Embase, and Ovid search engines was conducted. The following combination of search terms were used: “intraperitoneal chemotherapy”, “HIPEC”, “colorectal cancer”, “peritoneal carcinomatosis”, “peritoneal metastases”, “high risk”, “peritoneal recurrence”.

Results: Although opinions differ, CRC patients identified as “high risk” of PM included: limited, synchronous PM completely resected with the primary tumor, ovarian metastases (synchronous or metachronous) and spontaneous or iatrogenic perforation of the bowel by the primary tumor. Aggressive early treatment strategies currently used are: CRS and HIPEC for high-risk primary tumors and second-look CRS and HIPEC often following systematic chemotherapy for the primary resection. Positive results have been shown with both approaches in a number of studies. With CRS/HIPEC for the primary tumor, the overall survival in the two groups (25 patients treated with CRS/HIPEC vs 50 treated with conventional surgery) was significantly improved (p<0.03), as was disease-free survival (p<0.04). For second look surgery, in 29 patients treated with CRS and HIPEC, this resulted in 14% morbidity and 0% mortality and a 2-year disease-free survival rate in excess of 50%.

Conclusions: We are progressively moving to an era of individualised treatment strategies. The management of CRC patients with high risk of PM is ever evolving, with early detection and early treatment strategies showing promising results. The optimal timing of early surgery remains unclear and requires further evaluation. Should current and future randomized trials demonstrate long-term survival benefit, we may potentially see a change in treatment paradigm from current conventional surgery to a more aggressive, early radical approach as the standard of care.

Key words: colorectal cancer, high risk, peritoneal carcinomatosis, peritoneal metastases

Summary

Management of colorectal cancer patients at high risk of peritoneal metastases

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Introduction

CRC has the potential to spread within the peritoneal cavity, and this transcoelomic spread is termed “peritoneal metastases” (PM) [1]. PM occur in 20-50% of CRC patients [2,3] and are found synchronous with the primary cancer in 5-10% of these patients [4,5]. PM are also known to occur in up to 50% of patients with recurrent disease following curative resection [6,7].

Traditionally regarded as a terminal disease with a dismal prognosis, patients with PM from CRC origin were previously routinely treated with palliative systemic chemotherapy with studies showing median survival of 6-9 months [8,9]. Median survival has since improved with modern
chemotherapy and the adjunctive use of targeted agents to 15.2 months [10], but at best 5-year overall survival rates are still only 5-13% [11-14].

Sugarbaker introduced CRS and HIPEC as a radical strategy to treat selected CRC patients with resectable PM [15]. Emerging data following the use of CRS and HIPEC to achieve long-term survival with acceptable morbidity has yielded encouraging results [6,11,16]. Improved survival rates are shown when complete cytoreduction (CC0 resection) is achieved [5]. The peritoneal carcinomatosis index (PCI) [17] evaluates intra-operatively the extent of peritoneal cancerous spread within the peritoneal cavity and is a major prognostic factor following CRS and HIPEC [6,11,18-22]. In a series of 523 patients treated with CRS and HIPEC, 5-year survival was less than 10% in patients with a PCI above 20; in patients with a PCI below 7, 5-year survival was 49% [18]. These results would suggest that the early detection and treatment of PM is more likely to achieve complete cytoreduction and result in better oncological outcomes. Taking this a step further, identifying CRC patients at high risk of PM may lead to earlier treatment and even more improved survival in this subset of patients [23,24].

The aim of this article was to review the current evidence regarding the treatment of CRC patients at high risk of PM.

Methods

A review of articles on colorectal cancer patients with high risk of PM published up to December 2014 in PubMed, Medline, Embase, and Ovid search engines was conducted. The following combination of search terms/key words was used: “intraperitoneal chemotherapy”, “HIPEC”, “colorectal cancer”, “peritoneal carcinomatosis”, “high risk”, “peritoneal recurrence”. The relevant references of the retrieved manuscripts were manually scanned to further identify possible relevant studies. Case reports were excluded, as were studies published in a non-English language.

Results

Which CRC patients are at ‘high risk of PM’?

Multiple tumour characteristics have been reported by Sugarbarker as resulting in high risk of PM and are summarised in Table 1 [25]. In addition, Sammartino et al. suggest that patients with pT3/4 mucinous or signet-ring cell tumours are also at high risk [26].

Honore et al. performed a recent systematic review aimed to identify patients truly exhibiting high risk of PM after intended curative resection of primary CRC [23]. Only 16 articles were identified clearly specifying the incidence of recurrent post-operative PM. Honore et al. concluded there was a paucity of available literature, with low levels of evidence. Data were not robust enough for T3/4 or N+ tumours, mucinous, signet ring cell, occlusive or bleeding tumours, and tumours with positive peritoneal cytology to be considered as true high risks for developing PM [25]. Although not strongly supported in the literature, three tumour characteristics were identified as truly “high risk”:

1. Limited, synchronous PM completely resected with the primary tumor - these patients have a risk greater than 50% of developing PM [21,27], subsequently confirmed at a 12-month laparotomy [21].
2. Ovarian metastases (synchronous or metachronous).
3. Spontaneous or iatrogenic perforation of the primary tumour.

Patients with a perforated primary tumour have a 14-54% risk of developing PM [21,28-30]. The only study with systematic second-look laparotomy reported a 27% PM recurrence rate at 12 months for perforations above occlusive tumour. Free cancer cells can be disseminated from the primary tumour, either before or during surgery, and will enter the peritoneal cavity. Trauma caused by primary surgery may greatly increase the efficiency of cancer cell implantation in the peritoneal space [31]. Because surgery can disrupt the peritoneum and create a “sticky surface”, a high metastatic efficiency of cancer cells is expected. At low density, cancer cells will implant distant from the primary tumour and develop into PM. The cancer cells at “high density” will implant within the resection site [32].

In summary, the current literature is not able to identify strong evidence-based predictive factors for recurrent PM after curative surgery for CRC [23].

Conventional and early treatment strategies

Conventional

Conventional oncological principles are still the most commonly practised to treat CRC patients with high risk peritoneal carcinomatosis (PC). Meticulous dissection is mandatory to mini-
mize trauma and spillage of cancer cells from the tumour during mobilization and extraction of the primary tumour. More radical techniques including total mesocolic excision are less widely practised but have shown to have a positive impact on survival [33-36]. This technique adheres to the concepts of ‘total containment’ and ‘total clearance’ [35].

Early

The early treatments currently used are:

i. CRS and HIPEC with primary tumour

This strategy aims to remove the primary tumour and to remove target organs likely to harbour PM (omentum, adnexa and appendix), then combining the surgery with prophylactic HIPEC [26].

CRS techniques involve peritonectomy of involved peritoneum in combination with visceral resection to remove all visible (macroscopic) disease, as described by Sugarbaker [37]. HIPEC aims to destroy non-visible (microscopic) residual tumour cells. All macroscopic disease must be resected because intraperitoneal chemotherapy penetrates tumour only up to 1mm in size [38,39]. HIPEC should be administered immediately following surgery, thereby minimising the trapping of viable peritoneal cancer cells within adhesions/fibrin [40], and destroying tumour cells shed or disseminated during surgery.

ii. Second look laparotomy with CRS and HIPEC

This approach involves a planned second exploratory laparotomy following the primary resection and adjuvant chemotherapy, to assess the peritoneal cavity for PM [21]. CRS techniques and HIPEC are performed as described above. Meticulous adhesiolysis in second-look surgery is imperative as minimal residual PM may reside within adhesions.

Rationale for early treatment strategies

Current non-invasive assessments (clinical examination/imaging modalities/tumour markers) are unreliable at detecting early or recurrent PC. Computerised tomographic (CT) scans demonstrate a sensitivity of 60-79% but this falls to 30% or less when PM are smaller than 5mm [41]. Many have therefore turned to laparoscopy as a means of assessing PM. However, some experts feel that the very difficult re-exposure of every dissection plane and impossibility of palpating all tissues preclude the use of laparoscopy in this context [42,43]. Difficulties in accessing the peritoneal cavity and adhesions, with a risk of iatrogenic bowel injury, may also preclude safe assessment of PM extent. Despite this, laparoscopy does have a role in giving some indication of the extent of PM and in particular the extent of small bowel serosal involvement, which can assist in determining the operability of PM.

Some experts believe that the only method of reliably detecting early PM is systematic second-look surgery [21], or treatment of patients prophylactically before clinically detectable PC presents [26]. This maximally invasive approach may be effective in selected groups of high-risk patients.

Evidence for treatment strategies

1. CRS and HIPEC with primary tumour

There is emerging data in the literature to support proactive treatment strategies. Sammartino et al. performed proactive CRS and prophylactic HIPEC on 25 patients with CRC at high risk of peritoneal spread classified as pT3/4 and mucinous or signet-ring cell tumours [26]. When these patients were compared to 50 matched controls,
the incidence of recurrence was significantly lower in the proactive group (4%) vs the control group (28%) (p<0.03). Median survival was also significantly prolonged at 59.5 months in the proactive group vs 52 months in the control group (p<0.03). Disease-free survival was also significantly improved (p<0.04), while morbidity was similar in both groups.

Braam et al. reported on 72 patients with synchronous PM from CRC [44]. Twenty patients had simultaneous CRS and HIPEC and 52 patients had primary resection prior to HIPEC. In the latter group, 22/37 (59.5%) anastomoses from previous surgery resected demonstrated malignancy. It was postulated that simultaneous CRS and HIPEC may prevent extended bowel resections and permanent colostomy formation.

Tentes et al. [45] reported results of locally advanced T3/T4 CRC patients (following primary R0 resection) randomly assigned to receive HIPEC plus systemic chemotherapy or control group (conventional surgery plus systemic chemotherapy). The 5-year survival in the HIPEC and control groups was 100% and 72%, respectively. No recurrence was recorded in the HIPEC group, whilst there were 3 locoregional recurrences in the control group. The authors postulated that perioperative chemotherapy was able to eradicate cancer cells disseminated locoregionally at the time of primary resection.

Pestieau and Sugarbaker demonstrated that 5 patients undergoing definitive treatment of the peritoneal disease simultaneously with primary resection had a 5-year survival rate of 100%. The results of the patients treated proactively vs those treated after PM had occurred in follow-up were significant (p<0.0001) [46].

Noura et al. showed that 31 out of 52 CRC patients, all with positive peritoneal cytology, in the absence of macroscopic PM, treated with mitomycin C, had significantly improved survival rate (p<0.05) compared to similar patients who did not receive mitomycin C [47].

2. Second look laparotomy with CRS and HIPEC

Sugarbaker et al. published early results of 20 patients who had proactive treatment with colon cancer [48]. All 20 patients in this study, who had only 4 cycles of chemotherapy before second-look surgery, had evidence of progressive PM at the time of surgery. PCI ranged between 1 and 10 in 62% of them. CRS was achieved in 85% of the cases and the 2-year disease-free survival was 85% and long-term survival was 60% in these patients.

Elias’s group [21] performed second-look planned laparotomy in 29 asymptomatic patients with no signs of recurrence on imaging studies after 6 months adjuvant chemotherapy and 12 months follow-up. These patients had undergone primary resection but were deemed being at high risk of PM [23]. PM was found in 55% (16/29) of the cases at the time of second look surgery. At the time of primary surgery, 63% of the cases had synchronous PM, 75% ovarian metastases, and in 33% perforated primary tumours were found. In this study only patients with synchronous PM or PM discovered during second look surgery received HIPEC. In the subgroup of patients with no macroscopic PM, 17% of those undergoing HIPEC developed recurrence vs 43% of those not receiving HIPEC. CRS and HIPEC resulted in 14% morbidity and 0% mortality and a 2-year disease-free survival rate in excess of 50%.

A further study of 41 patients by Elias et al. [1] was based on three selection criteria for defining patients at high risk of PM: resected minimal synchronous macroscopic PM [25], synchronous ovarian metastases [8], and tumour perforation [8]. At second look surgery, the incidence of peritoneal recurrence was 55%, with median follow-up of 30 months. The morbidity rate was 9.7% and there was one postoperative death. The 5-year overall survival rate was 90% and 5-year disease-free survival 44% [21].

Delhorme et al. [49] performed second-look surgery in 14 patients for confirmed PM present with primary colorectal resection, finding 71% of the patients to have persistent or progressive peritoneal disease at the time of surgery; median PCI was 10. Postoperative morbidity (CTCAE V3 grade III/IV) was 7% and there was no postoperative mortality. The 2-year overall survival was 91% and disease-free survival 38%. Peritoneal recurrence was 8% in the group treated with second-look surgery and HIPEC compared to 100% of those treated in the conventional fashion (in press).

Rectal cancer with PC

What about management of rectal cancer patients at high risk of PC? Sugarbaker suggests that up-front proactive CRS and HIPEC with the primary rectal tumour maybe the only option [32]. Unfortunately rectal cancer rarely shows long-term survival with CRS and HIPEC [50]. Da Silva and Sugarbaker demonstrated that patients with rectal cancer and PM patients had a 17-month median survival and 5-year was zero [51]. They
pointed out that pelvic peritonectomy after anterior resection or abdomino-perineal resection is technically difficult to achieve. As a consequence of incomplete cytoreduction within the pelvis, results following CRS/HIPEC are poor [32].

Current trials

Prophylochip (clinical trial: NCT01226394) is a French multicentre trial [1]. Recruitment started in 2011 and as of February 2014, 130 patients had been enrolled. Patients with no radiological evidence of disease recurrence after 6 months of adjuvant FOLFOX chemotherapy are randomized to second-look laparotomy with HIPEC or standard surveillance (control group). The primary outcome measure is peritoneal recurrence.

Another randomized trial (NCT01095525) based in USA [52] is evaluating mandatory second-look surgery and HIPEC vs standard of care in patients with high risk of developing PM from CRC. Patients, who have undergone curative surgery and show no evidence of disease, are randomly assigned to either mandatory second-look CRS and HIPEC or standard surveillance care.

The results of these crucial trials are awaited.

Adjuvant HIPEC

Different approaches of adjuvant HIPEC have been investigated in high-risk patients. Initial studies used intraperitoneal catheters to enable adjuvant intraperitoneal 5-FU treatment [53-55]. This therapy can be administered in an ambulatory setting, but is subject to both morbidity and discomfort. It may also delay adjuvant systemic chemotherapy. Adjuvant HIPEC may also be performed simultaneously with resection of the primary tumour [26], in the early postoperative HIPEC or alternatively at the time of second look CRS surgery.

A recently registered trial [Adjuvant HIPEC in High Risk Colon Cancer (COLOPEC), (NCT02231086)] aims to determine the oncological effectiveness of adjuvant HIPEC, using intraperitoneal oxaliplatin with concomitant intravenous chemotherapy, following a curative resection of a T4 or intra-abdominally perforated colon cancer in preventing development of PM in addition to the standard adjuvant systemic treatment.

Laparoscopic adjuvant HIPEC within a few weeks following primary resection has been tested in pilot studies [56,57] and appears to be feasible, well tolerated and potentially more efficient than intraperitoneal chemotherapy via catheters [57].

A recent systematic review for adjuvant HIPEC in high-risk CRC [58] showed limited evidence, but HIPEC did possibly lead to reduction in the development of metachronous PM.

Systemic chemotherapy

Systemic chemotherapy plays an important role in the management of high-risk patients. Franke et al. showed that CRS/HIPEC combined with systemic chemotherapy improves median survival [59]. Improvements in outcomes may be due to effective targeted systemic chemotherapy [60]. Importantly, in some patients this treatment prior to CRS and HIPEC may reduce the PM tumour load and increase suitability for CRS [5].

New data also suggests that neoadjuvant chemotherapy maybe important, enabling selection of patients sensitive to chemotherapy and potentially improve survival [61]. However, the impact of various regimens of neoadjuvant and adjuvant chemotherapy on survival remains unclear and requires further evaluation.

Discussion

Changes in the treatment approach for CRC patients at high risk of PM are primarily due to recent data demonstrating that the extent of PM is a major prognostic factor for long-term survival following CRS and HIPEC. The earlier the patient is treated, the better the prognosis [23]. Studies have also suggested that high-risk patients are often only detected at laparotomy despite regular surveillance [23].

The current literature would suggest that there is a survival benefit using proactive and second-look strategies with acceptable morbidity and mortality rates. The data supports early referral of high-risk patients with PM from CRC. However, only a few such studies exist, each with limitations. No standardized outcomes assessments were used and the studies lacked rigorous methodology, whilst being relatively underpowered. All studies were non-randomised comparative studies with a high risk of bias. Further evaluation with randomised controlled trials is required prior to acceptance by both medical and surgical oncologists; the results of ongoing trials are currently awaited. The anticipated long-term survival following early treatment strategies of patients with a PCI less than 10 is expected to be between 50-70% [32].

Early, aggressive treatment strategies can
only be deemed safe if morbidity and mortality are within acceptable limits. Sugarbaker suggests morbidity should be in the region of 10% and mortality 1% for both proactive primary and second-look CRS/HIPEC [32]. Morbidity rates in the studies reported ranged between 4-14% (grade III/IV complications) [21,26], though Tentes et al. [45] did report a morbidity rate of 52% (grade III/IV). Mortality was reported between 0-1% [1]. Postoperative mortality, although low, underlines that early surgery is not without serious or fatal complications and, as such, each individual case needs to be carefully considered in multi-disciplinary team (MDT) meetings and selected patients counselled thoroughly. Appropriate selection of patients is therefore a crucially important factor for patients undergoing early treatment strategies.

It remains unclear which patients are considered ultimately high-risk of PM, with experts differing in their opinions [23,26,32]. This has an impact on the eligibility criteria for current proactive pathways [32] and randomised trials respectively. Further risk assessment studies and an international consensus statement would provide MDTs with clear eligibility criteria for referral of patients.

The optimal timing of early surgery also remains unclear and requires further evaluation. Timing of second look laparotomy has been suggested between 6-12 months [62], but some patients may benefit from earlier intervention [63]. Some HIPEC centers advocate proactive primary CRS surgery and preventative HIPEC, the rationale being that primary operation intends to prevent peritoneal spread before it becomes clinically evident. This may also prevent the need for a second intervention.

Another important aspect to consider is awareness and attitude [62]. Advocates of early treatment strategies believe that many suitable patients are currently not being referred [24,32]. Many medical oncologists still consider CRS and HIPEC treatment of PM with uncertainty [24]. It may also be difficult to justify to oncologists the need to refer patients for proactive primary or second-look approach that is potentially morbid and fatal, particularly in the absence of symptoms or radiological evidence of PM recurrence. Sugarbaker also suggests that it is the oncologists’ responsibility to provide patients with the relevant treatment options in a timely fashion [24]. Therefore, MDTs need to be fully informed of current proactive pathways/trials and the current evidence in order to refer appropriate patients. More importantly, these patients need to be fully counselled with regards to early treatment strategies in order to make an informed decision themselves.

Another key issue surrounding adjuvant HIPEC for high-risk patients is timing, with the optimal timing yet to be defined [57]. Results for adjuvant HIPEC are encouraging [54,64] and each of the various approaches to adjuvant HIPEC has benefits and drawbacks. Performing HIPEC simultaneously with the primary resection requires both pre- and intra-operative selection of suitable patients with difficult logistics (as discussed above). Early postoperative adjuvant HIPEC has the advantage of postoperative selection and referral of eligible patients from non-HIPEC centres. However, tumour cells may have become encapsulated in fibrin/adhesions during this period, negating the therapeutic effect of HIPEC. Considering the surgical approach for adjuvant HIPEC, laparoscopy can enable adequate catheter placement. The laparoscopic route may also allow more penetration to chemotherapy compared to open approach due to the increased abdominal pressure [65]. However, optimal exposure of the chemotherapy agents to peritoneal surfaces is questionable [40]. Surgeons advocating an open approach for prophylactic HIPEC point to more thorough inspection of the abdominal cavity to improve chemotherapy distribution. Overall, further work needs to be performed to optimise HIPEC regimens, as well as the role and timing of neoadjuvant and adjuvant systemic treatment. Well-designed randomised clinical trials are also needed to determine the oncological outcomes, quality of life and cost-effectiveness [58].

Conclusions

We are progressively moving to an era of individualised treatment strategies. The management of CRC patients with high risk of PM is ever evolving, with early detection and early treatment strategies showing promising results. Should current and future randomised trials demonstrate long-term survival benefit, we may potentially see a change in treatment paradigm from current conventional surgery to a more aggressive, early radical approach as the standard of care.
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