Review Article

Abdominal metastases from colorectal cancer: intraperitoneal therapy

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Contributions: (I) Conception and design: All authors; (II) Collection and assembly of data: H Guend, S Patel; (III) Data analysis and interpretation: All authors; (IV) Manuscript writing: All authors; (V) Final approval of manuscript: All authors.

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Abstract: Patients with peritoneal metastasis from colorectal cancer represent a distinct subset with regional disease rather than systemic disease. They often have poorer survival outcomes with systemic chemotherapy. Optimal cytoreductive surgery and intraperitoneal chemotherapy (IPC) offers such patients a more directed therapy with improved survival. In this review, we discuss the diagnosis, evaluation and classification, as well as rational for treatment of peritoneal carcinomatosis (PC) secondary to colorectal cancer.

Keywords: Colorectal peritoneal carcinomatosis (PC); intraperitoneal chemotherapy (IPC); cytoreductive surgery

Submitted Mar 05, 2015. Accepted for publication Jul 03, 2015.
doi: 10.3978/j.issn.2078-6891.2015.078
View this article at: http://dx.doi.org/10.3978/j.issn.2078-6891.2015.078

Introduction

The peritoneum represents the third most common site of metastatic disease of colon cancer, following the liver and lungs (1). The prevalence of synchronous peritoneal disease is 4.3%, while the peritoneum is the first site of subsequent metastasis in 4.8% of patients (2). Though there have been significant advances in systemic cytotoxic chemotherapy for extra-peritoneal metastatic colorectal cancer with overall improvements in survival (3), patients with peritoneal carcinomatosis (PC) treated with systemic chemotherapy continue to have poorer survival outcomes (4,5). A subset of PC is thought to represent regional rather than systemic disease and could be managed accordingly. In this circumstance, peritoneal implants appear to develop after shedding of malignant cells once a tumor has broken through the peritoneal lining of the organ; hence the rationale for regional therapy with optimal surgical cytoreduction and instillation of intraperitoneal chemotherapy (IPC) (6).

Historically, the median survival of patients with synchronous PC has been reported to be as short as 5.2-7 months, even when treated with systemic chemotherapy (7). Patients who present with malignant small bowel obstruction tend to have a particularly grim outlook with survival of 3-3.5 months (8,9). The median time to diagnosis of PC from colorectal cancer is 16-21 months (1). Risk factors for development of PC include right sided tumors, advanced T stage, positive lymph nodes, less than 12 lymph nodes being examined, emergency procedures, an incomplete resection of the primary lesion (R1/R2 resection), venous or perineural invasion, and liver metastases (2,10).

Prior to the concept of peritoneal debulking, PC was considered a terminal diagnosis that most oncologists palliated with systemic chemotherapy. However, cytoreductive surgery and IPC has shown improved survival outcomes in non-gastrointestinal malignancies, particularly ovarian cancer. For instance, in a randomized trial by Alberts *et al.* in which patients with ovarian peritoneal metastasis received a combination intraperitoneal cisplatin plus intravenous cyclophosphamide or intravenous cisplatin and cyclophosphamide, patients receiving IPC had significantly improved overall survival, with decreased toxicity in the

IPC group (11). Armstrong *et al*. randomized patients with ovarian cancer and no residual mass greater than 1 cm to intravenous paclitaxel followed with intravenous cisplatin or intraperitoneal cisplatin and intraperitoneal paclitaxel. Patients receiving IPC had overall improved survival, although a significantly higher proportion experienced severe or life-threatening complications on this regimen (12). Although such studies illustrated the improvement in survival that can be achieved with IPC, hence extending such concepts to other malignancies such as colorectal, there is more work necessary to optimize delivery methods, agents used, and overall treatment. The initial experience with cytoreductive surgery and IPC in gastrointestinal malignancies was first reported by Sugarbaker, who published his experiences with peritoneal disease with the expectation of improved survival (13,14).

Diagnosis of peritoneal carcinomatosis (PC)

Patients with PC commonly present with non-specific symptoms such as abdominal discomfort or pain, and extreme fatigue. They may also present with abdominal ascites causing abdominal bloating (15). Malignant obstruction tends to be a late presenting symptom that is an especially difficult problem to manage. Although abdominal imaging in the form of CT or PET/CT may be helpful in making the diagnosis, such imaging modalities have been shown to have poor predictive value of the extent of peritoneal dissemination (16-18). In an observational prospective study by Esquivel *et al*., the authors evaluated the accuracy of CT based peritoneal carcinomatosis index (PCI) in comparison to operative findings across multiple institutions. They found that CT based PCI significantly under estimated the intra-operative PCI in 33% of the cases. Utilizing a preoperative PCI of 20 as a threshold score for selection of patients eligible for treatment, 12% of patients selected for cytoreduction were deemed unresectable at time of surgery (16). This underscores the importance of consideration for a diagnostic laparoscopy to assess the extent of peritoneal disease before proceeding to debulking and IPC (19). However, laparoscopy may not be feasible in many patients due to benign or malignant adhesions to the abdominal wall and is used selectively.

Beyond making the diagnosis, predicting which patients are best suited for cytoreductive surgery and IPC is challenging without direct operative exploration. Van Oudheusden *et al*. attempted to define clinical characteristics that would predict resectability prior to the operating room; the presence of a prior colostomy or an American Society of Anesthesiologists (ASA) score greater than 3 were the only significant variables associated with suboptimal cytoreduction (20). These two variables are present in a minority of potentially eligible patients and stress the difficulty in predicting the true extent and location of peritoneal disease based on current clinical findings and imaging modalities.

Classification of peritoneal metastasis

There are six notable classification indices developed for the measurement of PC. Such indices attempt to quantify peritoneal disease and offer prognostication based on the severity of disease (21). The most commonly utilized measure is the PCI devised by Sugarbaker (21-23). This index divides the abdominopelvic region into nine regions. Additionally, another four regions are scored that include the peritoneal surfaces on the small bowel and its mesentery, extending from proximal jejunum to distal ileum. Each region is assigned a score from 0 to 3, for a total maximum score of 39. The scoring of each region is based on the largest lesion size (LS) after full lysis of adhesions. A score of LS-3 is assigned for lesions 5 cm or greater in diameter, LS-2 for lesions greater than 0.5-5 cm, and LS-1 from lesions less than 0.5 cm. A score of zero is given if no lesions are visible. A PCI score of less than 20 has been correlated with better survival and thus suggested it as a cut off for disease amenable to debulking (24). Although high PCI scores indicate more bulky disease that is more difficulty to optimally treat surgically, other variables such as location of disease, initial presentation, tumor histology, and lymph node status must also be taken into consideration when evaluating patients for debulking and IPC (20,24,25).

A second score developed by Jacquet and Sugarbaker is the completeness of cytoreduction (CCR) score; which aims to quantify the extent of disease after cytoreductive surgery (21,22). In this system, a score of 0 to 3 is assigned based on the largest size of lesion deemed un-resectable after cytoreduction. A CCR-0 implies no visible peritoneal disease is noted. A score of CCR-1 is assigned when peritoneal lesions less the 2.5 mm are left after cytoreduction, while a CCR-2 is for lesions between 2.5 mm and 2.5 cm. A CCR-3 score is assigned for lesions greater than 2.5 cm. IPC is suspected to work by diffusion, thus penetrating the outermost cell layers of a tumor (26-28). Hence optimal debulking to no visible disease or no lesions greater than

2.5 mm must be obtained and is considered appropriate for peritoneal chemotherapy penetration (23,29,30).

A newly introduced scoring system with prognostic significance is the Peritoneal Surface Disease Severity Score (PSDSS) (31). The PSDSS system is calculated based on three variables at the time of diagnosis: burden of carcinomatosis as define by the PCI, histopathology of the primary tumor, and presenting symptoms. Each one of the components is given a weighted score, and the sum of each gives the final PSDSS score. The PCI score is broken into three sub-categories (<10, 10-20, >20). The symptom severity is based on amount of weight loss, extent of ascites, and abdominal pain severity. The histopathology is based on the aggressiveness of primary tumor. After the final score is calculated, the PSDSS is broken into four groups (I-IV), each providing prognostic value (31).

The advantage of the PSDSS system is that it can be calculated at the time of diagnosis without operative exploration since the PCI is calculated based on imaging (CT ± F-18 FDG PET) and the histology utilized is the primary tumor histopathology (32). The prognostic utility of PSDSS was evaluated by the American Society of Peritoneal Surface Malignancies (ASPSM) in a multi-institutional study involving 1,013 patients with colorectal cancer PC (32). In patients in the PSDSS I group treated with chemotherapy alone, median survival was 45 months (95% CI: 1.1-89.6 months), while for the PSDSS IV group it dropped to 6 months (95% CI: 5.0-7.3 months). In patients treated with cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC), the median survival for the PSDSS I group was 86 months (95% CI: 64.4 to not available) and 28 months (95% CI: 19.9-32.0 months) for PSDSS IV group. In multivariate analysis, the PSDSS, as well as the location for where patients were enrolled, type of treatment, and timing of occurrence were independent prognostic factors for survival. The PSDSS IV group had a higher risk of death compared to the other scores (32).

Rational for cytoreduction and intraperitoneal chemotherapy (IPC)

It is commonly believed that PC develops after implants from the primary tumor are shed when the tumor breaks through the peritoneal lining of the organ (6). Systemic chemotherapy agents may have poor penetrance of the peritoneal cavity due to the peritoneum's poor blood supply and the rapid clearance of such agents. As such, directed therapy with instillation of chemotherapy agents into the peritoneum appear to provide higher drug concentrations and penetrance of tumor deposits (28,33). Additionally, agents with a higher molecular weight achieve greater concentration in the cavity since they do not readily diffuse across the parietal peritoneum into the systemic circulation. This also limits the systemic toxicity of such agents (33,34). Additionally, as mentioned previously, complete cytoreduction of peritoneal deposits prior to the administration of IPC appears to be critical to the success of IPC (23,29,30). The agents utilized in IPC are thought to penetrate tumor cells by diffusion (26-28). Therefore, complete cytoreduction allows IPC to treat the remaining disease not visible to the eye during exploration or small deposits less than 2.5 mm in which the agents can effectively diffuse the superficial layers of cells, providing potentially effective therapy.

Treatment of isolated peritoneal metastasis

Interest in resection of peritoneal metastasis from colorectal cancer has intensified over the last decade. Despite this, there have been only a limited number of randomized trials published in the literature.

The largest to date (30) included 105 patients with peritoneal metastasis from a colorectal cancer primary without evidence of liver or lung metastasis. Patients were randomized to systemic treatment (5FU and leucovorin) with or without palliative surgery or to cytoreductive surgery with HIPEC, followed by systemic therapy. The initial publication followed patients for a median follow up of 21.6 months. The authors found that patient in the cytoreductive surgery and HIPEC group had significantly longer survival (22.3 *vs.* 12.6 months, P=0.032) compared to the standard therapy patients. In addition, the authors found that survival was increased in those patients in which all macroscopic disease could be resected compared with those with gross residual disease (P<0.0001). The treatment related mortality was 8% in the cytoreductive surgery and HIPEC group. A follow up report of long term survival was published by the authors in 2008 (35). Median survival in those with an R1 resection was 48 months compared with 18 months in those with an R2a resection and 8 months in those with an R2b resection. This trial offered some evidence in support of the effectiveness of regional therapy for colorectal cancer; however, the trial's small numbers, high mortality, high rate of suboptimal cytoreduction, and use of now outdated systemic chemotherapy (5FU/leucovorin only) have limited the acceptance of this

approach. Furthermore, as cytoreductive surgery was performed only in the HIPEC arm, the incremental effect of IPC remains unknown.

The other attempted randomized controlled trial (RCT) in patients with peritoneal metastasis from colorectal cancer was terminated due to poor accrual (36). Only 35 of 90 patients were enrolled over the study period. The study attempted to assess the effect of early postoperative intraperitoneal chemotherapy (EPIC) plus systemic chemotherapy *vs.* systemic chemotherapy alone in patients who cytoreductive surgery. Patients with liver metastasis were included if there were 1 or 2 liver lesions that could easily be resected. A 60% 2-year survival was found after complete macroscopic resection of disease (R1 resection). Due to the small sample size and early termination, definitive recommendations could not be made.

Comparative retrospective studies were published by both Elias *et al.* (37) and Franko *et al.* (38) that compared cytoreductive surgery and HIPEC to standard therapy (chemotherapy ± palliative surgery). The study by Elias *et al.* included 48 patients in the cytoreductive surgery (CRS) + HIPEC group and 48 patients in the standard therapy group. Five year overall survival was 51% in the CRS + HIPEC group, compared with 13% in the standard therapy group. Median survival was 62.7 months in the CRS + HIPEC group, compared with just 23.9 months in the standard therapy group (P<0.05) (37). The study by Franko *et al.* included 67 patients undergoing CRS + HIPEC and 38 patients undergoing standard therapy. The CRS + HIPEC group had fewer patients with liver metastasis (15% *vs.* 35%, P=0.014). Median survival was longer in the CRS + HIPEC group (34.7 *vs.* 16.8 months, P<0.001) (38). These small studies had limited ability to control for confounding factors.

Larger observational studies published by Elias *et al.* (39) and by Glehen *et al.* (29) did not include systemic chemotherapy only patients. Both studies were authored by the same group, and the overlap of patients between studies was unclear. The study by Elias *et al.* included 523 patients with colorectal cancer treated by either HIPEC or EPIC following cytoreductive surgery. Both isolated peritoneal metastasis and combined liver-peritoneal metastasis patients were included. Postoperative mortality was 3.3% in the entire population, with 31% of patients experiencing grade 3 or 4 complications. Median survival was 30.1 months, with 5-year survival of 27%. Of those with an R1 resection, the 5-year survival was 29%, whereas those with nodules >2.5 mm remaining, the 5-year survival was 0%. There did not appear to be any advantage to HIPEC or EPIC in overall survival (P=0.965) (39). The study by Glehen *et al.* found similar results. Postoperative mortality was 4% and morbidity was 22.9%. There was a strong association between completeness of cytoreductive surgery and overall survival (P<0.0001). Again, no difference was seen between HIPEC or IPEC or HIPEC + EPIC (P=0.61). Median overall survival was 19.2 months, with a 5-year survival of 19% (29).

Importance of optimal cytoreductive surgery

Both of the large series reviewed above by Elias *et al.* (39) and Glehen *et al.* (29) assessed the importance of optimal cytoreductive surgery. In the study by Elias *et al.*, patients with no gross disease left *in situ* had a median survival of 33 months and a 5-year overall survival of 29%. This is in comparison with those with remaining tumor nodules <2.5 mm (20-month median survival, 14% 5-year survival) and those with tumor nodules ≥2.5 mm (7-month median survival, 0% 5-year survival). After adjusting for important prognostic variables, this difference persisted (P<0.001) (39).

Similar findings were published by Glehen *et al.* Their group found a median survival of 32.4 months in those with complete cytoreduction, compared with 24 months in those with tumor nodules <5 mm and 8.4 months in those with residual tumor nodules of ≥5 mm (P<0.0001). After adjusting for important prognostic variables, this difference persisted as well (P<0.0001) (29). These findings have been consistently upheld by other investigators and failure to achieve optimal cytoreduction is considered a contraindication to radical surgery except in the purely palliative setting.

Patients with combined peritoneal metastasis and liver metastases

The outcomes in patients with liver metastasis who underwent cytoreductive surgery and IPC chemotherapy have been evaluated; however, most series have a small subset of such patients. The largest series with such analysis are those by Elias *et al.* (39) and Glehen *et al.* (29) mentioned previously.

The study by Elias *et al.* (39) included 77 patients who had synchronous liver lesions which were resected. In the univariate analysis, this group had a similar median survival (23 *vs.* 31 months) and 5-year overall survival (21% *vs.* 27%) (P=0.15). However, the authors of the study performed a multivariable analysis adjusting for extent of carcinomatosis,

the institution performing the surgery, lymph node status and the use of adjuvant chemotherapy. This regression showed that the rate of death was higher in those with liver metastasis (hazard ratio 1.623, P=0.01).

Glehen *et al*. (29) also found that those with liver metastasis had a shorter median survival compared with those without liver metastasis (16.8 *vs*. 20.4 months, P=0.008). After multivariate, Cox regression (adjusting for important variables including completeness of cytoreductive surgery, preoperative chemotherapy and adjuvant therapy), the presence of liver metastasis negatively affected survival (Cox coefficient 0.52, P=0.004).

Conclusions

PC from colorectal cancer represents a distinct subtype of metastatic disease that is regional rather than systemic. Significant changes in our understanding of this disease pattern have allowed different strategies to target PC. Optimal debulking and IPC are critical variables in improving survival for this patient population. However, more studies are needed to define better patient selection, optimal therapy, delivery methods, and overall outcomes.

Acknowledgements

None.

Footnote

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

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Cite this article as: Guend H, Patel S, Nash GM. Abdominal metastases from colorectal cancer: intraperitoneal therapy. J Gastrointest Oncol 2015;6(6):693-698. doi: 10.3978/j.issn.2078-6891.2015.078