MANAGEMENT PERSPECTIVE

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Proactive management of peritoneal metastases from colorectal cancer: the next logical step toward optimal locoregional control

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Practice points

- The surgeon's primary responsibility in the management of colon and rectal cancer is to completely clear the malignant process and, in the act of clearance, to maintain perfect containment of the cancer cells.
- Despite perfect containment, some patients will develop locoregional recurrence (LRR) or peritoneal metastases (PM). Identification of these patients at high risk for LRR and PM is essential for optimal management.
- The use of hyperthermic intraperitoneal chemotherapy (HIPEC) with primary surgery has been shown to reduce LRR and PM.
- In patients for whom HIPEC is not available at the time of primary colorectal cancer surgery, a second-look procedure utilizing peritonectomy and perioperative chemotherapy with HIPEC should be considered as a treatment option.
- Second-look surgery should involve peritonectomy and HIPEC in order to maximize the benefits of the repeat intervention.
- Ten risk factors to indicate patients at high risk for LRR and/or PM were identified. A proactive approach to LRR and PM is indicated in order to utilize potentially curative treatments early in the natural history of colorectal cancer and thereby minimize these surgical treatment failures.

SUMMARY Although surgery for colorectal cancer has improved over the last decade, locoregional recurrence and peritoneal metastases continue as a mechanism of surgical treatment failure in 10–20% of patients. These patients have a dismal prognosis. Clinical information is available in order to identify patients who are at high risk for locoregional recurrence and peritoneal metastases. These patients, once identified, should be offered new treatment options shown to be of benefit in selected patients. Using perioperative chemotherapy at the time of colorectal cancer resection improves locoregional control and diminishes peritoneal metastases. Also, in patients at high risk, a proactive second-look surgery utilizing peritonectomy and hyperthermic intraperitoneal chemotherapy is of benefit, with reasonable morbidity and mortality.

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A majority of primary colorectal cancers (CRCs) are optimally managed by a technically perfect surgical procedure with or without systemic chemotherapy. Recent improvements in the surgical technology have decreased the incidence of surgical treatment failures from locoregional recurrence (LRR) or peritoneal metastases (PM). The benefits of total mesorectal excision have been established and a survival benefit published [1,2]. This survival advantage has been a result of the absence of tumor contamination because of meticulous dissection within the confines of the pelvis [3]. Also, the benefit of colon cancer resection using wide excision, generous lymphadenectomy and an intact mesocolic resection have been demonstrated [4]. Again, improvements were considered the result of decreased tumor cell contamination resulting from the surgical intervention itself. A complete absence of tumor cell contamination with primary CRC surgery has become an absolute requirement of CRC resections.

Although less frequent than in the past, LRR and PM continue to be observed in the follow-up of CRC patients. This recurrence of disease is difficult to diagnose and usually impossible to definitively control over the long term. It carries with it devastating quality-of-life consequences. The treatments of between 10 and 20% of CRC patients fail with LRR or PM; this is an estimated 20,000 unfortunate Americans every year. This article suggests that yet another step toward perfect containment of a primary CRC is necessary. Knowledgeable use of the clinical findings present in the patient with primary CRC indicates the need for individualized perioperative management. Management strategies are necessary over and above that which is available as a result of surgical technology combined with adjuvant systemic chemotherapy. There are currently additional treatments available. Improved locoregional control and diminished PM will occur by selectively integrating peritonectomy, hyperthermic intraperitoneal chemotherapy (HIPEC) and proactive second-look surgery into the management of primary CRC.

Poor prognosis of patients with PM

There is a paucity of data that compares the outcomes of patients with PM from CRC with patients with liver metastases. The biology of these two common sites for CRC dissemination is remarkably different. Liver metastases gain entrance to this organ through the portal vein. The metastatic process within the portal venous blood is usually metastatically inefficient [5]. Cancer cells become implanted within portal venules, through angiogenesis gain access to hepatic arterial blood and progress by expanding within the liver parenchyma. Their doubling time is approximately 3 months [6]. The progression is by expansion of the 3D mass; metastases to the lungs occur as selective pressure for survival of individual cancer cells forces malignant cells to escape into the pulmonary vein and then to lung parenchyma [7]. This process of metastases in the liver resulting in metastases in the lungs and other systemic sites may take many months and even years. It may not occur at all with a response to chemotherapy or if a liver resection is successful.

PM have a fundamentally different pattern of dissemination. Single cells or small nodules break away from the primary tumor into the free peritoneal space. Moved around passively by peritoneal fluid, the cancer cells become implanted in a characteristic pattern at multiple sites on peritoneal surfaces within the abdomen and pelvis. Tumor nodules with their own blood supply now progress in the absence of contact inhibition. Soon after implantation, the exfoliation of malignant epithelial cells from this peritoneal implant results in additional PM moving within the peritoneal space. This exfoliation into the peritoneal space represents a fundamental difference in the natural history of peritoneal as compared with liver metastases. Consequently, progression on the peritoneal surface can be much more rapid with PM than with liver metastases. These PM are less effectively treated by systemic chemotherapy, less amenable to successful surgical removal and show little or no host resistance through the multiple mechanisms involved in metastatic inefficiency (see **Figure 1**).

The differences in rates of progression of cancers at different metastatic sites have been studied by Franko and colleagues [8]. They reported a marked reduction in the survival of patients with PM as compared with metastases at other sites. The overall survival of PM patients was 12.7 versus 17.6 months for metastases at other sites. Progression-free survival in PM patients was 5.8 versus 7.2 months at other sites of metastatic disease. The p-value was significant for overall survival ($p < 0.001$) and for progression-free survival ($p = 0.05$). They conclude that PM is associated with a

significantly shorter overall survival and progression-free survival as compared with other sites of colorectal metastases.

A clinical impression is that PM show a remarkably poorer response to systemic chemotherapy than metastases to other anatomic sites, especially liver metastases. A frequent observation in patients having reoperative surgery for colorectal metastatic disease is a complete or near-complete response with parenchymal metastases to the liver but little or no response with PM when both sites of metastatic disease are present in the same patient. Chua and colleagues have recently reviewed evidence regarding chemotherapy responses in patients with PM [9]. They reported on four studies in which PM patients were treated with modern chemotherapy using oxaliplatin or irinotecan with or without biological agents. The median survival reported in these four studies ranged from 11 to 24 months and the 5-year survival ranged from 0 to 13%. Elias *et al.* in a highly selected group of PM patients reported a median survival time of 24 months. In this study, patients had isolated PM and the analysis excluded patients that progressed on systemic chemotherapy [10]. It has been shown that patients with PM who responded to systemic chemotherapy have a prolonged survival [11]. A more representative population that did not undergo such stringent selection criteria was reported by Catalano *et al.* [12]. Their study looked for predictors of poor response and overall survival in patients with CRC metastases treated with first-line oxaliplatin- and/or irinotecan-based chemotherapy. They reported that patients with PM had the poorest overall survival on multivariate analysis, with a median overall survival of 11 months. Throughout the literature, CRC with PM had a worse outcome as compared with metastases at other sites [13].

A final cause of poor prognosis in PM patients results from the unfortunate lack of definitive radiologic assessment early in the progression of the disease on peritoneal surfaces. A size threshold of 1–2 cm exists in the peritoneal cavity. The layering of cancer nodules on parietal or visceral peritoneal surfaces is poorly imaged by CT (computed tomography), MRI or PET–CT. Radiologists agree that small volume PM are woefully inadequately detected [14,15]. Patients on systemic chemotherapy, despite repeated abdominal and pelvic CT using the most meticulous technique, can progress to an untreatable and advanced stage of disease without warning.

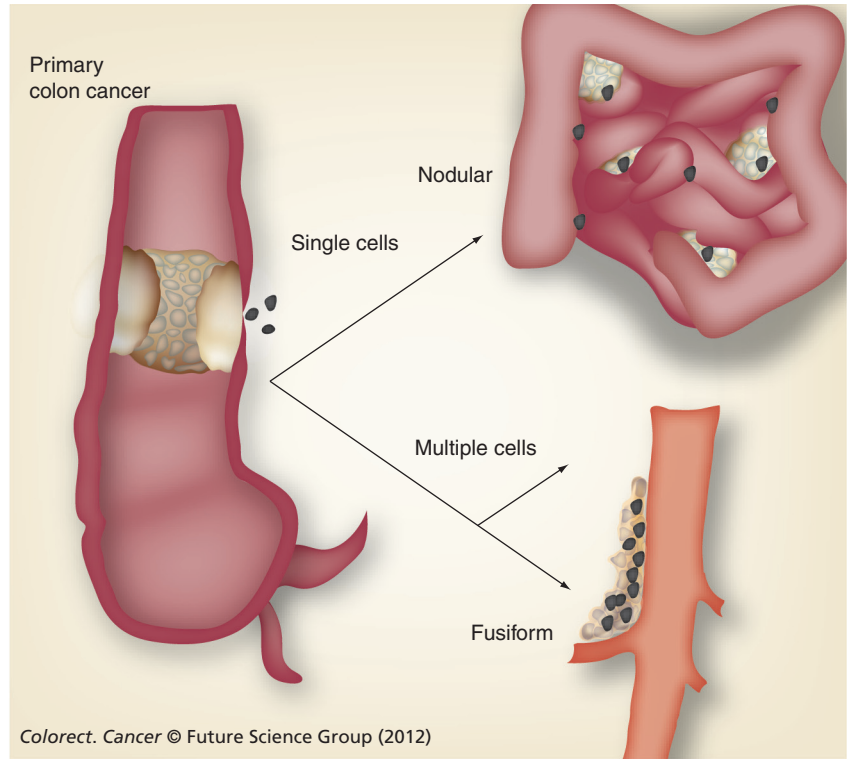

Figure 1. Anatomic sites of right colon cancer progression by the dissemination of cancer cells or minute nodules. The mechanism for right colon cancer implantation and progression at the cancer resection site along the superior mesenteric vessels or on peritoneal surfaces is similar.

Clinical information that indicates high risk of LRR & PM

LRR of CRC in the cancer resection site or within the abdominal incision may be closely related to PM in terms of causation [16]. Single cancer cells or minute nodules from the primary cancer can become entrapped in the fibrinous exudate that occurs as a first stage of the healing process. These cells, fixed at sites of wound healing, progress to become LRR. Single cancer cells or minute nodules from the primary cancer may gain access to the free peritoneal cavity and develop into PM **(Figure 2)**.

There are clinical findings in some primary CRC patients that signal the need for individualized treatments; they indicate that primary CRC surgery with or without systemic chemotherapy is not a sufficient management strategy. If a high risk of LRR or PM is evident, specialized additional treatments need to be considered. The patients at special risk of LRR and PM are listed in **Box 1**. In groups 1–5 listed in **Box 1**, patients have near 100% incidence of LRR and/or PM that will be observed with long-term

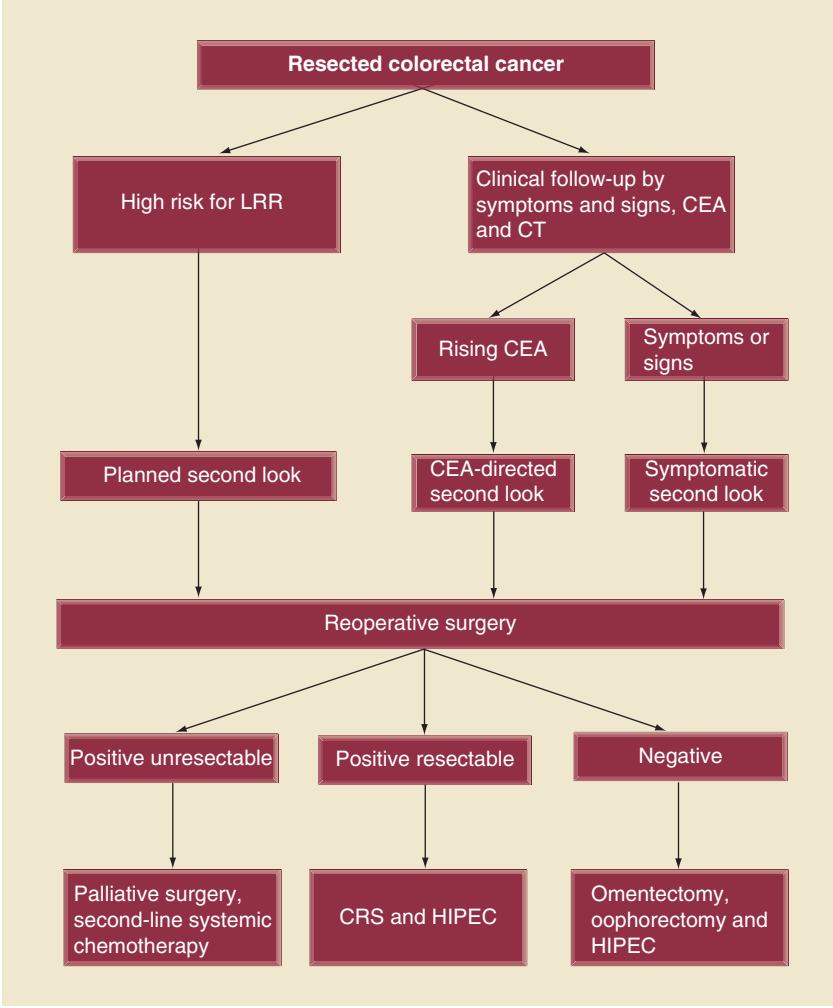

Figure 2. Algorithm for a planned second look in patients at high risk for locoregional cancer recurrence.
CEA: Carcinoembryonic antigen; CRS: Cytoreductive surgery; CT: Computed tomography; HIPEC: Hyperthermic intraperitoneal chemotherapy; LRR: Locoregional recurrence.
Reproduced with permission from [45].

follow-up. These groups include patients with PM present at the time of primary CRC resection, even if these metastases are completely resected with the primary cancer intervention [17–19]; ovarian metastases, even if resected with oophorectomy and hysterectomy [20,21]; perforation through the primary colorectal malignancy [22,23]; positive cytology at the time of primary cancer resection [24–26] and a positive margin of resection, usually a lateral margin [27]. The other clinical findings (numbers 6–10) have been shown to have a lower risk of LRR or PM. They are adjacent organ involvement or a cancer-induced fistula;T3 mucinous cancers [28,29]; T4 cancers or a positive imprint cytology from the primary malignancy [30], rupture of the cancer mass with resection [31] or obstruction as a result of the primary malignancy [22].

Data showing benefit for LRR & PM with perioperative chemotherapy in primary CRC patients with peritoneal seeding

Many oncologists have recognized the prominent role that LRR and PM have occupied in the natural history of gastrointestinal cancer (reviewed in [32]). Chemotherapy in the abdomen used as a planned part of a surgical intervention to control LRR and PM from CRC was proposed by Sugarbaker and colleagues [33]. They performed Phase I/II studies with 5-fluorouracil and mitomycin C administered directly into the peritoneal cavity on postoperative days 1–5 in CRC patients. There was a marked pharmacokinetic advantage of perioperative intraperitoneal chemotherapy with disseminated cancer cells as the targets of this treatment.

Experience with patients having peritoneal seeding recognized at the time of primary colon cancer resection was reported by Pestieau and Sugarbaker [34]. They identified five patients who had the definitive treatment for PM from colon cancer concomitant with the resection of the primary tumor. At the time of writing this article, the median disease-free survival for these patients had not been reached and their 5-year survival was 100%. The statistical difference between patients with concomitant treatment versus delayed management of carcinomatosis with cytoreductive surgery and early postoperative intraperitoneal chemotherapy (EPIC) in 44 patients was statistically significant ($p < 0.0001$).

Tentes and colleagues reported on the use of HIPEC in patients at high risk of LRR [35]. These were patients with locally advanced T3 or T4 CRC. Only patients with R0 resection were randomly assigned to HIPEC plus systemic chemotherapy versus conventional treatment, which was surgery alone plus systemic adjuvant chemotherapy. The 5-year survival for the HIPEC group was 100% and for the conventional group 72%. The difference in survival showed a trend toward significance ($p = 0.0938$). By univariate analysis, the nodal status, stage and degree of differentiation were related to survival. During follow-up two patients in the HIPEC group and eight patients in the conventional group were recorded with recurrence ($p = 0.002$). It is important to note that no LRR was recorded in the HIPEC group by contrast to the conventional group in

which three LRR were recorded. These authors suggest that HIPEC had no effect in the development of distant metastases but exhibited an advantage in eradicating viable cancer cells that were disseminated locoregionally.

Sammartino and colleagues studied colon cancer patients with clinical T3/T4, any N and M0 stage, and mucinous histology or signet cell histology [36]. Twenty five patients in the experimental group underwent carcinomatosis prevention strategies including complete omentectomy, bilateral salpingo-oophorectomy, hepatic round ligament resection and appendectomy. At the end of the resection HIPEC was delivered using hyperthermic oxaliplatin with intravenous fluorouracil. These experimental patients were compared with 50 matched control patients. All patients had a R0 resection. The morbidity in the two groups of patients was the same. The disease-free survival in the two groups was different with a p-value of 0.01. At 5 years the survival difference was not significant. Peritoneal recurrence developed in 4% of patients in the experimental group and 22% of controls, without increased morbidity ($p < 0.05$). These authors concluded that preliminary results show that a preventive surgical approach combined with HIPEC significantly reduced the incidence of peritoneal recurrence in patients with advanced mucinous colonic cancer, and also significantly increased disease-free survival compared with a homogeneous control group treated with a standard surgical approach and did so without increasing morbidity.

To date, the optimal perioperative chemotherapy treatment for prevention of LRR or PM has not been determined. The most successful plan may be EPIC. This was used by Pestieau and Sugarbaker owing to their good results [34]. Also, in the prevention of LRRs of gastric cancer, EPIC was shown by Yu *et al.* to be very successful in a prospective randomized controlled study [37]. It is possible that the single-dose intraoperative chemotherapy (HIPEC) is not as effective as a 5-day intraperitoneal lavage in the perioperative period (EPIC). However, EPIC has been thought to cause a higher incidence of adverse events.

Current data regarding benefits expected with proactive second-look surgery

In patients treated for primary CRC in institutions where cytoreductive surgery and HIPEC are not available, a second strategy for proactive management of patients at high risk for progression of PM must be formulated. The inclusion criteria for the patients included in this clinical pathway are the same as those listed in **Box 1**. Patients in groups 1–5 are those who must be recommended for a repeat surgical intervention (proactive second-look surgery) if a high likelihood of long-term survival as a result of optimal treatment is expected. Patients in the high-risk groups 6–10 need to be carefully monitored; laparoscopy rather than laparotomy is recommended for the planned second-look intervention.

In the USA, a long history of efforts to use second-look surgery to improve the survival of CRC patients has accumulated in the surgical literature. Wangensteen and colleagues first organized a planned approach to reoperative surgery in asymptomatic gastrointestinal cancer patients [38]. Griffen and colleagues summarized the long-term results of second-look surgery [39]. Minton and colleagues revisited this problem, suggesting that second-look surgery should be initiated by patients' symptoms (symptomatic second look) or a progressive increase in serial carcinoembryonic antigen assays obtained in follow-up [40]. The history of second-look surgery and its application to modern surgical oncology has been recently reviewed [41]. Two important changes in the second-look treatment strategy have occurred. First, patients selected for a repeat intervention in the absence of signs or symptoms of progressive disease are those patients listed in groups 1–5 of **Box 1**. As

Box 1. Patients with primary colorectal cancer identified to be at high risk for locoregional recurrence and/or peritoneal metastases.

1) Visible evidence of peritoneal metastases
2) Ovarian cysts showing adenocarcinoma suggested to be of gastrointestinal origin
3) Perforated cancer
4) Positive cytology either before or after cancer resection
5) Positive lateral margins of excision
6) Adjacent organ involvement or cancer-induced fistula
7) T3 mucinous cancer
8) T4 cancer or positive 'imprint cytology' of the primary cancer
9) Cancer mass ruptured with the excision
10) Obstructed cancer

recommended by the surgical literature that has been published in the past, the other patients who require a second look are those whose symptoms, signs, serial carcinoembryonic antigen assessments or radiologic studies suggest disease progression. The patients at high risk of LRR or PM, patients with a progressively rising carcinoembryonic antigen assay level and patients with symptoms or signs of cancer progression are recommended for a second look. The second important change is that this second look would be combined with cytoreductive surgery plus peritonectomy and HIPEC as a planned part of the repeat intervention.

The evaluation of this revised strategy for the use of second-look surgery must be prospective and thorough. The primary end point for the study is the percentage of patients who have a positive second look and as a result of the repeat surgical intervention enjoy long-term survival. To use the Wangensteen terminology, these are patients 'converted' from disease documented at the time of second-look surgery to a 5-year survival [39]. A second end point would be the percentage of patients who had a positive second look as compared with those who had a negative second look. This would provide an estimate of patients who had 'unnecessary surgery' as a result of the elective reintervention. Of course, a third end point would be a comprehensive morbidity and mortality assessment of both positive and negative second-look procedures. Elias and colleagues published their experience with second-look surgery for CRC patients at high risk of progression [42]. This was a highly selected group of patients who had biopsy-proven PM, ovarian PM or perforation confirmed at the time of primary CRC resection. The second-look surgery was performed within 1 year of the first surgery and 6 months after the end of systemic adjuvant chemotherapy. The patients treated by Elias were asymptomatic with a completely negative work-up. The authors detected additional PM in 63% of patients who had synchronous PM, 75% of patients with ovarian metastases and 33% of patients with a perforated primary tumor. Patients with macroscopic PM were treated with cytoreductive surgery plus HIPEC with no mortality, a low morbidity and a 2-year disease-free survival rate exceeding 50%. Patients without macroscopic PM received prophylactic PM surgery with or without HIPEC. It is interesting to note that, in this subgroup with no macroscopic PM, 17% who received HIPEC showed recurrence versus 43% among those who did not receive HIPEC.

Sugarbaker and colleagues prospectively followed 34 peritoneal mucinous carcinoma patients of appendiceal origin. All of these patients had documented PM at the time of their initial exploration. They were all treated with systemic chemotherapy using 5-fluorouracil–leucovorin–oxaliplatin (FOLFOX) and half of the patients received bevacizumab. The 5-year survival of this group of patients was 50% despite the fact that they all had high-grade PM [43]. At the time of reoperation, all patients underwent cytoreductive surgery to the lowest peritoneal cancer index possible combined with HIPEC mitomycin C plus doxorubicin. Interestingly, in this report is the group of patients documented to have a complete or near-complete response to neoadjuvant chemotherapy. This group had a greater than 50% survival at 5 years and this was statistically significantly improved over those patients who had merely disease stabilization or no response to the systemic chemotherapy [12].

Update on strategies for proactive surgical management of PM

The new concepts regarding the mechanism for LRR and PM have changed the surgical technologies for the modern management of primary CRC. First, extreme care is taken with the primary CRC resection to prevent trauma to the cancer specimen as it is removed. The concept of total containment of the malignant process during the cancer resection has been shown to be imperative [1]. A total mesorectal resection and a total mesocolic resection are the surgical requirements for containment of the malignancy during the intervention to remove the colon or rectal cancer [2–4]. Also, total relevant lymphadenectomy with lymph node resections carried out down to the superior mesenteric artery and vein on the right, or aorta on the left, has supporting data [44].

If PM are encountered at a primary colorectal resection or at the time of a proactive second look, peritonectomy should be utilized in order to provide an adequate resection [45]. The concept of the peritoneum as the first line of defense for PM at a majority of anatomic sites within the abdomen and pelvis guides the surgeon in the extent of peritonectomy [46].

Saline irrigation in the past has not been regarded as a reliable treatment for free intraperitoneal cancer cells [19]. However, recent experience with a larger volume of irrigation (10 l) has gained new interest. The concept of extensive

intraoperative peritoneal lavage has been found to be useful in patients with gastric cancer with positive peritoneal cytology. Extensive intraoperative peritoneal lavage was most effective when combined with HIPEC [47]. Also emerging as a standard of care is electrosurgical dissection with a ball tip and frequent irrigation of the operative site in order to thoroughly suction away debris including free cancer cells from the resection site of a malignancy [48]. In addition, emerging as a standard of care is gauze debridement with extensive local irrigation of the operative site and wound edges to diminish the likelihood of cancer cells being left behind at these prominent sites for LRR as a result of high-volume peritoneal seeding.

Perioperative chemotherapy has now become a standard of care for low-volume PM from CRC [49]. The most frequently used strategy involves HIPEC. However, EPIC, when used as a planned part of the surgical procedure before tumor cell entrapment can occur, was shown to be effective in gastric cancer [37]. Studies with EPIC, 5-fluorouracil and early postoperative intravenous chemotherapy with 5-fluorouracil in order to combine oxaliplatin with a therapeutic dose of this drug has been suggested as a treatment option. Finally, long-term adjuvant bidirectional chemotherapy with the intraoperative placement of a peritoneal port promises to add to the control of LRR and PM [Sugarbaker PH, Bijelic L. Adjuvant bidirectional chemotherapy using a peritoneal port (2011), Submitted].

Morbidity/mortality for the proactive approach

Of course, a new initiative for the comprehensive management of PM should not be implemented without strong evidence that it does not add to the complications that occur in this group of patients. In the 80 randomized patients presented by Tentes, there was one in-hospital mortality in the HIPEC group and three in the conventionally treated group. There was a 32% morbidity in the HIPEC group and a 22% morbidity in the conventionally treated group. This was statistically significantly higher in the HIPEC group, with a p-value greater than 0.05 [35]. In the manuscript presented by Sammartino and colleagues, there was a 4% combined grade III and IV toxicity. In the control group there was an 8% incidence of grade III and IV adverse events. There were no deaths in either group [36]. In a recent review of morbidity/mortality in colorectal and appendiceal patients who have had extensive cytoreduction combined with perioperative chemotherapy, Sugarbaker and colleagues showed a 0.6% mortality and a 12% grade IV morbidity [50]. These data taken together suggest that, once the learning curve has been ascended in patients who have cytoreductive surgery combined with perioperative chemotherapy, the morbidity and mortality compares favorably and is perhaps even lower than in patients who undergo advanced surgery for gastrointestinal malignancy.

Conclusion

This review and critical analysis of the prevention and management of LRR and PM shows that continued efforts to improve the surgical management of primary CRC are necessary. The concepts of cancer seeding from colorectal malignancy as a cause for treatment failure are not always accepted by surgeons performing colon and rectal cancer operations. Increased awareness of this cause for surgical treatment failure and the initiation of additional technology to prevent LRR and PM are necessary. It is unlikely that randomized controlled studies of surgical technology will have an impact in this regard [51]. Rather, a proactive approach to the management of PM is the next logical step to be tested in an individualized management plan. Precise data accumulation and analysis as compared with historical controls is the most likely source of reliable information. The most important data to be accumulated regard the survival of high-risk groups 1–10 treated with prophylactic HIPEC at the time of primary CRC resection, and high-risk groups 1–5 converted by proactive second-look surgery from disease present to 5-year survival.

The future demands improved intracavitary treatment modalities that can preserve the surgical complete response. These perioperative treatments must more adequately treat small volumes of cancer cells or small established cancer nodules on peritoneal surfaces. Monoclonal antibodies such as catumaxomab may be indicated [52]. Molecular agents used with a surgical procedure to prevent angiogenesis may present an opportunity for benefit. Also, combinations of current available chemotherapy used intraoperatively, early postoperatively and as adjuvant bidirectional chemotherapy (intravenous and intraperitoneal) need to be tested regarding their efficacy and safety in patients identified to be at high risk of progression of LRR or PM [53].

Future perspective

The role to be established for perioperative chemotherapy, including HIPEC, in the management of primary colon and rectal cancer has not yet been established. As laparoscopic CRC resection becomes the standard of care for this disease, laparoscopic exploration will identify the high-risk patients for LRR or PM. Once identified, these patients can be optimally treated with a single surgery that can utilize an optimal clearance and perfect containment of the primary malignancy. This would include peritonectomies and perioperative chemotherapy, including HIPEC. This revised treatment strategy would not only improve local control but is likely to have a definite impact on long-term survival. From a patient perspective, the trauma of cancer care will be considerably reduced with fewer reoperative procedures; furthermore, there will be a reduced likelihood of intraperitoneal cancer recurrence with its morbidity and mortality. The timing of the intervention is crucial in its effectiveness. The earlier in the natural history of the disease that perioperative chemotherapy is used, the more likely it is to have its full impact on reduction of LRR and PM and improvement in survival.

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