SPECIAL REPORT

Colorectal Cancer

Eradication of minimal residual disease in the perioperative period in primary colon cancer

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Practice points

- Cancer cells that gain access to the free peritoneal space will implant with great efficiency on traumatized peritoneal surfaces within the abdomen and pelvis.
- There is a narrow time interval for eradication of free cancer cells because wound healing causes cancer cells to become covered by fibrin clot.
- Although meticulous surgical technique can decrease the incidence of local recurrence and peritoneal metastases, the patients at high risk for local–regional treatment failure need to be identified for perioperative intervention.
- Patients at highest risk for surgical treatment failure have synchronous peritoneal metastases, ovarian metastases, perforation through the primary cancer or a T4 malignancy.
- Hyperthermic intraperitoneal chemotherapy and early postoperative intraperitoneal chemotherapy have been shown to eradicate minimal residual disease when used as a planned part of the primary colorectal cancer resection.
- Data accumulated to date show that perioperative cancer chemotherapy to eradicate minimal residual disease from the abdomen and pelvis does not increase the morbidity of primary colon or rectal cancer resection.

Colon adenocarcinoma is a disease process with a risk of local and regional treatment failure. This review seeks to identify the subset of patients with advanced primary disease who are at high risk for minimal residual disease after resection. These are the patients who may benefit from perioperative chemotherapy treatment that will improve the clearance of a small number of cancer cells disseminated prior to or at the time of the adenocarcinoma cancer resection. The selection factors for identifying these patients at high risk for local recurrence and peritoneal metastases and the special treatments they require are presented in this manuscript.

KEYWORDS

• carcinomatosis • colorectal cancer • cytoreductive surgery • EPIC • gastric cancer • HIPEC • hyperthermia • intraperitoneal chemotherapy • local recurrence • peritoneal metastases

The most effective strategy to combat disease is prevention. Prevention involves the identification of high-risk groups and application of effective management strategies in the early stage of disease. Because there are different manifestations of colon cancer treatment failure, the strategies employed in the treatment of the primary malignancy must be individualized. The surgery that is performed must provide a complete clearance of the primary cancer and its lymph node groups at risk for metastatic disease. The resection must be accomplished with perfect containment of the cancerous process [1]. However, there are patients who will develop peritoneal metastases and/or local recurrence despite all efforts to provide perfect clearance. Either prior to or at the time of colon cancer resection, perfect containment fails to occur. The surgeon must be aware of the fact that patients may enter the operating room with a contained malignancy and leave, as a result of surgical trauma, with local–regional dissemination of disease from malignant cells that are

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lost from the specimen into the resection site or free peritoneal cavity. This dissemination is most likely to occur when specific clinical or histopathologic features are present. Cancer cells that implant into the resection site result in local–regional recurrence; cancer cells that implant into the free peritoneal cavity result in peritoneal metastases. Minimal residual disease post resection can occur with open colon cancer surgery or with laparoscopic resection.

This manuscript is not a commentary on the majority of patients who have an early and uncomplicated colon cancer resection with a favorable prognosis. It concerns the approximately 15–30% of patients who have clinical or histopathologic features that can be identified in workup of the primary cancer or at the time of the cancer resection, which indicates a high likelihood of cancer cell contamination of the abdomen or pelvis. These patients with minimal residual disease may be substantially benefited by treatments specifically designed to prevent disease progression. Treatment of local–regional progression identified during follow-up in the months or years after resection is not likely to result in significant benefit. Emphasis is on management of minimal residual disease in the perioperative period to prevent a future metastatic process in a timely manner.

Pathophysiology of local recurrence & peritoneal metastases from colon cancer

• Primary colon cancer with local–regional or peritoneal surface progression

The mechanism of dissemination of resection site recurrence or peritoneal metastases is by direct extension of cancer cells from the primary malignancy into the free peritoneal space. This can occur as a result of full thickness invasion of the bowel wall by the primary malignancy. When this occurs, the surgeon may observe peritoneal metastases on the visceral or parietal peritoneal surface in the vicinity of the primary malignancy. This local–regional dissemination may occur in both colon and rectal cancer. Despite the fact that peritoneal metastases are present, cytological study of the peritoneal fluid is often negative. In women, a frequent site for progression of peritoneal metastases is the ovaries, especially in the premenopausal woman.

Metastases to peritoneal surfaces have a doubling time estimated between 58 and 74 days [1]. The peritoneal nodules expand in a predictable manner over time and when they reach a critical size will exfoliate viable cancer cells into the peritoneal space [2]. The nature of a normal epithelial cell is to exfoliate from the epithelial surface. Adenocarcinoma is a malignant transformation of epithelial cells that retains this capacity to exfoliate cells from its surface. Peritoneal metastases of adenocarcinoma will exfoliate free cancer cells into the peritoneal space. This exfoliation process may cause a rapid disease progression with all quadrants of the abdomen being brought into the metastatic process within a few months.

The metastatic efficiency of cancer cells within the blood is extremely low. The portal venous blood may be contaminated by millions of cancer cells and yet only a few implants grow within the liver parenchyma [3]. In marked contrast, the metastatic efficiency of peritoneal metastases is extremely high, exponentially different from the implantation of cancer cells within the portal blood. After a surgical procedure in which the peritoneum has been traumatized to create a 'sticky site', every cancer cell may result in an implant. It has been shown that the trauma produced by an operative intervention may greatly increase the efficiency of cancer cell implantation within the peritoneal space [4,5].

• Tumor cell entrapment hypothesis

With a primary colon cancer, the surgeon will encounter peritoneal metastases in approximately 5–20% of patients [6–12]. By contrast, patients who do recur, one estimates that as many as 60% will have local recurrence or peritoneal metastases detected at the time of diagnosis of recurrent disease [6]. For lack of an alternative explanation, cancer cells disseminated as part of the resection of the primary malignancy account for this steep increase in the incidence of peritoneal metastases observed in follow-up of an R-0 resection.

The tumor cell entrapment hypothesis provides a mechanism for the incidence of local recurrence and peritoneal metastases that occur in follow-up of colon cancer patients [13]. Trauma to the cancer specimen during the process of removal results in free cancer cells or minute nodules disseminated into the free peritoneal space **(Figure 1)**. As the cancer is resected, lymphatic channels must be transected. The release of lymph contaminated by cancer cells especially in patients with multiple lymph node metastases is a real possibility. Trauma to the

soft tissue surrounding the primary malignancy, especially if the mesocolic or mesorectal fascia is invaded by the primary cancer, may result in local–regional dissemination of cancer cells. Finally, if venous invasion is present, blood lost into the operative field may contain cancer cells. In the raw surface at the resection site, a high metastatic efficiency is present. These spilled cancer cells, even in limited numbers, are likely to implant and cause a local recurrence diagnosed in follow-up.

It is important to establish that the mechanism of resection site recurrence and peritoneal metastases is the same. Cancer cells are disseminated either prior to or at the time of the cancer resection. The cancer cells at high density will layer out within the bed of the resection site. Because the surgery has disrupted the peritoneum and created a 'sticky surface', a high metastatic efficiency will exist [4]. Single cells disseminated at a distance from the anatomic site of primary cancer resection will progress as peritoneal metastases.

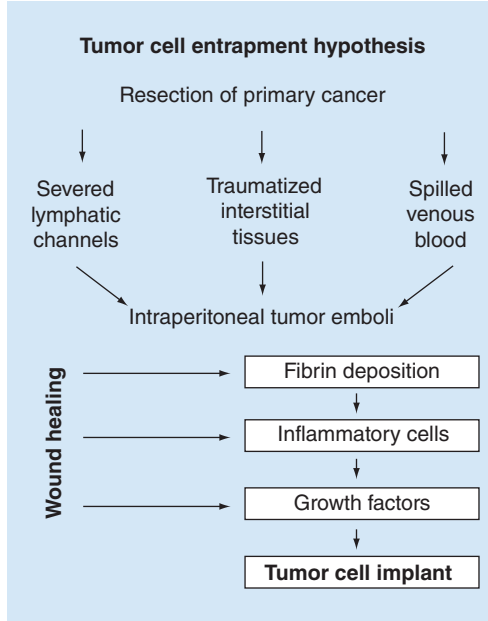

Figure 1. Tumor cell entrapment hypothesis suggests three mechanisms for microscopic residual cancer cells in patients having an R-0 colon or rectal cancer resection. Cancer cells or tiny nodules are disseminated prior to or at the time of surgery. The raw surface created by the surgical intervention causes a high metastatic efficiency.
Reproduced with permission from Cancer Therapy [13].

• Prevention of local recurrence & peritoneal metastases

Recent improvements in the surgical technology of colorectal cancer resection have decreased the incidence of treatment failures, both at the resection site or at a distance from the primary on peritoneal surfaces. The requirement for total mesocolic or mesorectal excision have been established and the survival benefit published [14]. This improved survival has been a result of the absence of tumor contamination because of a careful dissection which maintains a layer of tissue between the primary malignancy and the margins of resection [15]. Also, the requirements for colon cancer resection using wide excision, generous lymphadenectomy and an intact mesocolic resection have been published [16]. These improvements in surgical technology and therefore in survival are the result of decreased minimal residual disease resulting from the surgical event itself. A complete absence of tumor cell contamination with primary colorectal cancer open or laparoscopic surgery has become a strict requirement of optimal treatment. Dependence upon systemic chemotherapy to manage resection site disease or peritoneal metastases must be abandoned.

However, the complete clearance and containment of the colon cancer specimen is not possible in all cancer patients despite the most meticulous surgical technique to maintain an intact mesocolic or mesorectal fascia. Lymphatic leakage containing cancer cells cannot be completely prevented. Also, the most meticulous dissection around locally advanced disease may result in free cancer cells at the resection site. In summary, even the most perfect primary cancer resection cannot prevent local–regional surgical treatment failure in every patient. The individualized treatments proposed in this manuscript are a supplement to meticulous surgery in selected patients.

• Selection of patients for perioperative treatment

There are clinical and histopathologic features in approximately 20% of primary colon cancer patients present at the time of primary cancer resection that indicate is a high likelihood of cancer cell contamination [17]. These patients need individualized treatments to prevent local recurrence and peritoneal metastases. These clinical or histopathologic features

suggest that the primary cancer surgery, even performed in its most perfect manner with or without systemic chemotherapy, will be a suboptimal management strategy. If a high risk of local–regional recurrence or peritoneal metastases is evident, specialized additional treatments need to be added to deal with minimal residual disease present following resection. The clinical and histopathologic features of the colon cancer patients at high risk for local recurrence and peritoneal metastases are listed in **Table 1**. These patients should be considered for preventive measures for local recurrence and peritoneal metastases. In groups 1–4 in **Table 1**, patients can be considered to have greater than 50% incidence of local–regional recurrence and/or peritoneal metastases in the absence of special treatments. Synchronous peritoneal metastases are discovered serendipitously in 4.8% of the patients scheduled for curative surgery. Limited peritoneal metastases documented at the time of primary colon cancer resection will show progression with follow-up in 75% of patients even if these metastases are completely removed with the primary intervention. Ovarian metastases are associated in 0.8–7.4% of all colon cancers. Ovarian metastases, even if resected with oophorectomy and/or hysterectomy will have over 60% incidence of other sites of peritoneal dissemination in follow-up. Perforation through the primary cancer at the time of primary rectal cancer resection indicates a likelihood of local–regional or peritoneal progression in at least 50% of patients [17]. The rate of perforations ranges between 1 and 8%. A positive margin of resection, usually a lateral margin is not a rare histopathologic finding in colon cancer specimens.

The clinical findings 5–12 listed in **Table 1** have been shown to place the patient at risk for local recurrence or peritoneal metastases but with less frequency. Positive peritoneal cytology either before or after cancer resection, involvement of an adjacent organ or a cancer-induced fistula, T3 mucinous cancers, T4 cancers or a positive imprint cytology from the primary malignancy, rupture of the cancerous mass or obstruction at the time of presentation, and N2 involvement of lymph nodes, all would have an elevated incidence of local recurrence and peritoneal metastases [17].

Hompes and coworkers made a special study of T4 colon cancers regarding the risk of local–regional dissemination [18]. In 19 patients with T4 disease, five developed local recurrence and eight developed peritoneal metastases. Five of these patients also had systemic metastases. Thirteen of 19 patients (68%) could have benefited from an effective treatment to eradicate minimal residual disease.

Table 1. Clinical and intraoperative histopathologic features of the primary cancer as an estimate of the incidence of subsequent local recurrence and/or peritoneal metastases to guide proactive treatment with perioperative chemotherapy.

Clinical feature	Estimated incidence of local recurrence or peritoneal metastases observed in follow-up (%) colorectal cancer
Peritoneal nodules detected with primary cancer resection	70†
Ovarian metastases	60†
Perforation through the primary cancer (free or localized)	50†
Positive margin of resection‡	80
Adjacent organ or structure invasion	20†
Signet ring histology by endoscopic biopsy	20
Fistula formation	20
Obstruction of primary cancer	20
Positive peritoneal cytology before or after resection‡	40†
Positive imprint cytology‡	40
Lymph nodes positive at or near the margin of resection‡	20
T3 mucinous or T4 cancer‡	40†

†Data taken from [17].
‡Requires intraoperative histopathologic assessment by the pathologist who is a member of the multidisciplinary team evaluating the surgical specimen intraoperatively.
Data taken from [47].

• Data showing benefit from perioperative chemotherapy in patients with primary colon cancer with peritoneal metastases or at high risk of peritoneal metastases

Oncologists are well aware of the prominent role that local recurrence and peritoneal metastases have occupied in the natural history of colorectal cancer. Chemotherapy in the abdomen used as a planned part of a surgical intervention to control local–regional recurrence and peritoneal dissemination from colon cancer was proposed by Sugarbaker and colleagues [19]. They performed Phase I/II studies with 5-fluorouracil and mitomycin C administered directly into the peritoneal cavities in the early postoperative period before adhesions had progressed. There was a marked pharmacokinetic advantage of perioperative intraperitoneal chemotherapy with single cancer cells on peritoneal surfaces as the targets of this treatment.

A group of patients demonstrating peritoneal metastases documented at the time of primary colon cancer resection was reported from Washington, DC, by Pestieau and Sugarbaker [20]. They identified five patients who had definitive treatment of peritoneal metastases from colon cancer at the same time as the resection of the primary tumor. In the journal article, the median disease-free survival of these patients had not been reached and their 5-year survival was 100%. The statistical difference between patients who had perioperative treatment of their peritoneal metastases as compared with those who had delayed management with cytoreductive surgery (CRS) and early postoperative intraperitoneal chemotherapy (EPIC) was statistically significant ($p < 0.0001$).

Tentes and colleagues from Greece have reported their experience on the use of hyperthermic perioperative chemotherapy in patients at high risk for local–regional recurrence. They included in this study patients with locally advanced T3 or T4 colon cancer. Only patients with R-0 resection were assigned to receive hyperthermic intraperitoneal chemotherapy (HIPEC) plus systemic chemotherapy versus conventional treatments, which were surgery plus systemic adjuvant chemotherapy. The 5-year survival for the experimental group was 100 and 72% for the conventional group. Although not definite, the difference in survival showed a trend toward significance ($p = 0.0938$). During follow-up, two patients in the HIPEC group and eight patients in the conventional group were determined to have recurrence ($p = 0.002$). It is important to note that no local recurrence or peritoneal metastases was recorded in the HIPEC group. By contrast, the group treated in a conventional manner showed three patients with local–regional recurrence. These authors suggest that the perioperative chemotherapy had no effect in the development of distant metastases but exhibited an advantage in eradicating viable cancer cells that were disseminated local–regionally prior to or at the time of the colon cancer resection [21].

Noura and colleagues reporting from the cities of Osaka and Sakai, Japan reported on colon cancer patients with no clinically confirmed peritoneal metastases but a positive peritoneal lavage cytology. Thirty-one of 52 patients with positive cytology were treated by mitomycin C instillation through catheters after abdominal closure. Patients receiving perioperative chemotherapy had a significantly improved survival ($p < 0.05$). In a multivariate analysis, perioperative chemotherapy remained and independent prognostic factor for peritoneal recurrence-free survival [22].

Sammartino and colleagues from Rome performed a case controlled study of colon cancer patients with clinical T3/T4, any N and M0 stage, and mucinous histology or signet ring histology [23]. Twenty-five patients in the HIPEC-treated group underwent carcinomatosis prevention strategies including complete omentectomy, bilateral salpingo-oophorectomy, hepatic round ligament resection and appendectomy. At the end of the colon cancer resection plus carcinomatosis prevention resections, hyperthermic intraperitoneal chemotherapy using intraperitoneal oxaliplatin with intravenous fluorouracil was administered. These HIPEC-treated patients were compared with 50 matched controlled patients. All patients had an R-0 resection. The morbidity of the two groups of patients was the same. At 48 months, after the study closed, fewer patients in the proactive group than in the control group had recurrent disease (28 vs 42%). Peritoneal metastases and local recurrence developed significantly less often in the proactive group than in the control group (4 vs 28%; $p < 0.03$). Median survival was 59.5 months among the patients included in the proactive treatment and 52 months in the control group. The disease-free survival was different with $p < 0.05$. The overall survival was different with $p < 0.04$.

• Alternative strategies to eradicate minimal residual disease

Elias and colleagues presented an alternative strategy to definitively treat patients identified at the time of their primary colon cancer resection for a systematic second-look surgery. The systematic second-look study involved a second-look surgery on selected patients identified to have or be at high risk for subsequent peritoneal metastases. Sixteen of 29 cases (55%) were found to have at a subsequent second-look persistence or progression of the peritoneal metastases. Fifty percent of these patients remained disease-free long term [24]. This strategy for managing minimal disease is currently under study in a prospective randomized trial, PROPHYLO-CHIP [25]. Sugarbaker examined the potential risks and benefits of perioperative chemotherapy delivered at the time of a primary colon cancer resection as compared with the systematic second-look performed approximately 1 year later [26]. Of course, perioperative chemotherapy with the primary resection can only be used at institutions where HIPEC or EPIC is a routine management strategy. The use of perioperative chemotherapy versus second-look with HIPEC at a single institution was studied by Baum and colleagues from Nieuwegein, The Netherlands. They reported on a total of 72 patients with synchronous peritoneal metastases from colon cancer. In 20 patients (27.8%) the primary tumor was resected along with with HIPEC (early referral). In the other 52 patients (72.2%) the primary tumor was resected and then there was a second-look procedure with HIPEC (late referral). During CRS plus HIPEC with late referral, 22 (59.5%) of the 37 anastomoses of the primary resection were removed, revealing malignancy in 12 (54.5%) on histopathological examination. In 20 (27.8%) patients a permanent colostomy was necessary after late referral. The requirement for reoperation for complications was higher in patients after a repeat resection of a previous anastomosis (36.4%) compared with 12% in the rest of the patients ($p = 0.02$). Resection of the primary tumor simultaneously with HIPEC in patients with synchronous peritoneal metastases from colon cancer may prevent extended bowel resections and permanent colostomy. From a quality of life perspective, these data support early referral for HIPEC with the primary colon cancer resection of patients with peritoneal metastases [27].

At a majority of institutions in the USA and Europe, resection of colon cancer occurs but in only a few hospitals is HIPEC available. Also, the indications for perioperative chemotherapy with the primary colon cancer resection can be more liberal than those that would indicate a major repeat surgical intervention as a second-look with HIPEC [26].

An additional strategy to improve the results of a primary colon cancer resection rely on radiologic identification of patients at high risk for local recurrence or peritoneal metastases and preoperative systemic chemotherapy treatment of these patients [28]. The preliminary results of the FOxTROT trial has been published [29]. The FOxTROT and ECKINOXE trials are currently operative in order to test this strategy that may improve the results of treatment of primary colon cancer by downsizing the malignancy prior to its resection [30,31].

• Technology of perioperative chemotherapy to eradicate minimal residual disease

Currently, the optimal perioperative chemotherapy treatment for prevention of local–regional recurrence and peritoneal metastases has not been determined. It is possible that the best choice is EPIC. This was utilized by Pestieau and Sugarbaker to achieve good results [20]. From a logistical perspective, EPIC may be favored in that patients with unexpected peritoneal metastases will not have signed an informed consent for HIPEC. These patients can be treated with full consent in the early postoperative period. Also, because of short drug retention within the peritoneal surface, it is possible that a single dose of HIPEC is not as effective as the 5 days of EPIC. However, EPIC has many more logistical issues and has been shown to be associated with a higher incidence of adverse events but not a higher incidence of mortality [32]. The optimal perioperative chemotherapy agents (HIPEC vs EPIC or both) have not yet been determined.

Summary of available technology for prevention of peritoneal metastases & local recurrence of colon cancer

First, extreme care is taken with the primary colon cancer resection to prevent trauma to the cancer specimen as it is removed. The concepts of total clearance and total containment of the malignant process during the cancer resection has been shown to be imperative. A total mesorectal or mesocolic resection is the surgical requirement for containment of the malignancy

during intervention [14–16]. Also, total relevant lymphadenectomy with lymph node resections carried down to the origin of the inferior mesenteric artery on the aorta is required [16].

There are also perioperative technologies that must be considered for prevention of local recurrence and peritoneal metastases in resection of the primary malignancy. A report concerning a large volume of irrigation has gained new interest. This technology uses 10 l of saline 1 l at a time. The extensive intraoperative peritoneal lavage (EIPL) has been found by Kuramoto and coworkers to be used with benefit in patients with gastric cancer and positive peritoneal cytology. EIPL was most effective when combined with HIPEC [33].

There is no doubt that the surgical strategy for prevention demands peritonectomy procedures and visceral resections to achieve no visible evidence of disease. However, it is unclear at this point in time what the optimal perioperative chemotherapy treatment strategy should be. Perhaps the most widely used in Europe is high-dose intraperitoneal oxaliplatin with systemic 5-fluorouracil for a 30 min HIPEC treatment [34]. The Dutch group has used high-dose mitomycin C at 35 mg/m^2 given in three doses (½, ¼, ¼ at 30 min intervals) over a 90 min intraperitoneal lavage with 42°C heat [35]. A third regimen with extensive use in Washington, DC combines a lower dose of hyperthermic mitomycin C (15 mg/m^2) plus doxorubicin (15 mg/m^2) for a 90 min lavage with intravenous 5-fluorouracil (400 mg/m^2), EPIC is used for selected patients for four postoperative days [36]. To date, clinical trials to determine the most effective regimen with an acceptable morbidity have not been initiated. The concept that all HIPEC regimens are the same has been shown to be false [37]. It is likely that the ideal preventive HIPEC or EPIC will be different from the therapeutic HIPEC or EPIC so that adverse events are not increased by the perioperative chemotherapy treatments.

Morbidity/mortality for local–regional & peritoneal metastases prevention

Revised practice for the prevention of peritoneal metastases can be implemented only if strong evidence that it does not add to the complications is provided. In the 80 patients reported by Tentes, there was one in-hospital mortality in the HIPEC group and three in the conventionally treated group. The morbidity was 32% in the HIPEC group and 22% in the conventionally treated group. The incidence of complications was statistically significantly higher in the HIPEC group with a p-value greater than 0.05 [21]. In the report by Sammartino and colleagues, a 4% combined grade III and IV toxicity in the group with preventive HIPEC occurred. There was an 8% incidence of grade III and IV adverse events in the control group. There were no deaths in either group [23]. Sugarbaker and colleagues reported a morbidity/mortality in colorectal and appendiceal patients who have had extensive cytoreduction combined with perioperative chemotherapy of 0.6 and 12% grade IV morbidity [36]. These data taken together suggests that extensive experience with patients who have CRS combined with perioperative chemotherapy reduces the morbidity and mortality to compare favorably and is with patients who undergo advanced surgery for gastrointestinal malignancy.

Benefits of CRS & HIPEC for local recurrence & peritoneal metastases diagnosed in follow-up of colon cancer

CRS plus perioperative chemotherapy used to treat local recurrence or peritoneal metastases of colon cancer diagnosed in follow-up has been successful. Reports of survival benefits began to appear in publications in the 1990s. In 1995, Sugarbaker and Jablonski showed a 3-year survival of 35% in patients with peritoneal metastases from colon cancer treated with CRS plus intraperitoneal mitomycin C and fluorouracil [38]. In 2005, Verwaal and colleagues from Amsterdam published a 3-year projected survival of 38% in 54 patients treated by CRS and hyperthermic intraperitoneal mitomycin C with adjuvant systemic 5-fluorouracil [39]. Shen and colleagues accumulated patients between 1991 and 2002 [40]. Seventy-seven patients with nonappendiceal colorectal cancer underwent the combined treatment. These investigators concluded that a third of patients with complete resection have long-term survival and that systemic chemotherapy did not contribute to the control of peritoneal metastases. These studies performed in the absence of modern colorectal cancer chemotherapy (oxaliplatin and irinotecan) document the efficacy of CRS and perioperative chemotherapy to rescue approximately a third of patients with peritoneal metastases.

Since that time, multiple publications confirming the efficacy of the combination of CRS and perioperative chemotherapy to benefit patients with established peritoneal metastases have

been published. At the top of the list regarding evidence-based medicine for this treatment strategy is the Phase III study reported by Verwaal and colleagues in 2003 [35]. The durability of the benefit of CRS and perioperative chemotherapy was confirmed in a follow-up article in 2008 [41].

Lack of benefit of CRS & HIPEC for local recurrence & peritoneal metastases diagnosed in follow-up of rectal cancer

Although success has been documented with treatment of peritoneal metastases documented in follow-up from colon cancer, a valid question regard recommendations for rectal cancer patients. In these patients, the preventive management may be the only option. Verwaal and colleagues showed that rectal cancer patients with peritoneal metastases rarely show long-term survival with CRS and perioperative chemotherapy [42]. Da Silva and Sugarbaker reported that rectal cancer patients with peritoneal metastases treated with CRS and perioperative chemotherapy had a 17-month survival and a 0% 5-year survival as compared with colon cancer patients who had a 35 month median survival with a 30% 5-year survival. These authors postulated that pelvic peritonectomy after an anterior resection or abdomino-perineal resection makes an adequate peritonectomy difficult or impossible. With this incomplete cytoreduction in the pelvis after a rectal cancer resection, the results of CRS and HIPEC are poor [43]. There is no doubt that rectal cancer and colon cancer require contrasting management strategies for eradication of minimal residual disease in the perioperative period.

Conclusion & future perspective

Currently, the treatments for postoperative minimal residual disease is HIPEC, EPIC or both HIPEC and EPIC. Optimal treatment demands improved perioperative management that can supplement an R-0 surgical effort in colorectal cancer. These perioperative treatments should more adequately treat minimal residual disease such as cancer cells or small established cancer nodules on peritoneal surfaces. Antiangiogenesis agents used with a surgical procedure to prevent implantation of cancer cells may present an opportunity for benefit. Also, innovative combinations of currently available cancer chemotherapy used in the operating room and early postoperatively, as adjuvant bidirectional chemotherapy (intravenous and intraperitoneal) need to be pharmacologically studied and efficacy and safety tested in patients identified to be at high risk for progression of local recurrence and peritoneal metastases [44]. Currently, there are two prospective randomized studies designed to test HIPEC in colon cancer patients at risk for minimal residual disease and subsequent local recurrence or peritoneal metastases [45,46].

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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