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Management of Peritoneal Carcinomatosis from Colorectal Cancer

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Abstract

The management of peritoneal carcinomatosis from colorectal cancer is evolving. The introduction of new chemotherapeutic and biologic agents has certainly improved the outlook for many patients with metastatic colorectal cancer. Traditionally, patients with limited hepatic or pulmonary metastases were the only candidates for metastasectomy. However, patients with metastasis localized to the peritoneum have been shown to be candidates for metastasectomy with improved clinical outcomes. Cytoreductive surgery with the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) in this cohort of patients offers the only chance for long-term survival. Complete cytoreduction in combination with HIPEC for peritoneal surface disease has been demonstrated to produce survival outcomes similar to liver resection for hepatic metastases. This review will examine recent evidence pertaining to the evolving surgical oncology paradigm for management of colorectal peritoneal carcinomatosis.

Introduction

Dissemination and implantation of colorectal malignancies throughout the peritoneal cavity results in “peritoneal carcinomatosis” (PC). Traditionally colorectal PC is thought to result from trans-coelomic peritoneal spread of cancer cells, or seeding of the peritoneum during curative surgery. PC has been considered a form of systemic metastasis portending a terminal state of colorectal cancer for which only palliative surgery (such as diverting colostomy) and/or systemic chemotherapy was recommended. However, Sugarbaker et al[1] challenged this oncologic philosophy and defined PC as a local-regional occurrence of colon cancer for which a more aggressive approach is appropriate.

Peritoneal carcinomatosis is the second leading cause of death in patients diagnosed with colorectal cancer. In approximately 20 - 25% of patients with PC of colorectal origin, it has been noted that the tumor is primarily confined to the peritoneum with no discernable metastasis elsewhere[234]. Approximately 10% of patients are noted to have PC at the time of planned curative surgery, this in spite of advances in early detection of primary colorectal cancer.

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PC can present synchronously with discovery of the primary tumor, or metachronously after the primary tumor is resected. Precocious presentation of PC without a primary being found is unusual[5]. A review of the literature on the incidence of PC showed that the incidence of peritoneal seeding during potentially curative surgery for primary colorectal cancer varied widely from 3% to 28%[6].

Jayne et al[7] found of some 349 patients with PC; 214 had synchronous disease with a median survival of 7 months and 135 had metachronous carcinomatosis. A total of 125 patients (58 %) in the synchronous group were free of systemic metastases, 80 (64%) of whom had localized PC with a median survival of 9 months vs. 4 months for those with generalized PC. Therefore, they concluded that PC is a common mode of disease progression in patients with colorectal cancer, for the majority of patients the prognosis is poor, but a small number with localized disease may be suitable for further aggressive therapy.

Natural history of colorectal peritoneal carcinomatosis

Pathogenesis of PC involves tumor cells detaching from the primary tumor mass that has invaded the serosa, and gaining access to the peritoneal cavity, subsequently attaching to the peritoneal surface with subperitoneal invasion for proliferation and angiogenesis[89]. Other means of peritoneal dissemination include iatrogenic or spontaneous perforation of the primary cancer[10] or embolism from transected lymphatics and blood vessels during the course of surgical resection[11]. Spread of the cancer cells in the peritoneal cavity has been shown to be dictated by gravity, peristaltic gastrointestinal movement, and the mechanics of the negative pressure generated by movement of the diaphragm. The most common sites of disease localization include right lower quadrant, right diaphragm, hepatoduodoneal ligament, the omentum, pelvic viscera and parietal peritoneum[12]

A diagnosis of PC usually portends a poor prognosis for the patient; if untreated, PC from colon cancer is uniformly fatal with no long term survivors. Several studies have found a median survival after diagnosis of PC from colorectal cancer of 6 – 9 months[5, 7, 13], patients with PC typically die from bowel obstruction.

While newer agents have become available since these studies, patients with stage IV disease treated with modern systemic chemotherapy alone have a two-and five-year survival rates of 65 and 13 percent, respectively, and a median survival of 24 months. However, most patients so treated did not have peritoneal disease and there is little data evaluating outcomes with PC only compared to other sites of metastases. Patients with PC treated with cytoreductive surgery and HIPEC have a median survival of 63 months, and two- and five-year survival rates of 81 and 51 percent, respectively .[14]

Diagnostic Evaluation

As approximately half of patients diagnosed with PC are diagnosed at the time of surgery for the primary colorectal malignancy, it is crucial for the operating surgeon to note and describe the extent of PC in the operative note. Ascites when found, signs and symptoms of bowel obstruction, are signs of advanced disease process.

Current investigational modalities for evaluating and diagnosing PC include contrast-enhanced spiral computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), laparoscopy and serum tumor markers. An expert consensus statement stated that in “considering these current investigational modalities, a high quality cross-sectional imaging study, either contrast-enhanced spiral CT or MRI should be performed to evaluate patients. FDG-PET or preferably PET/CT should be at least selectively considered as part of preoperative workup in high-risk patients. Laparoscopic

exploration may supplement imaging modalities to allow direct visualization. However, the use of these investigations should be individualized and planned as part of a multidisciplinary approach. The role of CT, MRI and more latterly PET or PET/CT and laparoscopy in refining patient selection and improving prognosis remain to be closely evaluated"[15], as even state of the art imaging significantly understates the burden of PC found a laparotomy[16].

Treatment options

Systemic Chemotherapy

The introduction of newer more effective chemotherapeutic and biologic agents such as oxaliplatin, irinotecan, bevacizumab, cetuximab, panitumumab has improved the survival of patients diagnosed with metastatic colorectal cancer. A randomized multicenter trial reported a 19 month overall survival for patients with untreated metastatic colorectal cancer treated with fluorouracil, leucovorin and oxaliplatin (FOLFOX)[17]. Hurwitz et al[18] noted a median survival of 20.3 months; they observed that the addition of bevacizumab to fluorouracil-based combination chemotherapy resulted in statistically significant and clinically meaningful improvement in survival among patients with metastatic colorectal cancer. However the majority of the patient population in these studies consisted mainly of patients with liver or lung metastasis.

A more aggressive treatment approach with cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy has been advocated. Elias et al[19] reported a comparison of the long-term survival of patients with isolated and resectable PC to a comparable group of patients treated with systemic chemotherapy containing oxaliplatin or irinotecan or by cytoreductive surgery plus heated intra-peritoneal chemotherapy (HIPEC). They showed that patients with isolated, resectable PC achieve a median survival of 24 months with modern chemotherapies, while surgical cytoreduction plus HIPEC was associated with a median survival to 63 months, with a 5-year survival rate of 51%.

A single-institution randomized phase III study from the Netherlands, to confirm the findings from non-randomized studies that aggressive cytoreduction in combination with HIPEC is superior to standard treatment with systemic chemotherapy in patients with PC of colorectal cancer origin. They specifically reported that cytoreduction followed by HIPEC improves survival in patients with PC of colorectal origin. Following a median follow-up period of 21.6 months, the median survival was 12.6 months in the standard therapy arm treated with systemic chemotherapy (fluorouracil-leucovorin) with or without palliative surgery and 22.3 months in the experimental therapy arm managed by cytoreductive surgery with HIPEC, followed by fluorouracil-leucovorin .[20].

It is important to note that cytoreductive surgery with HIPEC is not suggested as therapy in lieu of systemic chemotherapy for PC from colorectal cancer. We and others continue to suggest best systemic therapy with cytoreductive surgery with HIPEC.

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

The principle underlying this therapeutic modality is the initial aggressive surgical resection of all visible macroscopic peritoneal disease, and subsequently treating any residual microscopic non-visible peritoneal disease with hyperthermic chemotherapy. The intraoperative administration has the advantage of delivery of agent to the entire peritoneum after all adhesions are lysed and before they have the opportunity to reform (which happens quickly after cytoreductive surgery). It is paramount during surgical resection that all peritoneal disease greater than 2.5 mm in size be resected; as experimental studies show that drug penetration is limited (1–2 mm in depth) under the surface of the tumor. In animal

models it has been demonstrated that the efficacy of intra peritoneal chemotherapy is maximal in the first 1.5 mm of the peritoneal surface of the tumor, equivalent to 50 to 75 cell layers[21]. Instillation of intraperitoneal chemotherapy leads to a high local concentration of the chemotherapeutic agent, vastly beyond levels which could be achieved with systemic administration with even the most aggressive dosing protocols. Intraperitoneal chemotherapy provides a substantial pharmacokinetic advantage to the treatment of loco–regional disease relative to systemic therapy because it bypasses the peritoneal–plasma partition. Early studies confirmed the presence of a peritoneal–plasma partition by demonstrating that drugs delivered into the peritoneal cavity have a clearance that is inversely proportional to the square root of its molecular weight[222324] Owing to this partition, drugs without lipophilic properties and high molecular weights have optimal pharmacokinetic profiles for intraperitoneal application.

The addition of hyperthermia results in a potentiation of cytotoxicity, and serves to rewarm the patient after a significant open procedure. Koga et al[25] elaborated the synergistic effect of hyperthermia with intraperitoneal chemotherapy in rats; with combined peritoneal perfusion (41.5 degrees) and mitomycin C, the mean survival times were significantly prolonged as compared to peritoneal perfusion at 41.5 degrees alone. Timing of instillation of intraperitoneal chemotherapy is also of crucial importance. Evidence suggests immediate instillation following surgical resection avoids entrapment of residual tumor cells in the post-operative adhesive film, and thus reduces the potential number of viable exfoliated cancer cells following resection[26].

Chemotherapeutic agents currently used for hyperthermic intraperitoneal chemotherapy

The ideal chemotherapeutic agent is one that has maximal efficacy, offering optimal regional therapeutic benefits, while minimizing systemic toxicity. Mitomycin-c is the most commonly used chemotherapeutic agent for hyperthermic intraperitoneal treatment presently.It is appealing as a HIPEC agent due to its high molecular weight, tissue penetration of up to 5mm, and a favorable pharmacokinetic profile that allows for increased intraperitoneal concentration with limited systemic absorption.[2728]. Cao et al[29] in a meta-analysis found the most common regimen consisted of 40 mg mitomycin-C for 90 – 120 min at 42°C. Newer, potentially more efficacious agents include; oxaliplatin, irinotecan, pegylated liposomal doxorubicin, paclitaxel and carboplatin. Oxaliplatin and irinotecan have been used by Elias et al[30], who have reported extensively on their experience with these chemotherapeutic agents documenting survival rates with use of intraperitoneal oxaliplatin as 83% at one year, 74% at 2 years, and 65% at 3 years. Use of intraperitoneal irinotecan is reported to be complicated by hematological toxicity. Recently, we reported our phase I trial of oxaliplatin for HIPEC from Wake Forest University, 200 mg/M^2 of oxaliplatin was found to be well tolerated and to be the maximum tolerated dose for a 2-hour chemoperfusion[31]

Patient Selection for Cytoreductive Surgery and HIPEC

Patient selection is an extremely crucial aspect of planning for treatment of patients with colorectal PC. A consensus statement from representatives from the major peritoneal surface malignancy centers from around the world listed eight clinical and radiographic variables associated with increased chances of achieving a complete cytoreduction:- Eastern Cooperative Oncology Group (ECOG) performance status two or less; no evidence of extra-abdominal disease; up to three small, resectable parenchymal hepatic metastasis; no evidence of billiary obstruction; no evidence of ureteral obstruction; no evidence of intestinal obstruction at more than one site; small bowel involvement: no evidence of gross disease in the mesentery with several segmental sites of partial obstruction; small volume disease in the gastro-hepatic ligament[32].

At Wake Forest University we utilize the following criteria:

- Patients must be medically fit to undergo the rigors of cytoreductive surgery and HIPEC
- There must be no extra-abdominal disease
- Peritoneal disease is potentially completely resectable
- Parenchymal hepatic metastases must be easily and completely resectable and or ablatable
- Bulk retroperitoneal disease must be absent

Results from studies at our institution show that patients with ECOG scores of 0 and 1 have significantly better overall survival when compared to patients with ECOG scores of 2 and 3 (21.7 months vs. 9.5 months). Furthermore, patients with bowel obstruction or malignant ascites and malnutrition were demonstrated to have a poorer overall survival compared those without these comorbidities (6.3 vs. 23.0 months)[33]. Although malignant ascites has been shown to predict a poor clinical outcome, HIPEC is an effective means by which to provide palliation. In a Phase I/II study of patients with peritoneal carcinomatosis (PC) and malignant ascites conducted at our institution, HIPEC prevented recurrence of malignant ascites in nine out of 12 patients, most of whom were chemotherapy failures. Furthermore, HIPEC is effective in preventing the development of ascites in all patients with positive intraperitoneal cytology.

Operative techniques

Complete cytoreductive surgery must precede institution of HIPEC to maximize its effect. As previously stated the goal of cytoreduction is not simply ‘debulking’ but resection of all visible macroscopic peritoneal disease. Debulking described as “optimal” in the gynecologic oncology literature (lesions < 1 cm)[3435] is not appropriate in this setting. Resection of all macroscopically visible tumor, with the largest residual tumor nodule measuring less than 5 mm (R2a resection or better) is what we advocate as adequate cytoreduction for peritoneal carcinomatosis of colorectal origin. This may entail resection of parietal and/or visceral peritoneum (peritonectomy), greater and/or lesser omentectomy, multivisceral resections, including: splenectomy, small and large bowel resection, gastrectomy, cholecystectomy, oophorectomy and hysterectomy. Anastomosis following bowel resection may either be completed prior to institution of HIPEC or after it. Ileostomy or colostomy (when needed) is matured at the end of the entire procedure.

Degree of completion of cytoreduction has been shown to be a significant prognosticator of survival. The cytoreduction classification system used at Wake Forest is derived from the American Joint Committee on Cancer (AJCC) staging manual and includes complete (R0: no gross disease with negative microscopic margins; R1: no gross disease with positive microscopic margins) versus incomplete (R2a–c) cytoreduction. A resection classification of R2a indicates residual tumor of up to 5 mm, R2b designates 5–20 mm of gross disease and R2c identifies more than 20 mm of gross residual disease. Data from our institution and others demonstrate a significant survival advantage for patients undergoing R0/R1 resection compared with those with R2 resections[32, 36,37].

Performance of HIPEC in patients in whom a significant degree of cytoreduction of their tumor burden cannot be achieved is rarely indicated as the 1-year survival in this cohort of patients is poor. A recent study of 56 patients with PC demonstrated a 79% 2-year survival rate in patients undergoing complete cytoreduction and HIPEC, while those undergoing incomplete cytoreduction had a 2-year survival rate of only 44.7%[38]

Similarly, in a study of 109 patients from our institution, patients undergoing complete Cytoreduction had superior outcomes compared with those who underwent incomplete Cytoreduction, regardless of the primary lesion site. patients undergoing R0/R1 resection followed by HIPEC experienced 3-year survival rates of 50 – 72.4%, while those undergoing R2a, R2b and R2c resections experienced 3-year survival rates of 44.0%, 22.2% and 9.3%, respectively[33] . Thus there is no role for limited debulking or partial cytoreductive procedures.

The HIPEC can be performed either through the open abdominal technique (Coliseum), which involves covering the abdomen with a plastic sheet during the circulation of hyperthermic chemotherapeutic agents with the hands, or through the closed technique where the hyperthermic chemotherapeutic agent is circulated through a closed circuit with two inflow and two outflow catheters placed in the peritoneal cavity. Proponents of the open abdominal cavity technique cite optimal thermal homogeneity and spatial diffusion as advantages to this technique, and proponents of the closed technique suggest that the increased intra-abdominal pressure of the closed abdomen enhances the penetration of the chemotherapeutic agents into the tissue, and that the closed system reduces the surgical team's risk of exposure to the chemotherapeutic agent. To date, no prospective trials have compared the two techniques[39]. We utilize the closed technique at Wake Forest University to avoid issues related to occupational exposure of the operative team to chemotherapy.

Clinical Outcomes for HIPEC for Colorectal Peritoneal Carcinomatosis

Multiple studies have investigated the efficacy of cytoreductive surgery (CS) and HIPEC as management modalities for colorectal PC. Single-institution reports have documented 3-year survival rates to range from 25 to 39%. These survival rates attest to the utility of CS and HIPEC in the management of colorectal peritoneal carcinomatosis.[24274041]. Recently, Glehen et al. presented an international registry of 506 patients undergoing HIPEC for PC from colorectal cancer at 28 institutions. The overall median survival was 19.2 months after HIPEC. Moreover, the 3- and 5-year survival rates were 39 and 19%, respectively[42] the 5-year survival in this setting is indeed remarkable, as such survivors without HIPEC are extremely rare.

As is apparent, the outcomes after complete cytoreduction and HIPEC approach that of complete resections of metastases at other sites. Gertsch et al[43], first described the remarkable similarity in overall survival achieved by radical resection of liver metastases and the complete resection of peritoneal carcinomatosis. Shen et al[44], reporting on our experience at Wake Forest University with cytoreductive surgery and HIPEC for peritoneal surface disease compared with liver resection for hepatic metastasis showed that R0/R1 resection during CS and HIPEC compared with margin-negative hepatic resection demonstrated no significant difference in overall survival. The 1-, 3-, and 5-year overall survival for the R0/R1 peritoneal surface disease patients was 91, 48, and 26%; while it was 87, 59, and 34% for the hepatic metastasis patients (P = 0.32). Perioperative morbidity was 42% versus 34% (P = 0.38) and mortality was 5.5% versus 4.2% (P = 0.71) between the peritoneal surface disease and hepatic metastasis patients, respectively. This study further elaborates the viable outcome of CS and HIPEC as a treatment option for select patients diagnosed with colorectal PC and limited hepatic disease.

A single-institution Phase III randomized trial of HIPEC with mitomycin-C has been reported by The Netherlands Cancer Center. Patients with colorectal carcinomatosis were randomized to undergo either systemic 5-fluorouracil/leucovorin with or without palliative surgery or cytoreduction followed by HIPEC and systemic chemotherapy. A median survival of 12.6 months was seen in the palliative chemotherapy arm, while the median survival of the experimental arm was 22.3 months (p = 0.032). The trial was stopped early

due to the large survival difference in favor of HIPEC[19] An update of this trial with median follow-up of almost 8 years was presented recently. In the chemotherapy-only arm, four patients are still alive; two with and two without disease. In the intraperitoneal perfusion arm, five patients are still alive, two with and three without disease. The median progression-free survival was 7.7 months in the control arm and 12.6 months in the HIPEC arm ($p = 0.020$). The median disease-specific survival was 12.6 months in the control arm and 22.2 months in the HIPEC arm ($p = 0.028$). The 5-year survival was 45% for those patients in whom a R1 resection was achieved. With 90% of all events having taken place in this randomized trial, it shows that cytoreduction followed by HIPEC does significantly impact survival in patients with PC from colorectal primaries. From these data, one can conclude that there is the possibility of long-term survival in selected groups of patients with peritoneal dissemination of colorectal cancer[45].

After careful consideration of the above and other data, a consensus statement for the management of peritoneal surface dissemination from colorectal cancers was formulated and issued in 2007 by the leading experts in the field[32].

The recommendations were:

1.) Diagnostic work-up: should include a complete colonoscopic evaluation, a CT scan of the chest, abdomen and pelvis with oral and IV contrast. A PET scan can be considered if there is any question of extra-abdominal disease.

2.) Systemic therapy: should include the best combination of cytotoxic chemotherapy and biological agents. However, as to the optimal timing for administration of systemic therapy neoadjuvant vs. adjuvant there is currently little data to base any recommendation, it is recommended that patients be evaluated by a surgical oncologists experienced in these techniques prior to embarking on systemic therapy alone for patients who may be candidates for HIPEC.

3.) If a complete cytoreduction, is achieved, then the patients should undergo HIPEC with mitomycin C. In those patients with symptomatic ascites in whom an adequate cytoreduction could not be achieved, HIPEC could be performed at the discretion of the surgeon with the intention of palliating the intractable ascites. In those patients with clear evidence of incomplete cytoreduction, surgery should be performed to relieve symptoms at the discretion of the operating surgeon.[32]

Morbidity Associated with Cytoreductive surgery with HIPEC

The principle morbidities associated with cytoreductive surgery with HIPEC are due to complications from the surgery and hematological toxic effects of the chemotherapeutic agents. On average the surgical procedure may take up to 6-12 h, necessitating complex anesthetic management, and post-op intensive unit care. The most common surgical complications include anastomotic leaks, intestinal perforation, pancreatitis, prolonged ileus, bile leak, intraabdominal bleeding/sepsis, wound dehiscence, pulmonary embolism and renal failure. Myelosuppression (neutropenia) is the most common morbidity encountered with HIPEC, but tends to be low grade. Morbidity rates between 20% - 50% have been reported after cytoreductive surgery with HIPEC, with associated mortality rates from 1% to 10%[46]. Reports have indicated a 28% incidence of myelosuppression with single-agent mitomycin-c intraperitoneal therapy[47]. Severe myelosuppression in the acute postoperative phase puts the patients at increased risk for life-threatening sepsis, and poor wound healing. .

Due to the extent and complexity of the surgery, and the several technical and procedural nuances involved, it is prudent that only those who have considerable experience should perform these procedures, as both the cytoreductive surgery and the administration of

HIPEC are technically demanding procedures for which learning curves exist[36]. In a study of learning curve for cytoreductive surgery with HIPEC involving a total of 323 procedures by Smeenk et al[48] , they documented that the peak of the learning curve, graded by the percentage of complete cytoreductions, was reached after approximately 130 procedures. Noting a decrease in postoperative morbidity rate from 71.2 to 34.1% , a decrease in the median duration of hospital stay from 24 to 17 days. They concluded that the learning curve of combined modality treatment for peritoneal surface disease is long, and reflects patient selection and treatment expertise. Levine et al reported a similar learning curve with the worst outcomes seen in the first 125 cases of a series of 501 at Wake Forest[36].

Postoperative Follow-Up/Role of Neoadjuvant and Adjuvant Therapy

Postoperative follow-up of these patients undergoing CS and HIPEC for colorectal PC is usually every 3-6 months following their procedure with surveillance imaging and tumor markers looking for signs of recurrence or progression. The role of repeat CS and HIPEC is as of yet undefined, generally, patients who are candidates for a repeat CS and HIPEC are those who have had a R0/R1 resection, are at least 1 year from their first procedure, and present with PC only that appears largely resectable. In evaluating patients for a second cytoreduction, the criteria that are used to select patients for the first remain important. Specifically, the patients must remain medically fit to tolerate a major operative procedure, be free of extra-abdominal or hepatic parenchymal metastases, and have disease that seems amenable to complete cytoreduction[49]. The goal is to select patients who may have a more favorable tumor biology who have the best chance of benefiting from an invasive and potentially morbid intervention.

The application of preoperative and postoperative systemic therapies for patients with PC who are being considered for CS and HIPEC is another area in which there is little published data. Patients who are felt to have high-volume disease with a histology that may respond to systemic therapy are usually recommended to undergo a course of systemic therapy in hopes of decreasing tumor burden and thus providing a better chance of achieving a R0/R1 resection status at time of CS. In addition, patients who are recovering from a recent laparotomy at another institution for diagnosis, relief of obstruction, or attempt at CS, often are given preoperative therapy if the histology is appropriate (higher grade lesions with aggressive behavior) to allow time for adhesions to improve before definitive attempt at CS and HIPEC. The use of adjuvant systemic therapy after CS and HIPEC is usually determined on a case-by-case basis after discussion with the patient's medical oncologist. Patients who are chemo-naïve are offered systemic therapy. Patients who received preoperative chemotherapy are usually observed without further treatment after HIPEC, if they have undergone a R0/R1 resection

Conclusions

Long term disease free survival is possible in selected patients with peritoneal dissemination from colon carcinoma. While this aggressive therapy is formidable, it offers the best outcome for these patients who had previously been relegated to palliative therapy. Recently the American College of Surgeons Oncology Group (ACOSOG) initiated a, "Phase III Randomized Trial Comparing Standard Systemic Therapy to Cytoreduction + Hyperthermic Intraperitoneal Mitomycin C + Standard Systemic Therapy In Patients With Limited Peritoneal Dissemination of Colon Adenocarcinoma". The objectives of this study include to compare the overall survival of patients with advanced limited peritoneal dissemination of colon adenocarcinoma treated with systemic therapy with versus without cytoreduction surgery and hyperthermic intraperitoneal mitomycin C. We support this and other future possible randomized studies, and are heartened by an organized effort to bring such trials to this modality.

CS and HIPEC for colorectal PC is a multimodality approach which has been established in investigational Phase II trials and a single well done phase III randomized trial to have therapeutic benefit. We approach PC similarly to isolated pulmonary or hepatic metastases, in which an aggressive surgical approach for complete resection is warranted. However, this approach should only be pursued in centers with demonstrated expertise.

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