Current Oncology Reports (2018) 20: 62
https://doi.org/10.1007/s11912-018-0703-0

GASTROINTESTINAL CANCERS (J MEYER, SECTION EDITOR)

Peritoneal Metastases from Gastrointestinal Cancer

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Published online: 8 June 2018

Abstract

Purpose of Review Peritoneal metastases may occur from a majority of cancers that occur within the abdomen or pelvis. When cancer spread to the peritoneal surfaces is documented, a decision regarding palliation vs. an aggressive approach using cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy must be made. The perioperative chemotherapy may be hyperthermic intraperitoneal chemotherapy (HIPEC) administered in the operating room or early postoperative intraperitoneal chemotherapy (EPIC) administered in the first 4 or 5 postoperative days.

Recent Findings This decision is dependent on a well-defined group of prognostic indicators. In addition to treatment, the clinical and pathologic features of a primary cancer can be used to select perioperative treatments that may prevent cancer cells within the abdomen and pelvis from progressing to established peritoneal metastases. In some clinical situations with appendiceal and colorectal cancers, the clinical or histopathologic features may indicate that second-look surgery plus perioperative chemotherapy should occur.

Summary Peritoneal metastases should always be considered for treatment or prevention.

Keywords Peritoneal metastases · Appendiceal cancer · Malignant peritoneal mesothelioma · Colon cancer · Recurrent ovarian cancer · Gastric cancer · Cancer prevention

Introduction

An increasing concern for improved management of peritoneal dissemination and local recurrence of cancers that occur within the abdomen and pelvis has been expressed by both surgeons and medical oncologists. This condition was, in the past, regarded as a universally fatal manifestation of cancer dissemination. It has been associated with early death and a miserable quality of life in those patients manifesting peritoneal dissemination and the progression of peritoneal metastases. In the past 30 years, a marked conceptual change in the possibilities to prevent or treat peritoneal metastases has occurred. Currently, management strategies for this condition from a large number of abdominal and pelvic cancers exist. It has become imperative for the multidisciplinary team (MDT) to consider options for prevention and treatment of peritoneal metastases. Table 1 lists the primary and recurrent cancers that must have special attention by the MDT if peritoneal metastases occur [1, 2••, 3, 4••, 5, 6•]. Systemic chemotherapy alone is not optimal management of selected patients with peritoneal metastases; also sometimes peritoneal metastases can be prevented.

This article is part of the Topical Collection on *Gastrointestinal Cancers*

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Treatment of Peritoneal Metastases Has Been Defined as an Oncologic Necessity

Why is it that a large number of world opinion leaders in gastrointestinal cancer and gynecologic malignancy have focused such great time and effort on peritoneal dissemination? Carcinomatosis has been a diagnosis treated by palliation for many decades. It is important to identify the stimulus for concerted efforts to improve the management of peritoneal metastases. I suggest that the origins for this new attitude had two beginnings. First, clinical research showed that the dissemination of cancer on peritoneal surfaces and at the surgical resection site was a terrible ongoing problem in gastrointestinal and gynecologic oncology. Something needed to be done. Chu

Table 1 Diseases with peritoneal metastases that may be recommended by the multidisciplinary team for definitive treatment of selected patients by cytoreductive surgery and intraperitoneal chemotherapy

Disease	Reference
Appendiceal cancer	[1]
Malignant peritoneal mesothelioma	[2••]
Colon cancer	[3]
Ovarian cancer	[4••]
Gastric cancer	[5]
Unusual abdominal/pelvic malignancies with dissemination limited to peritoneal surfaces	[6•]

and colleagues at the University of Arkansas in 1989 published a prospective study on peritoneal carcinomatosis from non-gynecologic malignancy [7]. They studied 100 patients with peritoneal metastases including colorectal cancer (45), pancreas cancer (20), gastric cancer (6), and a variety of other less common causes of peritoneal metastases. The mean survival of patients with colorectal metastases was 8.5 months, pancreas cancer 2.4 months, and gastric cancer 2.2 months. Chu and coworkers pointed out that these patients developed severe adverse symptoms such as bowel obstruction in over half of their patients, perforated viscus, enterocutaneous fistula, and debilitating ascites. Surgical procedures to alleviate these conditions were uniformly unsuccessful. The only prognostic factor that was associated with a disease-free survival following surgery was the disease-free interval ($p = 0.04$).

Another pioneer investigating the prognosis of patients with peritoneal carcinomatosis from non-gynecologic malignancy was Sadeghi and coworkers. They presented the results of a French multicenter prospective study known as, EVOCAPE 1 [8]. Again, the survival of patients with peritoneal metastases was very limited. Gastric cancer patients showed a mean survival of 6.5 months, colorectal carcinoma patients a mean survival of 6.9 months, and pancreatic carcinoma patients a mean survival of 2.9 months. Sadeghi and colleagues quantitated the extent of carcinomatosis in a staging system that assessed both the size and distribution of "malignant granulations." This staging system for the total of 370 patients treated significantly was associated with survival ($p = 0.001$). Those patients who had liver metastases in addition to peritoneal dissemination had a reduced prognosis ($p = 0.0009$).

Jayne and colleagues at the Singapore General Hospital in 2002 had 349 patients (13%) in their database identified as patients with peritoneal metastases [9]. Two hundred fourteen patients had synchronous disease and 135 had metachronous carcinomatosis. The survival of these patients was limited with a median survival of patients with synchronous disease of 7 months and a median survival for patients with metachronous carcinomatosis of 28 months from the initial diagnosis of colorectal cancer. These authors again noted that the extent of disease was a significant factor in predicting survival ($p = 0.009$). In the multivariate analysis, cancer differentiation and presence versus absence of liver metastases were not significant clinical predictors of survival.

Pharmacologic Data from Intraperitoneal Administration of Anticancer Drugs Showed the Potential for Control of Small Peritoneal Nodules and a Reduced Systemic Toxicity

The rationale for use of chemotherapy administration directly into the peritoneal space may have emanated from pharmacologic research in chronic ambulatory peritoneal dialysis [10]. The efficacy of this novel method for intraperitoneal drug delivery for peritoneal metastases patients has been slow to develop. Karnofsky and colleagues in 1948 used nitrogen mustard for the palliative treatment of carcinomatous ascites. The efficacy was such that FDA approval of nitrogen mustard for intraperitoneal administration was granted and remains in effect until this day [11]. However, the rationale for intraperitoneal chemotherapy administration came from pharmacologic research in patients who had cancer spread to peritoneal surfaces. It was recognized that some drugs would be especially appropriate for prolonged retention within the peritoneal space based on their molecular structure [12]. It was Dedrick and colleagues at the American National Institutes of Health who called attention to the potential benefits of intraperitoneal chemotherapy administration of cancer chemotherapy agents especially in ovarian cancer [13•]. The studies of Speyer and colleagues clearly identified 5-fluorouracil as an agent with high concentrations within the peritoneal space after intraperitoneal administration as compared to drug levels within the plasma [14]. The rapid metabolism of the 5-fluorouracil after absorption of this drug by the visceral peritoneum within the liver parenchyma resulted in a markedly enhanced exposure of cancer nodules on peritoneal surfaces [15]. Jones and colleagues recognized that a high volume of intraperitoneal chemotherapy solution (belly bath technique) was necessary to adequately distribute the drugs [16]. Ozols and colleagues investigated the pharmacokinetics of doxorubicin and McVee and colleagues the possible benefits of intraperitoneal cisplatin [17, 18]. With continued efforts to identify drugs appropriate for intraperitoneal chemotherapy administration, an extended list of possible chemotherapy agents and their pharmacologic advantage following intraperitoneal administration has been defined [19••].

Because of a large molecular size and hydrophobic surface, cancer chemotherapy agents were shown to have a slow clearance from the peritoneal compartment through the lining of the abdomen and pelvis to the body compartment. Also,

metabolism of the cancer chemotherapy in the body compartment was at all points in time faster than clearance from the peritoneal space. This resulted in a much greater concentration times time (area under the curve) of drug in the peritoneal space as compared to concentration times time measured in the blood. This results in an increased therapeutic effect on cancer nodules on the peritoneal surface and a reduced systemic toxicity [20].

Augmentation of Intraperitoneal Chemotherapy Cytotoxicity by Moderate Heat

The effects of intraperitoneal heat by itself were shown by Shiu and Fortner in an experimental animal to have a potential for application as an adjunct to cancer surgery [21]. It had been shown many times in the past that cancer chemotherapy could be augmented by heat [22]. However, it was left to Spratt and colleagues to first combine intraperitoneal chemotherapy with intraperitoneal heat in an attempt to maximize the control of peritoneal metastases as part of a treatment plan for gastrointestinal and gynecologic malignancy [23•]. In 1980, these efforts in Louisville, Kentucky by Spratt and colleagues were the first applications of hyperthermic intraperitoneal chemotherapy (HIPEC). In summary, the modern approach to the prevention and treatment of peritoneal metastases arises out of a well-described oncologic need for treatment of this condition. Favorable pharmacologic studies suggesting increased responses of peritoneal nodules combined with reduced systemic toxicity following intraperitoneal chemotherapy delivery. The application of heat within the peritoneal space along with a large volume of chemotherapy solution would increase the uniformity of treatment and augment its efficacy throughout the peritoneal space.

Prevention of Peritoneal Metastases as an Initial Successful Application of HIPEC

The case report by Spratt and colleagues regarding the use of HIPEC did not gain attention within the USA or Europe. It was the Japanese under the direction of Koga at Totori University who first recognized the potential application of HIPEC for the prevention of peritoneal metastases in patients with gastric cancer. Koga and colleagues introduced a new Japanese drug, mitomycin C, as the chemotherapy agent to be instilled in a large volume of fluid to prevent or to treatment peritoneal metastases. They took this concept to the laboratory and demonstrated that heat alone could reduce the progression of an intraperitoneal rat ascites hepatoma; mitomycin C alone was also capable of improving survival in this rat model. However, far and away, the longest median survivals of rats inoculated with an intraperitoneal tumor were those who were treated by mitomycin C with the presence of 41.5 °C heat for 60 min [24].

The group at Totori University in 1988 reported on a study of prophylaxis for peritoneal recurrence of gastric cancer using HIPEC with mitomycin C. In a group of patients matched to historical controls ($n = 38$) and in a randomized controlled study of 47 patients, there was an improvement in survival in those patients receiving HIPEC mitomycin C. The results, because of small numbers, were of borderline significance. These investigators noted that anastomotic leak, postoperative ileus, and possible chemical peritonitis were not induced by HIPEC mitomycin C. Their conclusion was that their results demonstrated a simple, safe, and readily applicable prophylactic therapy for peritoneal recurrence in patients with serosal positive gastric cancer [25]. Studies at Kanazawa University by Yonemura and colleagues and studies in Chiba, Japan by Fujimoto and colleagues showed positive results with HIPEC mitomycin C or HIPEC mitomycin C plus cisplatin for the prevention of peritoneal recurrence of gastric cancer. These were positive randomized controlled studies [26, 27]. To the great credit of these early investigators, a systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resected gastric cancer shows benefit. Yan and colleagues in 2007 found 13 reports of randomized controlled trials on adjuvant intraperitoneal chemotherapy for resected gastric cancer for appraisal and data analysis. Ten reports were judged to be of fair quality and subjected to their meta-analysis. There was a significant improvement in survival associated with HIPEC with a hazard ratio of 0.60 (95% CI = 0.43 to 0.83, $p = 0.002$) [28]. Recently, Feingold et al. performed a systematic review and random effect analysis to analyze current literature regarding the role of adjuvant intraperitoneal chemotherapy [29]. One of the randomized controlled trials using HIPEC in patients at risk for gastric cancer peritoneal metastases was reported by Yonemura et al. [30]. There were improved outcomes with HIPEC with a 5-year overall survival of 61% for surgery plus HIPEC versus 42% for surgery alone. This was significant with a p value of 0.019. By multivariate analysis, the relative risk for surgery alone was 3.075 with 95% confidence interval of 1.483 to 6.422. This remains the single most important study confirming HIPEC for adjuvant treatment of resected gastric cancer. Currently, a Western randomized controlled trial, GastriCHIP, is accruing patients [31].

Prevention of Peritoneal Metastases and Local Recurrence with Colon and Rectal Cancer

For peritoneal metastases to occur, cancer cells must be disseminated either prior to or at the time of the cancer resection. High density seeding 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 is expected. Single cells disseminated at a distance from the anatomic site of primary cancer resection will manifest as single cancer nodules [32–35].

Some patients are at special risk for local-regional recurrence and peritoneal metastases as listed in Table 2. In groups 1–4 in Table 2, patients can be considered to have 50–100% incidence of local-regional recurrence and/or peritoneal metastases in the absence of special treatments [36••]. This occurs even if these metastases are completely removed with the primary intervention [36••, 37]. The other clinical findings (# 5–10 listed in Table 2) have been shown to place the patient at a lesser risk for local-regional recurrence or peritoneal metastases.

Data Showing Benefit from Intraperitoneal Chemotherapy in Patients with Primary Colorectal Cancer with Peritoneal Seeding or at High Risk for Peritoneal Seeding

Local-regional recurrence and peritoneal metastases occupy a prominent role in the natural history of gastrointestinal cancer. Intraperitoneal chemotherapy used as a planned part of a surgical intervention to control local-regional recurrence and peritoneal dissemination from colorectal cancer was proposed by Sugarbaker and colleagues [38–40]. There was a marked pharmacokinetic advantage of perioperative intraperitoneal chemotherapy with single cancer cells on peritoneal surfaces as the targets of this treatment [41].

To date, 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 the early postoperative intraperitoneal chemotherapy (EPIC) [42–47]. From a logistical perspective, EPIC may be favored in that patients with unexpected peritoneal metastases who have not signed an informed consent for HIPEC can be treated with full consent in the early postoperative period. It is possible that a single dose of intraoperative chemotherapy (HIPEC) is not as effective as the 5-day intraperitoneal lavage used postoperatively (EPIC). However, EPIC has been shown to be associated with a higher incidence of adverse events but not a higher incidence of mortality [48, 49].

Table 2 Patients with primary colorectal cancer identified to be at high risk for local-regional recurrence and/or peritoneal metastases. Groups 1–10 are candidates for prophylactic HIPEC or EPIC as part of the primary colorectal cancer resection. Groups 1–4 are candidates for proactive second-look surgery

1. Visible evidence of peritoneal metastases
2. Ovarian cysts showing adenocarcinoma suggested to be of gastrointestinal origin
3. Perforated cancer
4. Positive margins of excision
5. Positive cytology either before or after cancer resection
6. Adjacent organ involvement of 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

Establishing Perioperative Chemotherapy as a Standard of Care for Selected Patients

Perioperative chemotherapy refers to either intraperitoneal or intravenous chemotherapy used as a planned part of a surgical procedure to prevent or treat peritoneal metastases. In most protocols, both intraperitoneal and intravenous chemotherapy agents are used. Prior reviews of proactive management of primary colorectal cancer to eradicate minimal residual disease in the perioperative period have been published [50, 51]. To bring these concepts into the standard of care, there are three randomized controlled trials active in Europe to test the efficacy of HIPEC in patients with colon cancer at high risk for the progression of peritoneal metastases [52–54].

Current Data Regarding Benefits Expected with Proactive Second-Look Surgery plus Perioperative Chemotherapy

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 peritoneal metastases must be formulated. Patients in Table 2 groups 1–4 are those who may 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 [55–57, 58•, 59]. Patients in the high risk—groups 5–10—need to be carefully monitored.

Patients with colon or rectal cancer are not only at risk for tumor cell entrapment. After a potentially curative resection of a pancreas cancer, disease recurrence has been recorded in the local and regional area in 50% of patients and on peritoneal surfaces in 40–60% of patients [60].

Surgical Treatment Strategies for Peritoneal Metastases Diagnosed in Follow-up

There are multiple reasons why the surgery to resect peritoneal metastases must be as complete as possible. Data from all studies thus far clearly establish that the outcomes of treatment are dependent on a complete cytoreduction. There are some exceptions to this rule but they are few. Complete visible removal of all abdominal and pelvic tumor is necessary because of limited penetration of the intraperitoneal chemotherapy solution. Estimates of one to several cell layers have been published. Gross nodules will only respond minimally or not at all. However, single cancer cells or minute nodules may be eradicated by an effective chemotherapy regimen. In order for the treatment of established peritoneal metastases to be treated, a new surgical technology was needed. That new surgical intervention was the peritonectomy procedure [61•].

Peritonectomy

In order to make a transition between perioperative intraperitoneal chemotherapy for prevention to treatment, a surgical technology to reduce the extent of abdominal and peritoneal cancer to a microscopic level was necessary. This requirement was necessary because of the very limited penetration of intraperitoneal chemotherapy [17, 18, 62]. The invention of the peritonectomy procedures was the necessary link between success with prevention and success with treatment of established peritoneal metastases [61•]. Normal appearing peritoneal surfaces are not resected. Perioperative chemotherapy occurs after the cytoreductive surgery and usually precedes bowel reconstruction and closure of the abdomen [19••, 61•].

Rationale for a Combined Treatment for Peritoneal Metastases Utilizing CRS Plus Perioperative Chemotherapy

Success in control of peritoneal metastases from gastrointestinal or ovarian cancer never occurred if CRS alone or intraperitoneal chemotherapy alone were used separately. Success was first recognized when the CRS with peritonectomy was combined with perioperative intraperitoneal chemotherapy as a planned surgical procedure [63, 64]. Interruption of contamination of the surgical resection sites with cancer cells requires that these implants be destroyed prior to their entrapment within scar tissue that is part of the healing process. Sugarbaker et al. hypothesized that attempts to eliminate cancer cells from peritoneal surfaces were limited to chemotherapy lavage administered within the first postoperative week [38]. These treatments would then occur before fibrosis sets in as a part of the healing of the surfaces of the abdomen and pelvis. In an ideal situation, in order to prevent entrapment of cancer cells within tissues that are sutured together, the chemotherapy solutions must be used in the operating room after the cytoreduction but prior to making an intestinal anastomosis, and prior to the closing of the abdominal wall [65].

The simultaneous use of cancer chemotherapy and heat strongly contributes to the control of peritoneal metastases. The heat significantly increases the cytotoxicity of a selected number of chemotherapy agents [22]. Also, the hyperthermia should always be applied while the chemotherapy is present within the peritoneal space. Knowledge of the proper length of time for HIPEC requires a comprehension of the pharmacologic parameters established for the intraperitoneal administration of the chemotherapy agent.

Quantitative Prognostic Indicators for Knowledgeable Patient Selection

There can be no doubt that definitive treatment of peritoneal metastases is a major intervention involving a large commitment from the patient, his/her family, and health care providers. In order to avoid a major intervention with limited benefit, knowledgeable patient selection is essential. This selection process indicates which includes a histologic assessment, review of chest, abdomen, and pelvic CT for concerning radiologic features, peritoneal cancer index (PCI) assessment at the time of abdominal exploration and determination of the completeness of cytoreduction score (CC score) at the completion of the cancer resection [66•]. In patients who have had prior surgery to resect peritoneal metastases, the prior surgical score (PSS) needs to be considered [66•].

The principles of management to select patients were initially described for use with appendiceal and colorectal peritoneal metastases patients [63]. However, not only they apply to appendiceal and colorectal malignancy, but also they have been used to more knowledgeably selected patients with colorectal cancer [67], gastric cancer [68], ovarian cancer [69], and mesothelioma [70, 71••]. A validation of these quantitative prognostic indicators in a large number of malignancies with peritoneal metastases allows knowledgeable selection of patients with rare abdominal and pelvic neoplasms that have peritoneal metastases for successful treatment by CRS and perioperative chemotherapy.

Histologic Criteria

The grade of a malignancy is not usually considered in the TNM staging of a malignancy. However, the invasive versus non-invasive character of peritoneal metastases is an estimate of the biology of the cancerous

process. In appendiceal malignancy, malignant peritoneal mesothelioma and ovarian cancer peritoneal dissemination, there is a wide variation in the biologic aggressiveness of the peritoneal dissemination. A minimally invasive cancer will be more effectively removed by peritonectomy with less involvement of sub-peritoneal lymphatics. With more complete CRS, the more effective perioperative chemotherapy will be in the eradication of microscopic residual disease. Even though the low-grade appendiceal malignancy may be extensive, with complete CRS, the prognosis is excellent [72]. Likewise, cystic mesothelioma may be of huge proportions and yet have long-term disease-free status expected after CRS plus HIPEC [73].

For gastric cancer and colorectal cancer, the histologic parameters are often less meaningful as a prognostic variable. However, at the extreme upper grades of malignancy, the prognosis with CRS and perioperative chemotherapy is guarded. For appendiceal cancer, poorly differentiated and signet ring carcinoma have a markedly reduced outcome with treatment [74].

Not only is there a larger risk of incomplete cytoreduction and more invasion of subperitoneal lymphatics with high grade malignancy, the incidence of cancer progression at other sites such as liver metastases, retroperitoneal, or pelvic lymph node metastases is greater. With the high-grade cancers, sometimes the peritoneal metastases may be controlled but the patient succumb to disease beyond the peritoneal surfaces.

As might be expected, other sites of metastatic disease in addition to peritoneal metastases confer a reduced prognosis after CRS and perioperative chemotherapy. For appendiceal malignancy of peritoneal mucinous carcinoma grade, lymph node involvement caused a small reduction in long-term survival. Sugarbaker's data on 967 appendiceal malignancy patients with peritoneal metastases showed 50% overall survival at 10 years in the absence of lymph node metastases and 25% when lymph nodes were involved ($p = 0.003$) [70]. For 156 colon cancer patients with complete cytoreduction, 50% showed overall survival at 5 years in the absence of lymph node metastases and 15% when lymph nodes were involved ($p = 0.03$) [67]. In patients with colorectal peritoneal metastases, limited resectable liver metastases are sometimes not an absolute contraindication to treatment with CRS and HIPEC. Elias et al. in 24 patients with colorectal peritoneal metastases reported a 5-year overall survival in the absence of liver metastases of 41.5% and if liver metastases were present 23.6% [75]. These data may be interpreted to show that other sites of metastatic disease reduce the prognosis when CRS and HIPEC are used to treat peritoneal metastases. However, they are not considered an absolute contraindication to an attempt at curative treatment.

Concerning Radiologic Features Seen on Preoperative CT

At the consensus conference for management of peritoneal metastases held in Milan in 2006, CT was declared the standard preoperative radiologic test from which the selection of patients for CRS plus perioperative chemotherapy should occur [76]. Other radiologic studies such as MRI or PET would be used to supplement CT of the chest, abdomen, and pelvis. The contribution of CT to patient selection is limited by the high false negative percent reported when small peritoneal implants are imaged [77, 78]. If nodules are 0.5 cm or less, 72% of nodules are not detected. If the size of implant is between 0.5 and 5.0 cm, the false negative percentage is 28%. Nodules greater than 5 cm are reliably imaged with a false negative percentage of 10% [77]. In all size categories, the false positive percentage was low. With CT detection of peritoneal metastases, if nodules are identified, they are very likely to indicate peritoneal involvement at that anatomic site. If nodules are not imaged, many small nodules are not ruled out.

Another strategy for interpreting CT findings on peritoneal metastases patients uses the concerning CT features [79••]. A series of 15 CT images describing a particular abdominal or pelvic pathology entity was described by Sugarbaker et al. In none of these 15 CT features existed, complete cytoreduction should be the outcome. If a single concerning radiologic feature was identified, the cytoreductive surgery should be more extensive and considered a greater risk for adverse events. If two concerning radiologic features are present, complete cytoreduction is unlikely [80–82]. Yan et al. published this concept for malignant peritoneal mesothelioma [81], Jacquet for mucinous appendiceal and colorectal cancer [80], Rivard et al. for colorectal cancer [82], and Suidan for ovarian cancer [83].

Peritoneal Cancer Index (PCI)

The peritoneal cancer index (PCI) provides an estimate of the extent of peritoneal metastases present within the abdomen or pelvis. It is determined at the time of complete abdominal and pelvic exploration in the early phases of a cytoreductive surgery. Both the distribution and size of peritoneal nodules are used to determine PCI. For many different diseases with peritoneal dissemination, the extent of disease as determined by PCI has a profound effect on prognosis in patients treated by CRS and perioperative chemotherapy. This has been shown to be true for appendiceal cancer [72], colorectal cancer [67], ovarian cancer [69], sarcoma, and malignant peritoneal mesothelioma. For colorectal cancer, peritoneal metastases treated in patients with a PCI ≤ 10 are expected to show a 50% long-

term benefit from treatment [67]. Patients with a PCI > 20 rarely achieve more than palliative benefit [84]. In contrast, patients with a low biologic grade of malignancy (similar to a low-grade appendiceal mucinous neoplasm) can benefit if the CRS is complete despite a very high PCI. For example, patients who had an appendiceal mucinous neoplasm with adenomucinosis and PCI > 20 has a 10-year survival of 50% [72].

Completeness of Cytoreduction Score

The most important prognostic variable is the completeness of cytoreduction score (CC score). A complete cytoreduction (CC-0) is greatly preferred and indicates that no visible tumor remains at the completion of the cytoreductive surgery. CC-1 indicates residual tumor nodules less than 2.5 mm. A CC-2 score indicates residual tumor nodules between 2.5 and 5 mm. A CC-3 score indicates residual tumor nodules greater than 5 mm or a layering of malignancy on peritoneal surfaces [66•] with few exceptions. Until more effective perioperative treatments become available, to select a patient for elective CRS and HIPEC, the end result of the surgery should be predicted to be a complete CRS.

However, even if the cytoreduction is complete (CC-0 or CC-1), the extent of disease recorded by the PCI has a profound effect on prognosis after CRS and HIPEC. Aggressive treatment with CRS and HIPEC is restricted to those with a PCI of ≤ 20 if the malignancy is high grade.

Some exceptions to the statement that the only CRS of high value is a CC-0 or CC-1 resection. Ovarian cancer and peritoneal mesothelioma frequently have bowel and bowel mesentery involved with multiple small cancer nodules that cannot be reduced to CC-0/CC-1 status. Using peritonectomy procedures and visceral resections, all other sites of disease can be resected to no visible evidence of disease. These patients with a limited extent of CC-2 residual disease can be treated by CRS and perioperative chemotherapy with prolonged benefit [85, 86]. Also, pseudomyxoma peritonei patients with CC-2 cytoreduction may profit from CRS plus perioperative chemotherapy [87]. For gastric cancer, colorectal cancer and peritoneal mucinous carcinoma from appendiceal cancer, a CC-0 cytoreduction must be the goal for CRS.

Prior Surgical Score

Less emphasis has been placed on prior surgical score than on other prognostic variables. However, from a theoretical and now clinical perspective, it may have profound implications for outcome. The prior surgical score (PSS) estimates the extent of tumor cell entrapment that may have occurred as a result of prior surgical interventions performed when peritoneal metastases were present [66•].

Assuming that the peritoneum acts as a "first line of defense" against peritoneal metastases, the greater the disruptions of peritoneum prior to CRS and perioperative chemotherapy, the less perfect the cancer implant resection. Reseeding of cancer cells into a retroperitoneal dissection or into a surface stripped of its peritoneum is not likely to be resected at the definitive CRS. Also, perioperative chemotherapy is not likely to eradicate cancer cells trapped in adhesions or scar tissue.

Prior surgical score has been shown to be an important prognostic variable in appendiceal cancer [72], ovarian cancer [88], sarcoma [89], and most recently, colorectal cancer [90]. These data for colon cancer, as well as rectal cancer may have implications for treating the 5–10% of colorectal cancer patients who are found to have peritoneal metastases and at the same time the primary cancer is discovered [35].

Perioperative Chemotherapy

The important factors for performing perioperative chemotherapy are the following: (1) A proper selection of chemotherapy agents. (2) The appropriate duration of HIPEC as part of the combined treatment for peritoneal metastases. (3) A rational level of heat for hyperthermia appropriate for a particular chemotherapy agent. (4) Selection of a methodology for HIPEC delivery. (5) Selection of an appropriate commercial hyperthermia pump. (6) Realization that an important aspect of HIPEC by the open technologies is commercially available table-mounted retractors.

Proper Selection of Chemotherapy Agents for HIPEC

It is important for HIPEC to be successful for a response to be elicited by the chemotherapy agent. Although response to systemic chemotherapy and intraperitoneal chemotherapy may not always be similar, this is one criterion for drug selection. A second important criterion is intraperitoneal exposure. This can best be estimated from the area under the curve ratio of intraperitoneal concentration times time divided by the intravenous concentration times time that have been determined pharmacologically. [91, 92•, 93–97].

The chemotherapy agents frequently used for perioperative chemotherapy are listed in Table 3 [94]. The table presents the intraperitoneal half-life, the time at which 80% of the drug has cleared from the peritoneal space, and the AUC of peritoneal concentration times time divided by the intravenous concentration times time [20, 96, 98].

Table 3 Chemotherapy agents used for perioperative intraperitoneal chemotherapy. From [19••], reused with permission from AME Publishing Company

Druh	Molecular weight	Type	AUC ration	$T^{1/2}$ (mins)	$T^{80\%}$ (mins)	Dose	Carrier solution	Incompat-ability in solution	Heat synergy	Heat stability	Depth of penetration
Doxorubicin	579.99	Antitumor antibiotic	230	20	80	15 mg/m^2	1.5% detrose dialysis solution	Heparin, fluorouracil	Yes	42 °C	4–6 cell layers
DOXIL (liposomal doxorubicin)	579.99	Anti-tumor antibiotic	1040	180	NA	100 mg/m^2	1.5% detrose dialysis solution	Heparin, fluorouracil	Yes	42 °C	4–6 cell layers
Etoposide	588.58	Anti-tumor antibiotic	65	NA	NA	25–350 mg/m^2	5% dextrose	Plastic devices; acrylics; antibiotics	Yes	42 °C	NA
5-fluorouracil	130.08	Anti-metabolite	280	30	75	650 mg/m^2 (× 5 days)	0.9% sodium chloride; 1.5% dextrose dialyses solution; Icodextrin	Doxorubicin daunorubicin idarubicin cisplatin diazepam icytarabine	Minimal	43 °C	0.2 mm
Floxuridine (FUDR)	246.2	Anti-metabolite	75	NA	NA	500 mg/m^2 twice daily (× 3 days)	0.9% sodium chloride	NA	Minimal	43 °C	NA
Gemcitabine	299.5	Pyrimidine antagonist	205	40	75	1000 mg/m^2	0.9% sodium chloride	NA	At 48 h	42.5 °C	NA
Irinotecan	677.19	Anti-tumor antibiotic	NA	NA	NA	200 mg/m^2	1.5% dextrose dialysis solution	NA	No	44 °C	NA
Melphalan	305.2	Alkylator	56	33	69	70 mg/m^2	0.9% sodium chloride	NA	Marked	42 °C	NA
Mitomycin C	334.3	Anti-tumor antibiotic	27	40	90	15 mg/m^2	1.5% dextrose dialysis solution	Bleomycin	Yes	42.5 °C	2000 μm
Mitoxantrone	517.41	Anti-tumor antibiotic	115–255	NA	NA	28 mg/m^2	0.9% sodium chloride; lactated Ringer's solution	Heparin	Yes	43 °C	5–6 cell layers
Pemetrexed	471.4	Multi-targeted antifolate	70	90	260	500 mg/m^2	1.5% dextrose dialysis solution	NA	NA	NA	NA
Carboplatin	371.25	Alkylator	10	NA	NA	300 mg/m^2	0.9% sodium chloride	NA	Yes	41.5 °C	0.5 mm
Cisplatin	300.1	Alkylator	10	30	90	90 mg/m^2	0.9% sodium chloride	NA	Yes	41.5 °C	1–3 mm
Oxaliplatin	397.3	Alkylator	16	40	60	460 mg/m^2	5% dextrose	Aluminum alkaline or NaCI solutions	Yes	46 °C	1–2 mm
Paclitaxel	853.9	Antimitotic	1000	NA	NA	120–180 mg (total dose)	1.5% dextrose dialysis solution; 6% hetastarch	Plastic containers and tubes	No	42.5 °C	>80 cell layers
Doxetaxel	861.9	Antimitotic	552	NA	NA	45 mg/m^2	0.9% sodium chloride	Plastic containers and tubes	No	NA	NA

AUC, area under the curve; $T^{60\%}$, time for 80% clearance of drug from peritoneal space; *NA*, data not available

Level of Hyperthermia

The mechanisms whereby hyperthermia will increase the tumor response to cancer chemotherapy are threefold. First, heat alone has a small direct anti-tumor effect [99]. The second and perhaps more important mechanism whereby hyperthermia increases cell kill is by augmentation of chemotherapy cytotoxicity [100]. The third mechanism for increased cell kill of peritoneal metastases with hyperthermia is related to increased penetration of the cancer chemotherapy into tumor nodules [101–103]. Finally, the extent of intraperitoneal heat must be matched to the intraperitoneal cancer chemotherapy agent [104].

Technologies for HIPEC

Different apparatus for administering HIPEC exists in the management of peritoneal surface malignancy. The open technique with a vapor barrier created by smoke evacuators has been used extensively at the Washington Cancer Institute [105]. The coliseum technique is with the open abdominal incision covered by a plastic sheet [106]. In contrast, some groups close the abdomen prior to the HIPEC administration. Table 4 lists the credits and debits of the open versus closed abdomen technique [94].

Diseases

In this review, we have selected six diseases or disease category that merit emphasis regarding disease-specific treatments and a summary of expected outcomes.

Appendiceal Mucinous Neoplasms

Appendiceal mucinous neoplasms have been treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for over 30 years [72]. As the cytoreductive surgical procedures improved and the HIPEC became more refined, this new treatment option for mucinous appendiceal neoplasms was accepted as a new standard of care for this disease [1] Fig. 1 compares the results of cytoreduction plus HIPEC to serial debulking procedures plus systemic chemotherapy or delayed intraperitoneal chemotherapy at four prominent cancer centers [1]. A systematic review evaluated the results from the world's literature in the treatment of appendiceal mucinous neoplasms. Yan and colleagues concluded that cytoreductive surgery plus HIPEC showed promising long-term results as compared to historical control [107].

Peritoneal Mesothelioma

Peritoneal mesothelioma is another rare disease process in which cytoreductive surgery combined with perioperative intraperitoneal chemotherapy has emerged as a new standard of care. Four groups have now reported on approximately 300 malignant peritoneal mesothelioma patients. The National Cancer Institute in Bethesda, MD [108], The Washington Cancer Institute in Washington, DC [86], The Columbia Mesothelioma Center in New York [109], and the National Cancer Institute in Milan, Italy [110]. All groups presented data with cytoreductive surgery and HIPEC with treatment results markedly improved over those reported in the past with conservative management by palliative surgery and systemic chemotherapy.

Table 4 Credits and debits of two different technologies for hyperthermic intraperitoneal chemotherapy. From [19••], reused with permission from AME Publishing Company

Features	Open abdomen manually distributed	No surgery during chemotherapy
Environmental hazard	No aerosols detected	Perception of increased safety
Distribution	Uniform distribution of heat and chemotherapy solution, tissues close to skin edge not immersed	Possible poor distribution to dependent sites and closed spaces
Pressure	No increased intraabdominal pressure	Increased intraabdominal pressure may increase chemotherapy penetration into tissue
Pharmacology	Allows pharmacokinetic monitoring of tumor and normal tissue	Tissue uptake of chemotherapy cannot be determined
Abdominal incision and suture lines	Treated prior to performing the suturing	Risk of recurrence in abdominal incision and suture lines
Diaphragm perforation with peritonectomy	Pleural space treated by hyperthermic chemotherapy my prevent seeding of pleural space	Diaphragm closed prior to hyperthermic intraperitoneal chemotherapy so pleural space is not treated
Intestinal perforation	Detected by observing immersed bowel loops	Not detected
Hyperthermia	Increased heat necessary to maintain 42 °C	Less heat required to maintain 42 °C

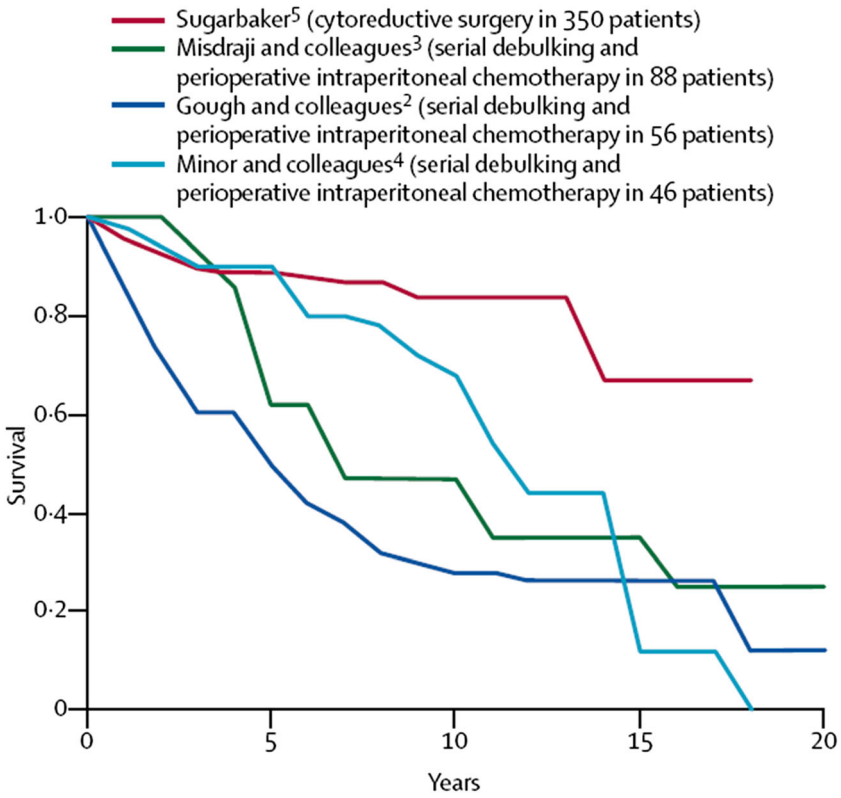

Fig. 1 Survival in patients with pseudomyxoma peritonei syndrome treated at four different institutions. Reprinted from The Lancet Oncology, Volume 7, Sugarbaker PH, "New standard of care for appendiceal epithelial malignancies and pseudomyxoma peritonei syndrome," pages 69–76, ©2006, with permission from Elsevier

Colorectal Cancer

Colorectal cancer peritoneal carcinomatosis is a result of transcoelomic invasion by the primary cancer or intraperitoneal seeding during surgical manipulation. In contrast to lymphatic, liver and pulmonary dissemination, colorectal cancer peritoneal metastases may be regarded as a local-regional extension of disease rather than a manifestation of systemic metastasis [32–34, 36••, 37, 39, 64, 65].

Management of Peritoneal Metastases Diagnosed in Follow-up

Survival benefits for peritoneal metastases from colon and rectal cancer using cytoreductive surgery and perioperative chemotherapy began to appear in publications in the 1990s. Although a small percentage of these patients had synchronous peritoneal metastases (less than 5%), a great majority had peritoneal metastases diagnosed in follow-up. In 1995, Sugarbaker and Jablonski showed a 3-year survival of 35% in patients with peritoneal metastases from colon cancer treated with cytoreductive surgery plus perioperative intraperitoneal mitomycin C and fluorouracil [63]. In 2003, Verwaal and colleagues from Amsterdam published a 3-year projected survival of 38% in 54 patients treated by cytoreductive surgery and hyperthermic intraperitoneal mitomycin C with adjuvant systemic 5-fluorouracil [111]. Shen and colleagues accumulated patients between 1991 and 2002 [112]. Seventy-seven patients with non-appendiceal colorectal cancer underwent the combined treatment. All of these early reports concluded that one-third of patients with complete resection have long-term survival and that systemic chemotherapy did not contribute to the control of peritoneal metastases.

The literature has confirmed the efficacy of the combination of cytoreductive surgery and perioperative chemotherapy to benefit patients with established colorectal peritoneal metastases have been published. Glehen and colleagues, in a multi-institutional retrospective study of 506 patients from 28 institutions, reported an overall median survival of 19.2 months in patients with peritoneal metastases from colorectal cancer treated with the combined approach [48]. Patients in whom the cytoreductive surgery was complete had a median survival of 32.4 months compared with 8.4 months in patients in whom cytoreduction was not completed ($p < 0.001$). The morbidity was 22.9% and the mortality was 4%. These investigators concluded that the therapeutic approach of combining cytoreductive surgery with perioperative intraperitoneal chemotherapy achieved long-term survival in a selected group of patients with peritoneal metastases of colorectal origin with acceptable morbidity and mortality. The complete cytoreduction was the most important prognostic indicator.

Elias and colleagues reported on colorectal peritoneal metastases in a retrospective analysis of 523 patients from 23 French-speaking centers [113]. The overall median survival

was 30.1 months and the 5-year overall survival was 27%. Eighty-four percent of the patients had a complete cytoreduction, with a median survival of 33 months. These investigators concluded that cytoreductive surgery and perioperative chemotherapy are now considered the gold standard in the French guidelines for management of peritoneal metastases. The survival of 562 patients at 10 years was 37%.

At the top of the list regarding evidence-based medicine for this treatment strategy is the phase 3 study reported by Verwaal and colleagues in 2003 [114]. The Dutch trial compared 105 patients with colorectal peritoneal metastases who were randomly assigned to receive either standard treatment with systemic 5-fluorouracil and leucovorin compared with an aggressive cytoreductive surgery with perioperative chemotherapy using hyperthermic mitomycin C. The patients in the experimental therapy arm also had systemic 5-fluorouracil chemotherapy. After a median follow-up of 21.6 months, the median survival was 12.6 months with systemic chemotherapy and 22.3 months with cytoreduction and perioperative chemotherapy ($p = 0.032$). These investigators reported that a complete cytoreduction and a limited extent of disease were important determinants of benefit. The durability of the benefit of cytoreductive surgery and perioperative chemotherapy was confirmed in a follow-up article in 2008 [115]. Currently, this treatment strategy is the standard of care in Holland and there are five regional centers of excellence open for peritoneal metastases patients.

Yan and colleagues performed a systematic review to estimate the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for patients with peritoneal carcinomatosis from colorectal carcinoma [116]. The median survival varied from 13 to 29 months, and 5-year survival rates ranged from 11 to 19%. Patients who received complete cytoreduction benefited most, with median survival varying from 28 to 60 months and 5-year survival ranging from 22 to 49%. The overall morbidity rate varied from 23 to 44%, and the mortality rate ranged from 0 to 12%.

In the 2017 National Comprehensive Cancer Network Guidelines, cytoreductive surgery and perioperative chemotherapy were included as an approved treatment option. "The panel currently believes that complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. The panel recognizes the need for (additional) randomized clinical trials that will address the risks and benefits associated with each of these modalities" [3].

Gastric Cancer

Combined peritoneal carcinomatosis and resection site disease occurs in as high as 50% of patients who recur following gastrectomy. This pattern of recurrence is most prominent in patients who have stage III or resectable stage IV disease. Xu and colleagues performed a meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for advanced gastric cancer [117]. Eleven trials involving 1161 patients were included

Table 5 Current clinical trials in peritoneal metastases from gastrointestinal cancer

Update on clinical trials in colorectal cancer
Proactive protocols
ProphyloChip: CRS and HIPEC with second-look surgery Diane Goere, MD, PhD—Villejuif, France
PRODIGE 7: adjuvant ± HIPEC for peritoneal metastases from colon cancer Francois Quenet, MD—Montpelier, France
COLOPEC: adjuvant HIPEC for primary colon cancer Pieter J. Tanis MD, PhD—Amsterdam, The Netherlands
PROMENADE: prophylactic HIPEC for primary colon cancer Paolo Sammartino, MD, PhD—Rome, Italy
Prophylactic: HIPEC for cT4 colon cancer Alvaro Arjona-Sanchez, PhD—Cordoba, Spain
Treatment Protocols
ICARus EPIC FUDR versus HIPEC after optimal cytoreductive surgery (CRS) for neoplasms of the appendix, colon, or rectum with isolated peritoneal metastasis Garrett M. Nash, MD, MPH—New York, USA
Surgery and oxaliplatin or mitomycin C in treating patients with tumors of the appendix Edward A. Levine, MD—Winston-Salem, USA
Cytoreduction and intraperitoneal chemotherapy versus systemic chemotherapy in colorectal peritoneal carcinomatosis Peter H. Cashin, MD, PhD—Uppsala, Sweden
COMBATAC: combined anticancer treatment of advanced colon cancer Pompiliu Piso, MD, PhD—Regensburg, Germany
NIPOX adjuvant intraperitoneal oxaliplatin for colorectal cancer with peritoneal metastases Francois Quenet, MD—Montpelier, France
Mitomycin C versus melphalan for HIPEC on colorectal peritoneal metastases Mazin Al-Kasspooles, MD—Kansas City, USA
Update on clinical trials in gastric cancer
GastriCHIP gastrectomy ± HIPEC as adjuvant for primary gastric cancer Olivier Glehen, MD, PhD—Lyon, France
GASTRIPEC cytoreductive surgery (CRS) with/without HIPEC in gastric cancer with peritoneal carcinomatosis Beate S. Rau, MD, PhD—Berlin, Germany
Phoenix GC neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) for gastric cancer with peritoneal metastases Hironori Ishigami, MD—Tokyo, Japan
Update on clinical trials in pancreas cancer
Resection plus HIPEC gemcitabine vs. resection alone in resectable pancreas cancer Antonios-Apostolos K. Tentes, MD—Athens, Greece
Resection plus HIPEC gemcitabine vs. resection alone to inhibit carcinomatosis of pancreas cancer origin David Padilla Valverde, MD—Ciudad Real, Spain

for data extraction. The meta-analysis indicated that hyperthermic intraperitoneal chemotherapy after resection of advanced primary gastric cancer is associated with an improved overall survival. An adequately powered trial called GastriCHIP in Western gastric cancer patients is currently in progress [118].

Conclusions: Future Prospects

Very often, the first step in finding new treatments for cancer involves studies in patients with advanced disease. A response that results in improved or prolonged life is then taken to patients with less advanced disease. Usually, this second step in development involves randomized controlled trials (RCT). Currently, cytoreductive surgery plus HIPEC is being tested in RCT for colorectal, gastric, and ovarian cancer (Table 5).

Compliance with Ethical Standards

Conflict of Interest Paul H. Sugarbaker declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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