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Theoretical Considerations for Optimal Cytoreductive Surgery Plus Hyperthermic Perioperative Chemotherapy

Domenico Sabia[1] **and Paul H. Sugarbaker**[2,*]

[1]*Hospital Sant Joan Despí - Moisès Broggi (C.S.I.), Barcelona, Spain*

[2]*Center for Gastrointestinal Malignancies, MedStar Washington Hospital Center, Washington, DC, USA*

[*]**Corresponding author:** Paul H. Sugarbaker, MD, FACS, FRCS, MedStar Washington Cancer Institute, 106 Irving St., NW, Suite 3900, Washington, DC 20010 USA, Tel: (202) 877-3908; Fax: (202) 877-8602; E-mail: Paul.Sugarbaker@medstar.net

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Abstract

Background: The concepts regarding the definitive management of peritoneal metastases seems straightforward in that surgery is to remove all visible disease and then intraperitoneal chemotherapy is used to eradicate minimal residual disease. However, implementation of this management strategy presents numerous patient-related, methodologic, and pharmacologic variables.

Methods: In order to optimize cytoreductive surgery (CRS) and hyperthermic perioperative chemotherapy (HIPEC), important theoretical considerations for implementation of this management strategy are presented. The aim of the study is to integrate these modifications in the treatment of abdominal and pelvic malignancy into practice and thereby improve outcomes.

Results: Surgical technology to achieve a complete response is necessary but not sufficient to optimally pursue a curative treatment option. Strategies to initiate treatments with the lowest possible peritoneal cancer index (PCI) involve proactive treatments of the primary gastrointestinal cancer, neoadjuvant chemotherapy, initiation of treatments at the first diagnosis of peritoneal metastases, and the use of laparoscopy and radiology to select patients. Tumor cell entrapment should be avoided. Mechanical removal of cancer cells by vigorous irrigation techniques carries minimal risk and may reduce residual disease. Chemotherapy agents that cause a response, result in prolonged intraperitoneal drug retention and show a high peritoneal to plasma concentration ratio are recommended. Finally, long-term bidirectional adjuvant normothermic chemotherapy (BANC) has been shown in randomized trials in ovarian cancer to improve survival and may be of value in other diseases.

Conclusions: Despite the complexity of patient management using CRS and HIPEC, application of six basic principles promise to contribute to the results of treatment of peritoneal metastases.

Keywords: Cytoreductive surgery; Hyperthermic perioperative chemotherapy (HIPEC); Early postoperative intraperitoneal chemotherapy (EPIC); Peritonectomy; Proactive treatment; Adjuvant HIPEC; Prophylactic HIPEC; Second-Look surgery with HIPEC

Introduction

As cytoreductive surgery (CRS) and hyperthermic perioperative chemotherapy (HIPEC) have evolved over three decades [1-8], multiple variables that have an effect on outcome have been identified. There is a universal opinion regarding the surgery that the more complete the cytoreduction, the greater the benefits that can be expected [9-12].

However, it is obvious from a survey of the literature that no standardized perioperative chemotherapy treatment currently exists.

Table 1 identifies patient-related variables for CRS and HIPEC, methodological variables for perioperative chemotherapy and itemizes the use of chemotherapy agents that are currently available for administration in the operating room [13] or in the postoperative period as early postoperative intraperitoneal chemotherapy (EPIC) [14].

Over 30 variables are listed as potential differences for the application of CRS and HIPEC. Although there may be some important clinical studies that would select the important differences in treatment, no comprehensive answers will soon be available.

The goals of this manuscript are to establish theoretical requirements for cytoreductive surgery and perioperative chemotherapy delivery.

Patient-related variables:
5 different diseases (colorectal, appendiceal, gastric, and ovarian cancer, malignant peritoneal mesothelioma)
20+ unusual indications for CRS and HIPEC
Prevention protocols
Treatment protocols
Extreme treatment protocols
Methodologic variables:
HIPEC vs. EPIC or HIPEC + EPIC
No hyperthermia (<41°C) vs. moderate hyperthermia (≥41-43°C) vs. extreme hyperthermia (>43-45°C)
Carrier solution volume - 3L vs. 1.5 L/m^2 vs. 6L
Carrier solution type - saline vs. 1.5% dextrose PDS vs. D5W vs. lactated ringer's solution vs. dextran solutions
Intraperitoneal irrigations – saline vs. distilled water vs. 0.75% peroxide vs. Betadine
Volume of intraperitoneal irrigation – Extensive intraperitoneal lavage (10 L one liter at a time) vs. other
Open vs. closed vs. Coliseum vs. Landager vs. closed then open
Timing – 30 minutes vs. 60 minutes vs. 90 minutes vs. 180 minutes
IP epinephrine vs. no epinephrine
Chemotherapy solutions vs. aerosols
Pharmacologic variables:
Route of administration – IP vs. IP and IV
Naked drugs vs. nanoparticles
Single vs. multiple drugs
Mitomycin C
Oxaliplatin
Irinotecan
Cisplatin
Doxorubicin
5-fluorouracil
Melphalan
Gemcitabine
Carboplatin
Docetaxel
Paclitaxel
Pemetrexed
Mitoxantrone

Table 1: Possible variables in the application of cytoreductive surgery and hyperthermic perioperative chemotherapy as a treatment for peritoneal metastases.

Materials and Methods

Six basic concepts that must be considered for optimal CRS and perioperative chemotherapy treatments have been selected. First, the surgical technology to achieve a complete cytoreduction needs to be incorporated into practice. Secondly, patients need to be treated at a maximal low peritoneal cancer index (PCI). Third, tumor cell entrapment, as a part of the natural history of surgically treated gastrointestinal malignancy, must be prevented. Fourth, the small volume residual disease that remain after complete cytoreductive surgery must be reduced with mechanical removal of cancer cells by irrigation. Fifth, a maximal cancer chemotherapy response by HIPEC and/or EPIC is necessary. Finally, the benefits of BANC used long-term must be considered (Table 2).

1. The surgical technology to achieve a complete cytoreduction needs to be incorporated into practice.
2. Patients must be treated at a maximal low peritoneal cancer index (PCI).
3. Patients must be managed to maximally avoid tumor cell entrapment.
4. Mechanical removal of cancer cells and small nodules by irrigation is mandatory.
5. Small volume residual disease requires chemotherapy treatment that will result in a maximal cancer response.
6. The benefits of bidirectional adjuvant normothermic chemotherapy (BANC) used long-term must be considered.

Table 2: Principles of management of peritoneal metastases.

Surgical Technology to Achieve a Complete Response Prior To Perioperative Chemotherapy

Cytoreductive surgery is the more powerful treatment for peritoneal metastases that must be initiated prior to the less robust treatment which is the perioperative chemotherapy. The cytoreductive surgery is a combination of peritonectomy procedures and visceral resections with a goal of no visible disease at the completion of the surgical event [15]. Table 3 lists the six most important peritonectomy procedures and itemizes the visceral resections most commonly required for complete cytoreduction.

Peritonectomy Procedures	Visceral Resection
Anterior parietal	Greater omentum
Right subphrenic	Spleen
Left subphrenic	Uterus and ovaries
Pelvic	Rectosigmoid colon
Omental bursa	Right colon
Mesenteric	Lesser omentum
Glisson's capsule	Stomach
	Small Bowel

Table 3: Surgical technology to achieve a complete response.

The perioperative chemotherapy strategies are, at this point in time, limited to HIPEC [16,17] and EPIC [18,19]. One should use HIPEC and EPIC in an attempt to preserve the surgical complete or near complete response that was achieved with the peritonectomy and visceral resections [20,21]. The perioperative chemotherapy has a goal of eradication of minimal residual disease on the surfaces of the abdomen and pelvis [22]. The goal of BANC is to prevent the progression of minimal residual disease on abdominal and pelvis surfaces long-term.

Strategies to Initiate Treatments with the Lowest Possible PCI

Proactive treatment used to obtain a low PCI

Perhaps the most meaningful efforts to utilize low PCI comes through proactive treatments initiated early in the natural history of gastrointestinal cancer [23,24]. Prophylactic (adjuvant) HIPEC used in selected patients at the time of primary cancer resection should theoretically result in treatment at the lowest PCI possible in the natural history of the patient's disease [25,26].

Table 4 lists the clinical and histopathologic variables that identify patients for prophylactic HIPEC or HIPEC plus EPIC. This treatment has been clinically evaluated for gastric cancer [27-30], pancreatic malignancy [31] and is a prominent strategy for comprehensive management of appendiceal or colorectal malignancy [32-35].

Also included in Table 4 is the predicted incidence of local recurrence and/or peritoneal metastases in colorectal cancer patients if they do not receive the prophylactic HIPEC or EPIC.

Clinical and Histologic Feature	Estimated Incidence of Peritoneal Metastases Observed in Follow-up (%)
1. Peritoneal nodules detected with primary cancer resection+	70
2. Ovarian metastases+	60
3. Perforation through the primary cancer (free or localized)+	50
4. Adjacent organ or structure invasion	20
5. Signet ring histology by endoscopic biopsy	20
6. Fistula formation	20
7. Obstruction of primary cancer	20
8. Positive margin of resectiono +	80
9. Positive peritoneal cytology before or after resectiono	40
10. Positive imprint cytologyo	40
11. Lymph nodes positive at or near the margin of resectiono	20
12. T3/T4 mucinous cancero	40

Table 4: Clinical and intraoperative histopathologic features of the primary colorectal cancer as an estimate of the incidence of subsequent local recurrence and/or peritoneal metastases to guide prophylactic cytoreductive surgery with perioperative chemotherapy. °Requires intraoperative histopathologic assessment by the pathologist who is a member of the multidisciplinary team.+If HIPEC was not used with primary cancer resection, second-look with perioperative chemotherapy should be considered.

Neoadjuvant chemotherapy used to induce a low PCI

A robust response (complete or near complete disease eradication) by neoadjuvant chemotherapy can better prepare a patient for CRS and HIPEC [36]. The studies of Bijelic et al. in high grade mucinous appendiceal neoplasms [37] and Glehen et al. in patients with colorectal cancer [38] suggests that a response to neoadjuvant chemotherapy is a predictor of profound benefit when CRS and HIPEC was preceded by effective neoadjuvant chemotherapy.

Neoadjuvant treatment for gastric cancer with peritoneal metastases monitored by serial laparoscopy to obtain a low PCI

Recent reports suggest that prolonged treatment of primary gastric cancer with limited peritoneal metastases with neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) monitored by serial laparoscopy, can help select patients for potentially curative gastrectomy with cytoreductive surgery. The results of Yonemura and coworkers show that approximately 30% of patients have the disease eradicated from peritoneal surfaces by NIPS [39]. He also reports that 30% of those patients who are selected for combined gastrectomy with peritonectomy can achieve a long-term survival with this otherwise devastating clinical situation [40]. Fujiwara showed improved survival in NIPS patients whose treatment caused negative intraperitoneal cytology [41]. Yamaguchi has recently initiated and reported on

treatments with intravenous and intraperitoneal paclitaxel [42]. By laparoscopic monitoring, 71% of patients had the disease visibly eradicated from their peritoneal surfaces. Although Yamaguchi did not use HIPEC when resecting residual disease on these patients, he did report approximately 30% long-term good results.

Initiate CRS and HIPEC at first diagnosis of peritoneal metastases in patients undergoing follow-up of their primary disease to keep PCI at lowest level

All too often, when peritoneal metastases are diagnosed in patients with colorectal cancer as a site of surgical treatment failure, systemic chemotherapy is initiated and then continued for an extended time period. Although a brief treatment with systemic chemotherapy may be a judicious management plan, the use of multiple cancer chemotherapy agents over a long time period is to be avoided. Patients who show in follow-up peritoneal metastases need to be brought immediately to the attention of the multidisciplinary team. Those who are potential candidates for CRS and perioperative chemotherapy should go rapidly to this treatment rather than being subjected to protracted systemic chemotherapy treatments with multiple cancer chemotherapy agents. The lack of sensitive radiologic tests by which to diagnose small volumes of peritoneal metastases makes the "watch-and-wait policy" a dangerous management plan for patients who are candidates for definitive treatment [43]. Also, patients' symptoms are not a reliable monitor of progression of a small extent of disease.

This failure of radiology of the abdomen and pelvis to adequately monitor small volume disease has been repeatedly demonstrated [43]. MRI, CT-enteroclysis, or PET-CT may diagnose recurrent intestinal-type with greater sensitivity than the routine CT but none of these tests monitor small volume peritoneal metastases [44-46].

Role of laparoscopy in patient selection for a low PCI

Accepting the fact as stated above that radiologic tests are inadequate to diagnose progression of a small extent of disease in patients with peritoneal metastases, laparoscopy has been suggested a more reliable test to better select patients for treatment [47). Valle et al. have presented data suggesting that 14% of patients undergoing a laparoscopy prior to cytoreductive surgery can be shown to have an extent of disease incompatible with complete cytoreduction [48]. Ramos et al. reported on 107 consecutive laparoscopies. They observed in 77.7% of cases a correlation between laparoscopic-PCI and the findings recorded for PCI at laparotomy [49].

Prognostic scores prior to CRS and HIPEC to select patients for complete cytoreduction and a maximal low PCI

A formula for selection of colorectal cancer patients with peritoneal metastases for treatment was proposed by Verwaal et al. [50]. Cashin and the group from Uppsala, Sweden has generated a normogram which they report minimizes the likelihood of an open and close procedure [51]. Pelz, Esquivel et al. have devised the Peritoneal Surface Disease Severity Score (PSDSS) [52,53]. They suggest that a normogram based on patient's symptoms, the CT-PCI, and the histologic assessment of the colorectal malignancy can stratify patients into four groups for benefit expected from the CRS and HIPEC.

Jacquet and Sugarbaker identified a list of concerning radiologic features for patients with mucinous colorectal and appendiceal adenocarcinoma to be used preoperatively to select patients for complete cytoreduction using the statistical tool of a decision tree analysis [54]. They determined that two radiologic features could be used to select patients for an optimal cytoreduction and exclude patients from a sub-optimal cytoreduction. Rivard et al. listed seven concerning radiologic features [55]. They also concluded that any two of these features predicted incomplete cytoreduction in a statistically significant manner whereas a single concerning radiologic feature did not. A list of concerning radiologic features identified in patients with gastrointestinal malignancy to help select patients for an optimal surgical event is shown in Table 5.

Bowel obstruction or partial obstruction at more than one site
Non-mucinous ascites
Mesentery drawn together by tumor (clumped)
Tumor infiltrating leaves of small bowel mesentery
Mesenteric or para-aortic lymphadenopathy
Hydroureter
Psoas muscle invasion
Gastric outlet obstruction
Tumor ≥ 5 cm in lesser omentum or subpyloric space
Tumor ≥ 5 cm in jejunal regions
CT-PCI > 20 (excluding pseudomyxoma peritonei)

Table 5: Concerning radiologic features as a prognostic assessment.

Optimizing CRS and Perioperative Chemotherapy by Prevention of Tumor Cell Entrapment

The concept of tumor cell entrapment was introduced by Sethna and Sugarbaker as a prominent part of the natural history of surgically treated gastrointestinal cancer [56]. The two essential features of the tumor cell entrapment are as follows: First, either prior or at the time of cancer resection, malignant cells are released into the free peritoneal cavity. Second, cancer cells implant, adhere, and then progress more efficiently at a wounded site than on an intact vascular or peritoneal surface. This is the phenomenon of metastatic efficiency within a traumatized peritoneal space as compared to metastatic inefficiency of cancer cells within vascular structures such as the liver. Cancer cells may also be stimulated by factors involved in the wound healing process when they are entrapped within a wounded site.

The tumor cell entrapment hypothesis demands that there be a respect for the peritoneum as a first line of defense against progression of peritoneal metastases. If patients with gastrointestinal malignancy show peritoneal metastases or are at high risk for the development of peritoneal metastases, special treatments should be initiated in the operating room in order to minimize the possibility for tumor cell entrapment. The tumor cell entrapment hypothesis mandates that cytoreductive surgery and perioperative chemotherapy occur as concomitant rather than sequential treatments. HIPEC should be used in the operating room immediately after extensive irrigation which follows the peritonectomies and visceral resections.

Mechanical Removal of Cancer Cells by Thorough Intraoperative Irrigation Prior to HIPEC and Perioperative Chemotherapy

In performing cytoreductive surgery for peritoneal metastases large numbers of cancer cells will be present within the ascites fluid, will be

disrupted from peritonectomy specimens, or released from resected tumor nodules on the viscera. Frequently throughout the cytoreductive surgery dissection sites should be irrigated copiously and thoroughly aspirated. This frequent irrigation is to remove blood, tissue debris and stray cancer cells. Finally, at the completion of the cytoreduction and prior to HIPEC, an irrigation with a cytotoxic non-chemotherapeutic agent should occur. Peroxide at 0.25% in 3 liters of warm saline is frequently used [57]. Others use 3 liters of distilled water [58]. Still others utilize a dilute povidone-iodine 10% solution (Betadine) [59]. Following this irrigation, many liters of warm saline should be used to thoroughly wash all of the parietal and visceral peritoneal surfaces to finalize the mechanical removal of unattached cancer cells [60].

HIPEC, Necessary but not Sufficient to Maintain the Surgical Complete Response

As listed in Table 1, there are multiple methodologies by which to administer HIPEC and there are multiple drugs that can be chosen for use in the operating room or in the perioperative period [61,62]. Those drugs that are used in the operating room with heat are acute phase drugs that can exert their effect in the absence of cell proliferation [63]. Those drugs that are used for EPIC are drugs selected because they are not augmented by heat and they require cell division for their optimal effects. Such drugs are 5-fluorouracil and paclitaxel [18,64].

Currently, a major flaw in the use of HIPEC may be the lack of drug retention within the peritoneal space. Some HIPEC regimens have assumed that a very high dose of chemotherapy delivered to the abdominal and pelvic surfaces over a short time period will achieve the necessary effect. For example, oxaliplatin instilled into the peritoneal space has a half-life of approximately 12 minutes [65]. By the end of 30 minutes of hyperthermia the drug has the same concentration as plasma.

There are currently two drugs which show prolonged retention within the abdominal and pelvic space. One of these is pegylated liposomal doxorubicin which can be administered for prolonged HIPEC and maintains a high level of drug within the abdominal and pelvic space for the entire treatment [66,67]. The area under the curve ratio of pegylated liposomal doxorubicin is 800-1200. Also, the heat will rapidly deploy the intraperitoneal doxorubicin that is contained within the nanoparticle. The second drug which has proven itself to have value in the management of peritoneal metastases is intraperitoneal paclitaxel [64]. This drug has an area under the curve ratio of 1000. Paclitaxel is used postoperatively usually at low dose over 5 days. The drug is retained within the peritoneal space for approximately 23 hours. Its local-regional effects are greatly magnified over the systemic effects. The dose of paclitaxel that is used when combined with HIPEC is usually 20 mg/m^2/day for 5 days for a total of 100 mg/m^2. Combinations of pegylated liposomal doxorubicin as HIPEC and paclitaxel as EPIC are currently being evaluated. If paclitaxel is used as a single agent, the dose can be as high as 40 mg/m^2 but this dose will cause neutropenia in patients with compromised bone marrow from long-term prior chemotherapy.

Another strategy for prolonged exposure of peritoneal metastases to cancer chemotherapy is continuous intravenous infusion during the HIPEC procedure. To heat-target disease on peritoneal surfaces, a heat-augmented drug such as ifosfamide, cisplatin or oxaliplatin can be continuously infused. The cytotoxicity of these drugs are maximized at the heated peritoneal surface [68,69].

Normothermic Intraperitoneal Chemotherapy Long-Term to Maintain the Surgical Complete Response

A sixth and final principle of management of peritoneal metastases has not as yet been well established for gastrointestinal cancer. However, BANC used long-term is potentially of great value. The major obstacle for more comprehensive utilization is the requirement for a long-term intraperitoneal port. These intraperitoneal ports are associated with a moderate to high incidence of adverse events especially when used after cytoreductive surgery. There is no doubt that BANC in ovarian cancer has shown itself to be of benefit. Alberts et al., Markman et al., and Armstrong et al., clearly demonstrated a benefit for BANC [70-72]. Armstrong et al. showed the survival of patients with peritoneal metastases from ovarian cancer was increased from 50 months to 66 months (p=0.03) [72].

Conclusions

In this revised approach to the management of peritoneal metastases the most basic principles of management for an optimal treatment strategy have been integrated. Initially, the disease within the abdomen and pelvis, including the peritoneal metastases, are resected using cytoreductive surgery. In order to facilitate this complete cytoreduction patients are treated at the lowest extent of disease as measured by the peritoneal cancer index. Unresectable disease growing out deep to the peritoneum must be prevented by avoiding tumor cell entrapment from unnecessary prior dissections beneath the peritoneum. Stray cancer cells can be removed through irrigation techniques. Free and minute cancer cells require perioperative chemotherapy for their eradication and complete eradications requires a response to the cancer chemotherapy. Finally, these combined intraperitoneal and systemic chemotherapy treatments can be continued long-term through the use of bidirectional adjuvant normothermic chemotherapy for up to six months postoperatively. The goal is to optimize treatment of abdominal and pelvic cancer through the eradication of local-regional recurrence and peritoneal metastases.

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