Theoretical Considerations for Optimal Cytoreductive Surgery Plus Hyperthermic Perioperative Chemotherapy

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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. T e 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.

T e 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]. T e perioperative chemotherapy has a goal of eradication of minimal residual disease on the surfaces of the abdomen and pelvis [22]. T e 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 e forts 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. T is 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. oRequires 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]. T e 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 bene f t when CRS and HIPEC was preceded by e f ective 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. T e results of

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

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. T is frequent irrigation is to remove blood, tissue debris and stray cancer cells. Finally, at the completion of the cytoreduction and

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