

Title: Protocol for the Implementation of Treatment of Patients with Peritoneal Surface Malignancy with Hyperthermic Intraoperative Intraperitoneal Chemotherapy and Normothermic Early Postoperative Intraperitoneal Chemotherapy.

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Number of Patients: 20  
Age: 16-80 years

Sex: male and female

Estimated duration of study: 3 years

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## Clinical Summary

Perioperative intraperitoneal chemotherapy has been shown to be of benefit to patients with limited cancer dissemination on peritoneal surfaces. Long-term survival has been shown in a variety of cancers if all visible disease is resected prior to the intraoperative intraperitoneal chemotherapy instillation. The patient is scored by the peritoneal cancer index prior to resection in an attempt to select patients most likely to benefit from these treatments. The resections of peritoneal surface cancer are accomplished by a series of parietal and visceral peritonectomy procedures that attempt to reduce the cancer burden to microscopic residual disease. Patients are treated prior to reconstructive procedures such as bowel anastomoses. The hyperthermic chemotherapy agents selected for treatment of gastrointestinal adenocarcinoma are mitomycin C and for mesothelioma and ovarian cancer cisplatin and doxorubicin. The heat and the chemotherapy solution are uniformly distributed by manual separation of all peritoneal surfaces continuously throughout the chemotherapy treatment. Patients with adenocarcinoma will also be treated with early postoperative intraperitoneal 5-fluorouracil and other patients with early postoperative intraperitoneal paclitaxel.

## Lay Summary

In the past cancer spread to the lining of the abdomen and pelvis has been regarded as a terminal condition. Systemic chemotherapy and palliative surgery have been recommended to help alleviate suffering. Recently, a curative approach appropriate for selected patients has been reported in the peer-reviewed literature. This treatment calls for the complete removal of all visible cancer from the abdomen and pelvis using a new surgical approach called "peritonectomy." Following resection, the abdominal cavity is flooded by a heated solution containing chemotherapy. During the hyperthermic chemotherapy treatment, the surgeon washes the surfaces and separates the intestines to evenly distribute the heat and chemotherapy. After the chemotherapy treatment, the intestines are sutured together in a routine fashion. In selected patients additional normothermic chemotherapy will be instilled into the abdominal cavity for the first five postoperative days.

## 1.0 Background Information

### 1.1 Rationale for an omnibus protocol

The safety of perioperative intraperitoneal chemotherapy has been established in the peer-reviewed literature at a single institution.<sup>(1)</sup> Also, the efficacy of heated intraoperative intraperitoneal chemotherapy has been established in the peer-reviewed literature.<sup>(2)</sup> However, the procedure is technically demanding and may present special risks to patients and hospital personnel as it is initiated. A steep "learning curve" is expected as the team necessary for heated intraoperative intraperitoneal chemotherapy gains proficiency. In order to standardize the technique and protect physicians, nurses and institutions during the initiation phase, a pilot protocol has been prepared and is to be approved by the institutional review board for approximately 20 patients.

### 1.2 Carcinomatosis from colorectal cancer

A significant proportion of colorectal cancer patients are diagnosed at the stage of disease when adjacent organ involvement, perforation through tumor, free cancer cells in peritoneal cavity or established peritoneal seeding are present. Zeng and colleagues<sup>(3)</sup> have demonstrated that in 24-50% of patients with curatively resected colon cancer with T3-4 tumors, carcinoma cells were detected on the serosal surface of the bowel. In the similar group of patients other investigators have detected free cancer cells in peritoneal washings in 10-25% of cases.<sup>(4-7)</sup> It also has been shown that tumor penetration of bowel in node negative cases reduces a 5-year survival by 23%.<sup>(8)</sup> Up to 40% of patients after curative surgery will experience recurrence of the disease and in 80-90% of cases this will occur within 2 years after surgery.<sup>(9,10)</sup> It is estimated that among those who relapse 35-40% will have local operative bed recurrence and/or peritoneal seeding. Operative bed recurrence will take place in 27% of cases with full thickness penetration of bowel wall and in 69% of cases with adjacent structures involvement. Peritoneal seeding was observed by Russel and colleagues<sup>(9)</sup> in 36% of cases and was associated with local recurrence in 42% of patients. In 58% of patients carcinomatosis took place in the absence of local recurrence. Peritoneal seeding is a major cause of death of colorectal cancer because it develops into carcinomatosis, intestinal obstruction and a cascade metastatic phenomenon. The median interval between primary tumor removal and development of bowel obstruction due to metastatic disease was 19 months.<sup>(10)</sup> Chu and colleagues showed a 6 month survival between the diagnosis of peritoneal carcinomatosis and death.<sup>(11)</sup> Recently Sadaghi and colleagues performed a prospective study of carcinomatosis of gastrointestinal origin and confirmed the 6 month survival statistic.<sup>(12)</sup>

There is no established definitive treatment for colorectal cancers with clinically developed peritoneal carcinomatosis. The only options available for these patients are limited palliative resection, by-pass procedures and enterostomies

with or without additional systemic chemotherapy. The effect of this treatment, resulting mainly from surgery, is short-lasting.<sup>(13-16)</sup>

In recent years it has been shown that combination of cytoreductive surgery with intraperitoneal chemotherapy has been successful in achieving long-term survival in selected patients with digestive tract malignancies.<sup>(1,2,17,18)</sup> Overall long-term results were decidedly better in the appendiceal primary group.<sup>(18)</sup> With pseudomyxoma peritonei the 10-year survival disease-free was 85%. In the colorectal cancer group complete cytoreduction and absence of distant intraabdominal metastases was associated with a 43% 5-year disease-free survival in patients with established peritoneal carcinomatosis.<sup>(17)</sup> In several pilot and phase I studies it was demonstrated that intraperitoneal hyperthermic peritoneal perfusion was associated with 18-20% 2-year survival.<sup>(19-21)</sup> A phase III study performed at the Netherlands Cancer Institute showed a median survival of 22.3 months in the group receiving combined therapy and 12.6 months with standard treatment (p=0.032). From these preliminary studies it is evident that patients whose tumors can be maximally cytoreduced with no visible or small volume of the disease left behind benefit from these combined treatments.

### 1.3 Carcinomatosis from gastric cancer

Intraabdominal spread of gastric cancer is the major site of failure after curative surgery. Local recurrence, retroperitoneal lymph node metastases, peritoneal spread and liver metastases occur in about 90% of patients with recurrent disease.<sup>(23-29)</sup> Systemic adjuvant chemotherapy and/or radiotherapy have not been shown to improve survival in randomized trials.<sup>(30,31)</sup> After extended lymphadenectomy, peritoneal carcinomatosis and liver metastasis are major sites of failure.<sup>(23-25)</sup> Recurrences at these sites are usually documented within 18 months after curative resection.<sup>(32)</sup> Overall, peritoneal spread of gastric cancer occurs in 40-50% of patients.<sup>(27-29)</sup> Clinicopathological studies demonstrated that it was more frequent in diffuse, poorly differentiated adenocarcinomas or linitis plastica (60-70%).<sup>(33-38)</sup> Contrary to that, intestinal, differentiated adenocarcinomas tended to metastasize more often hematogenously and to spread to the peritoneal surfaces in 20-30% of cases. Clinical reality is a mixed pattern of dissemination in 30-40% of all cases. The incidence of lymph node involvement has shown no definite association with cancer histology but is consistently associated with the level of stomach wall invasion.

There is no established treatment for gastric cancer with peritoneal seeding. If there is malignant contamination of the peritoneal surfaces documented, all patients die.<sup>(39,40)</sup> Recently the literature was reviewed regarding an aggressive approach to primary gastric cancer. Using gastrectomy, peritonectomy and perioperative intraperitoneal chemotherapy Sugarbaker and Yonemura concluded that the combined treatment represented a valid treatment option for this group of patients.<sup>(41)</sup>

#### 1.4 Peritoneal mesothelioma

In patients with peritoneal mesothelioma and other primary peritoneal surface malignancies the major cause of morbidity and death is tumor progression within the peritoneal cavity. Antman and coworkers demonstrated that 78% of patients with peritoneal mesothelioma die from direct complications of the disease confined to the abdomen.<sup>(42)</sup> Similar findings were reported by other investigators.<sup>(43-45)</sup> These facts provide strong rationale for intensive regional therapy. Intraperitoneal chemotherapy with cisplatin- and doxorubicin-based regimens was shown to be of benefit for control of debilitating ascites and prolongation of survival.<sup>(46-50)</sup> Markman and Kelsen stressed that, when technically feasible, there should be major tumor debulking prior to institution of intraperitoneal chemotherapy.<sup>(51)</sup>

Recently, reports from the National Cancer Institute, USA and Washington Cancer Institute show that cytoreductive surgery combined with perioperative intraperitoneal chemotherapy can result in long-term survival with peritoneal mesothelioma.<sup>(52-53)</sup> Cytoreductive peritonectomy is a major prognostic factor associated with statistically significant improvement in survival if tumor can be cytoreduced to a size compatible with penetration of intraperitoneal chemotherapy.<sup>(53)</sup> Near complete cytoreduction was associated with a median survival of 67 months. Similar survival was reported by Markman and Kelsen in a subset of 4 out of 19 patients with “optimal debulking.”<sup>(51)</sup>

Several studies suggested clinical and radiological remission in these patients. However on surgical restaging most patients with peritoneal mesothelioma never achieved a complete response. Nevertheless, these patients continue to have good quality of life, are free of ascites and maintain enteral nutrition without difficulty.<sup>(47,53)</sup>

#### 1.5 Carcinomatosis from ovarian cancer

Most women with advanced ovarian cancer die of intraabdominal progression of the disease. Standard adjuvant chemotherapy with platinum-based regimens is associated with 40 months median survival in patients with stage III disease.<sup>(54,55)</sup> In an attempt to maximize activity, chemotherapy was administered intraperitoneally in a number of investigational studies.<sup>(56)</sup> Some phase II studies suggested improved survival in patients after near complete or complete cytoreduction.<sup>(57)</sup> A randomized trial comparing intraperitoneal route of drug delivery with intraperitoneal following cytoreductive surgery for primary tumor demonstrated improved survival and fewer side effects in patients receiving intraperitoneal cisplatin.<sup>(58)</sup> Evidently even with limited intraabdominal distribution of a drug administered in the early postoperative period, the route of delivery is of major importance in tumors that tend to spread on peritoneal surfaces.

## 1.6 Sarcomatosis

Patients with abdominal or pelvic sarcoma frequently fail surgical treatment with long-term survival of only 20-30%.<sup>(59-62)</sup> These surgical treatment failures occur at the resection site and on peritoneal surfaces (sarcomatosis) in approximately 75% of patients who recur.<sup>(63,64)</sup> Early recurrences especially within the first 18 months after sarcoma resection are almost exclusively manifested as local and regional spread of sarcoma.

Systemic chemotherapy and radiation therapy are of no demonstrated benefit to abdominal and pelvic sarcoma patients either as treatment of the primary disease or with the treatment of recurrence.<sup>(65-74)</sup>

Reports that suggest favorable results with a combined treatment of sarcomatosis have been published. Berthet and colleagues used perioperative intraperitoneal doxorubicin and cisplatin along with aggressive cytoreductive surgery to achieve a 25% long-term survival.<sup>(75)</sup> Patients with limited disease progression showed a 55% 5-year survival; the benefits of the combined treatments were related to an early treatment of limited disease recurrence and a complete cytoreduction. Eroglu and colleagues have published similar results using a similar intraperitoneal chemotherapy.<sup>(76)</sup> Eilber and colleagues showed favorable results when reoperative surgery was combined with intraperitoneal novantrone.<sup>(77)</sup>

## 1.7 Summary of data regarding peritoneal surface malignancy

Data regarding the treatment of peritoneal surface malignancy can be summarized as follows. All historical controls suggest a universally fatal outcome when cancer cells exist within the peritoneal cavity either prior to or after a cancer resection. Systemic chemotherapy or radiation therapy is of no benefit either as adjuvant treatment of primary disease or in the palliation of recurrence. Numerous single institution phase II efforts show benefit but with a substantial morbidity and mortality. These favorable results are most pronounced when the combined treatments are initiated with a small volume of peritoneal surface malignancy and a complete cytoreduction occurs. No long-term survival has been reported if reoperative surgery alone or intraperitoneal chemotherapy alone was the treatment. In colorectal cancer and in gastric cancer treatment of small volume peritoneal spread along with resection of the primary cancer was associated with a superior result.<sup>(78)</sup>

## 1.8 Significance of cancer dissemination: Spread versus metastases.

Treatment for peritoneal carcinomatosis with cytoreductive surgery and intraperitoneal hyperthermic chemotherapy will not benefit all patients. Some patients with intraperitoneal spread will have concomitant or subsequent distant metastases. In these patients the effectiveness of treatment is palliative in that debilitating ascites and progressive intestinal obstruction may be averted.

Absence of extraperitoneal and unresectable liver metastases is a major requirement for a curative approach using this management.

The benefits of combined cytoreductive surgery plus heated intraoperative intraperitoneal chemotherapy may not be limited to curative treatments. Patients with debilitating ascites may have more limited goals and less aggressive treatments and yet have real benefits. Symptomatic and progressive malignant ascites unresponsive to systemic chemotherapy should be considered for treatment.<sup>(79)</sup> These patients may profit even though limited systemic or liver metastases are present. Also, patients with isolated foci of disease recurrence causing intestinal obstruction with limited systemic or liver metastasis may benefit.

## 1.9 Mechanisms of peritoneal dissemination

Peritoneal spread following “curative” surgery for cancer is due to two sources of tumor cells: free intraperitoneal cancer cells shed from serosal surfaces prior to surgery and those disseminated during surgical manipulation. The former are detected as positive peritoneal fluid cytology prior to dissection in 25-30% of patients amenable to curative resection<sup>(80-82)</sup> for gastric cancer and colon cancer.<sup>(3)</sup> This incidence is higher in patients with serosal invasion and increases progressively with extent of serosal invasion. Surgical dissection causes dramatic increase in the rate of intraperitoneal cancer cell dissection (up to 50-60%).<sup>(83)</sup> These free cancer cells were shown to be viable and able to implant.<sup>(84-85)</sup> Demonstration of cancer cells in the free peritoneal cavity of gastric cancer patients is associated with 100% cancer mortality.<sup>(39,40)</sup>

## 1.10 Tumor cell entrapment

Free intraperitoneal cancer cells become attached to peritoneal surfaces within minutes and cannot be dislodged by irrigation. They demonstrate preferable adhesion to the abraded (wound) surfaces.<sup>(86-88)</sup> Later they are entrapped by fibrin accumulations and their growth may be stimulated by healing wound growth factors.<sup>(89)</sup> Sutures used for reconstruction of gastrointestinal tract continuity may embed cancer cells within tissues. Delayed administration of antitumor therapy may have no effect on cancer cells trapped within the operative field.<sup>(89-91)</sup> Hence, a perioperative timing of adjuvant treatment aimed at prophylaxis of peritoneal carcinomatosis is of paramount importance. Prophylactic perioperative use of antibiotics is a reasonable analogy demonstrating importance of timely treatment.

## 1.11 Peritoneal-plasma barrier

- 1.11.1 The peritoneal-plasma barrier is anatomically defined by the tissue that exists between the fluid within the peritoneal cavity and the most accessible capillary bed. It causes a marked delay in the clearance of drugs from intraperitoneal fluid.<sup>(92)</sup> The rate of drug clearance is closely related to the molecular size of

the chemotherapy and its hydrophilic properties. Extensive peritonectomy causes a small increase in drug clearance. The area under the curve ratio of intraperitoneal to intravenous drug is dependent on the rate of diffusion across the peritoneal-plasma barrier and the rate of drug metabolism or excretion from the plasma.

1.11.2 The possibility of intraperitoneal chemotherapy administration as an alternative to its systemic delivery in patients with resectable gastric cancer was raised over a decade ago.<sup>(93)</sup> In six randomized studies, in patients with gastric cancer it was associated with a decreased incidence of peritoneal spread and a tendency for improved survival.<sup>(94)</sup> In another phase III randomized trial, patients with stage III gastric cancer, T3-4 tumors (serosal invasion) and N1 lymph nodes (regional resectable) had a marked survival advantage compared to those treated with surgery alone.<sup>(95)</sup>

1.11.3 As with every method of regional chemotherapy, the pharmacokinetic advantage of intraperitoneal chemotherapy is limited to the abdominal and pelvic surfaces.<sup>(96)</sup> Also, intraperitoneal chemotherapy acts mainly by direct diffusion of drug and high concentration tissue penetration is limited to 1-2 mm from the surface.<sup>(97-99)</sup> That is why perioperative intraperitoneal distribution of a drug carrying solution before adhesions are formed is crucial for its therapeutic effect.<sup>(91-93)</sup> Studies in patients with pseudomyxoma peritonei treated by cytoreductive surgery and intraperitoneal chemotherapy demonstrated that cancer tends to recur on unexposed surfaces not treated due to a compromised distribution of intraperitoneally administered drug.<sup>(100)</sup>

## 1.12 Pharmacokinetics and pharmacodynamics of intraoperative intraperitoneal chemotherapy

Duration of exposure of cancer cells to the regional chemotherapy are important for the effectiveness of intraperitoneal chemotherapy. At the same time, intraoperative administration prolongs operative time. It is obvious that duration of intraperitoneal chemotherapy should be limited to the shortest reasonable period of time. In vitro studies of human gastrointestinal cancer cells exposed to chemotherapeutic drugs for 1 hour have demonstrated that concentrations of 10 mcg/ml of mitomycin C and cisplatin produced cytotoxic effect in 70-80% of cancer cells.<sup>(101)</sup> Pharmacokinetic studies of intraoperative intraperitoneal chemotherapy demonstrated that 75% to 90% mitomycin C and cisplatin was absorbed during the first hour.<sup>(102,103)</sup> Consequently, duration of intraoperative intraperitoneal chemotherapy should be approximately one hour.

## 1.13 Hyperthermic potentiation of chemotherapy effect

There are several ways of potentiating cytotoxic effects of chemotherapy and among them is hyperthermia. It can help overcome drug resistance by increasing tissue penetration, inhibiting cell repair mechanisms and by temperature-

dependent increase in drug action.<sup>(104,105)</sup> Barlogie and co-authors observed a sharp increase in cell line cytotoxicity with simultaneous administration of mitomycin C and heat (42-43° C).<sup>(106)</sup> Wallner and Li detected the greatest cytotoxic effect with simultaneous administration of drug and heat at a 1 hour exposure.<sup>(107)</sup> Clinical experience with intraoperative hyperthermic peritoneal perfusion with chemotherapeutic drugs has been reported by several authors both as an adjuvant and palliative modality.<sup>(21,22,108,110)</sup>

#### 1.14 Rationale for manual distribution of heated chemotherapy solution

A failure analysis of intraperitoneal chemotherapy used with a closed abdomen revealed anatomic sites at increased risk for recurrence; the lesser omentum, the base of the leaves of small bowel mesentery, the pelvis and within suture lines.<sup>(100)</sup> These areas were shown to remain unstained by intraperitoneal dye studies with the abdomen closed. When dye studies were used with the abdomen open there was uniform staining of all abdominal and pelvic surfaces.

#### 1.15 Utilization of the peritoneal cancer index

The peritoneal cancer index is a quantitative prognostic indicator.<sup>(112)</sup> It is scored after the abdominal exploration with a complete lysis of adhesions. By scoring both the distribution and the mass of peritoneal surface cancer the likelihood of complete cytoreduction and long-term survival can be estimated. The peritoneal cancer index is not useful for scoring grade 1 or less tumors such as pseudomyxoma peritonei or cystic mesothelioma. The diagrams used to compute the peritoneal cancer index are shown in the Appendix.

#### 1.16 Utilization of the completeness of cytoreduction score

The completeness of cytoreduction score is another quantitative prognostic indicator.<sup>(113)</sup> It is used to score the volume of cancer in the abdomen after completion of cytoreduction. Patients with a complete cytoreduction have an opportunity for long-term survival. Incomplete cytoreduction is rarely, if ever, associated with cure. The scoring system used to assess completeness of cytoreduction is shown in the Appendix.

#### 1.17 Disclaimer regarding the non-standard treatments proposed in this protocol.

None of the therapies included in the combined treatment of peritoneal surface malignancy can be considered as standard of care at the present time. The peritonectomy procedures do not have an assigned current procedural terminology (CPT code) by the American Medical Association. The drugs used for intraperitoneal chemotherapy have never been Food and Drug Administration (FDA) approved for intraperitoneal administration or for administration with heat. The apparatus used for hyperthermic perfusion is not an FDA approved device.

## 2.0 Objectives

- 2.1 To evaluate the feasibility, morbidity and mortality of cytoreductive surgery followed by hyperthermic intraoperative intraperitoneal chemotherapy.
- 2.2 To document the patterns of failure and overall survival rates associated with cytoreductive surgery followed by intraperitoneal chemotherapy as compared to historical controls.
- 2.3 To determine the long-term effects these treatments produce in the management of malignant ascites.

## 3.0 Patient Eligibility

- 3.1 Patients with primary gastric, colorectal, small bowel, and appendiceal cancers with full thickness invasion of bowel wall, involvement of adjacent structures, positive peritoneal cytology, perforated cancer, ovarian involvement, and limited or low volume peritoneal seeding.
- 3.2 Patients with recurrent gastrointestinal cancer. This includes patients in whom complete or near complete surgical cytoreduction is possible regardless of the extent of the peritoneal seeding.
- 3.3 Patients with symptomatic malignant ascites.
- 3.4 Patients with primary ovarian cancer stage III.
- 3.5 Patients with intraabdominal recurrence of ovarian cancer after treatment failure of the primary disease.
- 3.6 Patients with peritoneal mesothelioma confined to the abdomen that can undergo complete or near complete surgical cytoreduction.
- 3.7 Patients with primary or recurrent intraabdominal sarcomas whose tumor can be resected but with a risk of intraoperative tumor spillage and consequently peritoneal sarcomatosis.
- 3.8 Pathologically proven diagnosis of malignancy by either preoperative biopsy or intraoperative frozen section examination.
- 3.9 Signed IRB-approved informed consent form which conforms to federal and institutional guidelines.
- 3.10 Age greater than 16 years.

- 3.11 Satisfactory cardiopulmonary function as evidenced by clinically acceptable risks to undergo laparotomy and respective resection. No clinical history of acute myocardial infarction within six months prior to operation (patients after revascularization procedures with satisfactory cardiac function will be included).
- 3.12 Adequate hepatic function with SGOT (AST) less than 45 IU/L and total bilirubin less than 1.3 mg/dl.
- 3.13 Satisfactory renal function with BUN and creatinine levels within normal limits.
- 3.14 Normal white blood cell (greater than 4,000 per mm<sup>3</sup>) and platelet counts (greater than 150,000 mm<sup>3</sup>).

#### 4.0 Patient Ineligibility

The presence of one or more of the following will render the patient ineligible for entry into the study:

- 4.1 Patients who are less than 16 years or greater than 80 years of age.
- 4.2 Evidence of unresectable distant disease involving liver, lymph node involvement beyond regional draining groups or other distant sites of disease. Malignant ascites will be considered peritoneal disease. Peritoneal surface malignancy is not considered distant disease.
- 4.3 Prior chemotherapy or whole abdomen radiation within one month of protocol treatments.
- 4.4 Patients with an active second malignancy regardless of site.
- 4.5 Patients with a performance status of 3 or 4.
- 4.6 Patients with psychiatric or addictive disorders which would preclude obtaining informed consent.
- 4.7 Patients with unresectable large volume peritoneal carcinomatosis in multiple abdominal regions as evident by abdominal CT or with layering of high-grade tumor on peritoneal surfaces.

## 5.0 Study Parameters

	Preoperative	Postoperative			Follow-up (as indicated)**	6 months postoperative
		Day 1-6	Week 1	Week 2		
CBC	X	X	X	X	X	
Platelet Count	X	X	X	X	X	
Lab panel	X	X	X	X	X	
PT, PTT	X	X*	Opt	Opt		
Appropriate tumor marker	X		X	X	X	X
EKG	X					
Chest X-ray	X					
CT (chest, abdomen and pelvis)	X				X	X

\*Opt = optional, as determined by clinical indications and by the P.I. until return to normal

\*\*CT of chest, abdomen and pelvis and tumor marker – q6 months or as clinically indicated.

## 6.0 Treatments Using Chemotherapy Agents

6.1 Selection of drugs for perioperative intraperitoneal chemotherapy is based on the ability of the drug(s) to produce direct cytotoxic effect within a short period of time; consequently, their action must not be cell cycle phase specific. Mitomycin C, doxorubicin and cisplatin meet this requirement. Furthermore, these drugs are potentiated by concurrent heat administration. Use of these chemotherapeutic agents in the operating room with heat is likely to achieve maximal possible cancer cell kill.

6.1.1 Mitomycin C (MMC): MMC is an antitumor antibiotic which selectively inhibits the synthesis of DNA. It was found to be more toxic to tumor cells under hypoxic conditions and with low cellular pH. MMC is non-cell-cycle specific. After intraperitoneal administration area under the curve ratio IP/IV is 20:1. Approximately 70% of the dose is absorbed from the peritoneal cavity in 1.0 hour. About 70-80% of the drug is excreted in the urine. The dose of MMC recommended for intraperitoneal administration is the same as that recommended for intravenous administration.

6.1.2 Cisplatin (CDDP): CDDP is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis- position. It has biochemical properties similar to that of bifunctional alkylating agents producing inter- and intrastrand cross-links in DNA. It is non-cell-cycle specific. Approximately 95% of the dose is absorbed from the peritoneal cavity in 1.0 hour. CDDP concentrates in the liver, kidney and intestine and is excreted by the kidneys. The dose of CDDP recommended for intraperitoneal administration is the same as that recommended for intravenous administration.

- 6.1.3 Doxorubicin (DOX): Dox is an antitumor antibiotic that binds with high affinity to DNA, inhibits its replication and RNA transcription. The drug is metabolized in the liver and excreted in bile with about 10% of urine excretion. Dox is a vesicant drug that causes a progressive necrosis of normal tissue at elevated concentration. Dose escalation studies suggest a concentration of 10 µg/ml for intraoperative heated chemotherapy.<sup>(114)</sup>
- 6.1.4 5-fluorouracil (5-FU): 5-FU is an antimetabolite of the pyrimidine analog type. It is cell cycle specific for the S-phase of cell division. Despite rather rapid clearance from the peritoneal cavity it has a large peritoneal concentration to plasma concentration ratio because of a rapid metabolism as a single pass through the liver within the portal blood. 5-FU should be withheld if liver dysfunction is suspected or a history of prior severe toxicity to intravenous 5-FU is elicited. After intraperitoneal administration the area under the curve ratio of peritoneal fluid to plasma is 250. The dose of drug recommended for bolus intraperitoneal administration is approximately 1.5 times that recommended for bolus intravenous administration.
- 6.1.5 Paclitaxel: Paclitaxel is a cytotoxic antineoplastic drug that results in tumor cell kill by producing excessive polymerization of tubulin and dysfunctional microtubules. Paclitaxel undergoes metabolism in the liver, which makes it an ideal candidate for intraperitoneal drug delivery. Agents undergoing extensive hepatic metabolism possess the greatest regional advantage with intraperitoneal instillation. Evaluation of several established cell lines has shown that the biological effects of paclitaxel depend on both duration of exposure and drug concentration; features that potentially can be optimized with intraperitoneal instillation. After intraperitoneal administration area under the curve ratio peritoneal fluid to plasma in humans is 1000. The dose of drug recommended for intraperitoneal administration is approximately twice that recommended for intravenous administration.

## 6.2 Additional regional or systemic chemotherapy treatments

- 6.2.1 Further systemic antitumor therapy is recommended for patients with lymph node positive colon cancer.
- 6.2.2 Further systemic antitumor therapy is recommended for patients with ovarian cancer.
- 6.2.3 Some patients may benefit from second look surgery, further cytoreduction and additional treatment with perioperative intraperitoneal chemotherapy.

### 6.3 Toxicities of intraoperative intraperitoneal chemotherapy

- 6.3.1 Cisplatin. The major dose-limiting toxicity of CDDP is dose-related and cumulative renal insufficiency. Other toxicities include ototoxicity, mild myelosuppression, nausea and vomiting, hair loss and peripheral neuropathy.
- 6.3.2 Mitomycin C. The toxicity of this drug includes nausea and vomiting, myelosuppression that begins 3-4 weeks after administration, pneumonitis and renal insufficiency. When given through the intraperitoneal route MMC has been associated with scarring of peritoneal surfaces. Fistulization has been seen in some patients, however control of the dose of this drug should prevent this process. The patient's total lifetime dose should not exceed 100 mg in order to avoid the hemolytic uremic syndrome which is usually a fatal complication.
- 6.3.3 Doxorubicin. The most frequent side effects of Dox are myelosuppression, alopecia and gastrointestinal symptoms. Cardiac toxicity is related to cumulative dose and peak plasma concentration. High dose intracavitary therapy was associated with sclerosing peritonitis. Administration is associated with radiation recall phenomenon. Dox is a vesicant drug that will cause progressive necrosis if high concentrations of drug are extravasated into tissue.
- 6.3.4 5-fluorouracil. The most frequent side effect of 5-FU is myelosuppression. It is usually of limited duration and its duration shortened by neutrophil stimulating agents. Genetic enzyme deficiencies causing delayed metabolism and cardiac toxicity are very rare.
- 6.3.5 Paclitaxel. The adverse side effects of perioperative use of paclitaxel are likely related to slow wound healing within the abdomen and pelvis as a result of the prolonged high local-regional concentration of drug. Although neutropenia is the dose limiting effect with intravenous administration it is rarely seen after intraperitoneal administration. Repeated intraperitoneal administration over several months may result in peritoneal inflammation and fibrosis thought to be caused by a hypersensitivity reaction. This allergic reaction has not been observed after early postoperative intraperitoneal administration.
- 6.3.6 Adverse effects associated with intraperitoneal chemotherapy include increase in abdominal pressure causing discomfort and shortness of breath, pancreatitis causing fever, chills and abdominal tenderness, chemical peritonitis manifested as abdominal pain, and leakage of chemotherapy which may require additional purse string suture.
- 6.3.7 Potential risks associated with indwelling catheters and surgical drains include hemorrhage, infection, loss of patency of catheter, fibrosis of the peritoneal

surfaces immediately adjacent to the catheter, and pain upon catheter or drain removal.

6.3.8 Potential risks of poor wound or anastomotic healing are theoretically possible but have not been shown to have an increased incidence.

6.3.9 Potential complications associated with intraperitoneal hyperthermia include tissue necrosis and stuff that may precipitate the development of intestinal fistulas or anastomotic breakdown. Slow return of bowel function requiring prolonged nasogastric drainage and potential feeding is common. Other possible side effects include thermal toxicity in the brain.

6.3.10 The heated intraoperative intraperitoneal chemotherapy will add approximately 80 minutes to the anesthesia time of the surgery.

#### 6.4 Drug treatment regimens

6.4.1 MMC 15 mg/m<sup>2</sup> – Colon, appendiceal, gastric cancer.

6.4.2 CDDP 50 mg/m<sup>2</sup> + DOX 15 mg/m<sup>2</sup> – Ovarian cancer, peritoneal mesothelioma, intraabdominal sarcoma, gastric cancer.

6.4.3 All intraperitoneal drugs used intraoperatively will be delivered in 3,000 cc of 1.5% dextrose peritoneal dialysis solution.

6.4.4 5-FU 650 mg/m<sup>2</sup> per day for 5 days in one liter of 1.5% dextrose peritoneal dialysis solution for colon and appendiceal cancer. The treatment is given as early postoperative intraperitoneal chemotherapy for the first five postoperative days.

6.4.5 Paclitaxel 20 mg/m<sup>2</sup> per day for 5 days in one liter of fluid for gastric and ovarian cancer.

#### 7.0 Operative Procedure

7.1 Eligible patients will undergo standard resection as dictated by location and stage of the primary tumor. In addition to resection of the primary tumor cytoreductive surgery with peritonectomy procedures will be performed as needed to reduce volume of residual peritoneal disease to that compatible with the action of intraperitoneal chemotherapy.<sup>(115)</sup> The goal of the procedure is that the patient is macroscopically disease-free or has low volume peritoneal disease with implants 1-2 mm in greatest dimension. The treatment strategy is designed to cure or palliate the patient with a reasonable intraoperative or postoperative risk. Peritonectomy procedures are to be used to resect implants on the parietal peritoneum. Electroevaporative surgery is used with great care to resect or debulk implants on bowel surfaces. A greater and lesser omentectomy are to be

performed on all patients as is possible in order to facilitate the distribution of chemotherapy solution to the lesser sac (omental bursa). A generous use of ileostomy is necessary to avert fistula formation and anastomotic disruption.<sup>(116)</sup> If a total gastrectomy is performed a high jejunostomy may be recommended.<sup>(117)</sup>

7.1.1 Absolute indications for a temporary ileostomy are as follows:

1. Extensive trauma to small bowel surfaces as a result of electrosurgical debridement of tumor nodules located on this organ.
2. Extensive colon resection so that an ileorectal or right colon to rectum anastomosis is necessary.
3. Prior radiation therapy to the pelvis with a colorectal anastomosis.
4. Cytoreductive surgery performed on obstructed bowel.
5. Extensive lysis of adhesions so that multiple plications of the seromuscular layer of the bowel are required.

7.1.2 Relative indications for a temporary ileostomy

1. Prior intraperitoneal chemotherapy.
2. Prior radiation therapy to the abdomen or pelvis.
3. Extensive enterolysis of adhesions required during cytoreduction.

7.2 Heated Intraoperative Intraperitoneal Chemotherapy

7.2.1 Following resection the intraoperative hyperthermic perfusion will take place. After the completion of the perfusion anastomoses will be performed and the abdomen closed in a routine fashion.<sup>(118)</sup>

7.2.2 Intraoperative hydration prior to hyperthermic perfusion will be performed by appropriate volume expansion with crystalloid and colloid solutions. Continuous intravenous infusion of low-dose dopamine (2-5 mcg/kg/min) will be initiated. Attempts will be made to maintain urine output at a minimum of 100 cc/hour during the perfusion and for at least one hour thereafter. If necessary furosemide 10-20 mg will be administered to maintain urine output.

7.2.3 Following resection four 10 mm closed-suction drains will be placed through the flanks and positioned in the upper abdomen (2) and in the pelvis (2). A Tenckhoff catheter will be placed through the abdominal wall and positioned near the resection bed to serve as an in-flow line. These temperature probes will also be placed into the abdomen and positioned in the upper, middle and lower abdomen to facilitate monitoring of the intraperitoneal temperatures during perfusion. The skin will be elevated on the intraperitoneal chemotherapy containment instrument. In addition a smoke evacuator is placed under this instrument and will be used to evacuate vapors through a charcoal filtration system. After the test of the perfusion circuit for leaks with

peritoneal dialysis solution, chemotherapeutic drugs will be added to the perfusate immediately prior to perfusion.

7.2.4 During the perfusion which will last for 1 hour, a heat circulator, heat exchanger and roller pumps will maintain continuous perfusion at a rate of approximately 1 L/min into the peritoneal cavity. The infusate will be heated to between 45° and 48°C. The temperature within the abdominal cavity will be maintained between 41° and 43°C.

7.2.5 Intraoperative management of the heated intraoperative intraperitoneal chemotherapy. The following guidelines should be followed:

7.2.5.1 The perfusion circuit is to be tested with one liter of 1.5% dextrose peritoneal dialysis solution.

7.2.5.2 The total of three liters of chemotherapy solution will be used in the abdomen and pelvis by keeping the reservoir as empty as possible but avoiding spillage. Additional fluid may be added to keep bowel loops covered by the heated chemotherapy solution.

7.2.5.3 The viscera will be separated from itself and from parietal peritoneum on a regular basis by the surgeon. Running the small bowel, lifting the right liver, finger debridement of the caudate process and omental bursa, pelvis and retroperitoneum are performed on a regular basis. All portions of bowel to be used in an anastomosis should be especially washed.

7.2.5.4 All visceral resections and peritonectomies are to be performed prior to the intraperitoneal chemotherapy treatment. Continued electroevaporation of implants from the surface of the small bowel may occur during the heated chemotherapy perfusion. All bowel anastomoses and reconstruction are to be performed after the heated chemotherapy perfusion.

7.2.5.5 The temperature at the heater/cooler should not exceed 48°C, at the heat exchanger should not exceed 46°C, at the in-flow should not exceed 43°C and at a distant site not exceed 43°C. At the end of the procedure the solution will be drained and appropriately discarded and temperature probes removed. Drains and Tenckhoff catheter will be left behind.

7.2.5.6 Continuity of gastrointestinal tract will be restored as needed and abdomen closed. In the immediate postoperative period abdominal irrigation and early postoperative 5-fluorouracil or paclitaxel will be used.

## 8.0 Morbidity and Mortality of Combined Treatment

8.1 Effects of wound healing. Intraperitoneal chemotherapy used perioperatively may compromise wound healing and reduce strength of intestinal anastomosis. In

experimental studies<sup>(119)</sup> patency of intestinal anastomoses was high and leak rates were low (3-7%) and similar to those after surgery alone. Clinical studies have not detected increased rates of anastomotic disruption.<sup>(120-123)</sup> No such increase was noticed with the use of HIIC as well.<sup>(124)</sup> In a randomized study of early postoperative (day 1-5) intraperitoneal chemotherapy an increased rate of intraabdominal septic complications without anastomotic leak was detected during the learning curve phase of the study. Incidence returned to normal as the clinicians gained experience.<sup>(122)</sup> If intraperitoneal chemotherapy was combined with cytoreductive surgery the morbidity was more associated with the extent of surgery and previous treatments, especially radiation therapy.<sup>(124)</sup>

8.2 Morbidity. The most common adverse effect was a prolonged ileus. Fistula formation, the most dangerous postoperative enteric complication after cytoreductive surgery was 4%. Hematologic toxicity was uncommon but if it did not occur it was associated with a mortality of 75%.<sup>(125)</sup> Combination of surgical intraabdominal complications such as anastomotic leak or bowel fistula and hematogenous toxicity was the most morbid type of complication that occurred in less than 2% of patients. Intraoperative abdominal hyperthermia of 43°C was associated with compromised splanchnic oxygen transport, pooling of blood in abdominal viscera, decreased mean arterial pressure, increased tissue oxygen consumption and edema of tissues.<sup>(126)</sup> Generous fluid replacement during the hyperthermia is necessary and knowledgeable anesthesia management.<sup>(127)</sup> Cisplatin and mitomycin C are toxic to the kidneys so that brisk diuresis (200 cc every 15 minutes) is maintained during treatment. Finally, intraperitoneal chemotherapy disrupts local non-specific immunity. Strict aseptic technique must be maintained intraoperatively.

8.3 Postoperative management to minimize morbidity and mortality.

8.3.1 Prolonged intestinal ileus and gastric paresis.

8.3.1.1 Nasogastric suctioning maintained until bile drainage ceases, gas per rectum or bowel movements have occurred and nasogastric output is less than 750 cc/day.

8.3.1.2 Total parenteral nutrition is maintained until the patient is able to ingest food to full caloric requirement.

8.3.2 Prolonged bladder atony after pelvic peritonectomy.

8.3.2.1 A Foley catheter is maintained for 10 days or until the patient is fully ambulatory.

8.3.2.2 Every patient has a catheterization for residual urine 8 hours after the Foley catheter is discontinued.

8.3.2.3 If the residual urine is greater than 50 ml the patient is taught intermittent catheterization.

8.3.2.4 Urinary tract infections are treated with appropriate antibiotics.

8.3.3 Prophylaxis against peripancreatitis.

8.3.3.1 A closed suction drain is left in the left upper quadrant.

8.3.3.2 If the patient becomes febrile the drainage from the left upper quadrant drains should be sent for amylase and lipase.

8.4 Safety Considerations for Operating Room Personnel

8.4.1 One liter of 1.5% dextrose peritoneal dialysis solution is circulated to test the integrity of the system before chemotherapy is added.

8.4.2 The open abdomen is covered by the intraperitoneal chemotherapy containment instrument.

8.4.3 Smoke evacuation that removes air from beneath the plastic cover and passes it through a filtration system is maintained while chemotherapy is in the abdomen.

8.4.4 Double gloves with the outer glove elbow-length and secured with adherent gauze.

8.4.5 Impervious gown.

8.4.6 Eye protection for all personnel in the operating room while the chemotherapy is in use.

8.4.7 Hazardous waste containers available.

8.4.8 Precaution labels on all biological fluids and specimens.

9.0 Evaluation of Response

9.1 Toxicity of therapy will be documented from the time of operation through treatment and follow-up for all patients. A morbidity/mortality assessment will be utilized that is specific for this protocol.

9.2 All patients will be followed to assess overall survival.

9.3 Patterns of failure will be documented to determine the effect of intraperitoneal chemotherapy on this disease.

## 10.0 Statistical Analysis

A total of 20 patients will be treated in this protocol which is a single arm, phase I/II study designed to evaluate the safety and feasibility of surgical resection combined with hyperthermic intraoperative intraperitoneal chemotherapy for locally advanced intraabdominal malignancies or intraabdominal malignancy with peritoneal seeding. Drug toxicity, patterns of failure and overall survival will be assessed. Morbidity and mortality of the combination of surgery and chemotherapy will be recorded.

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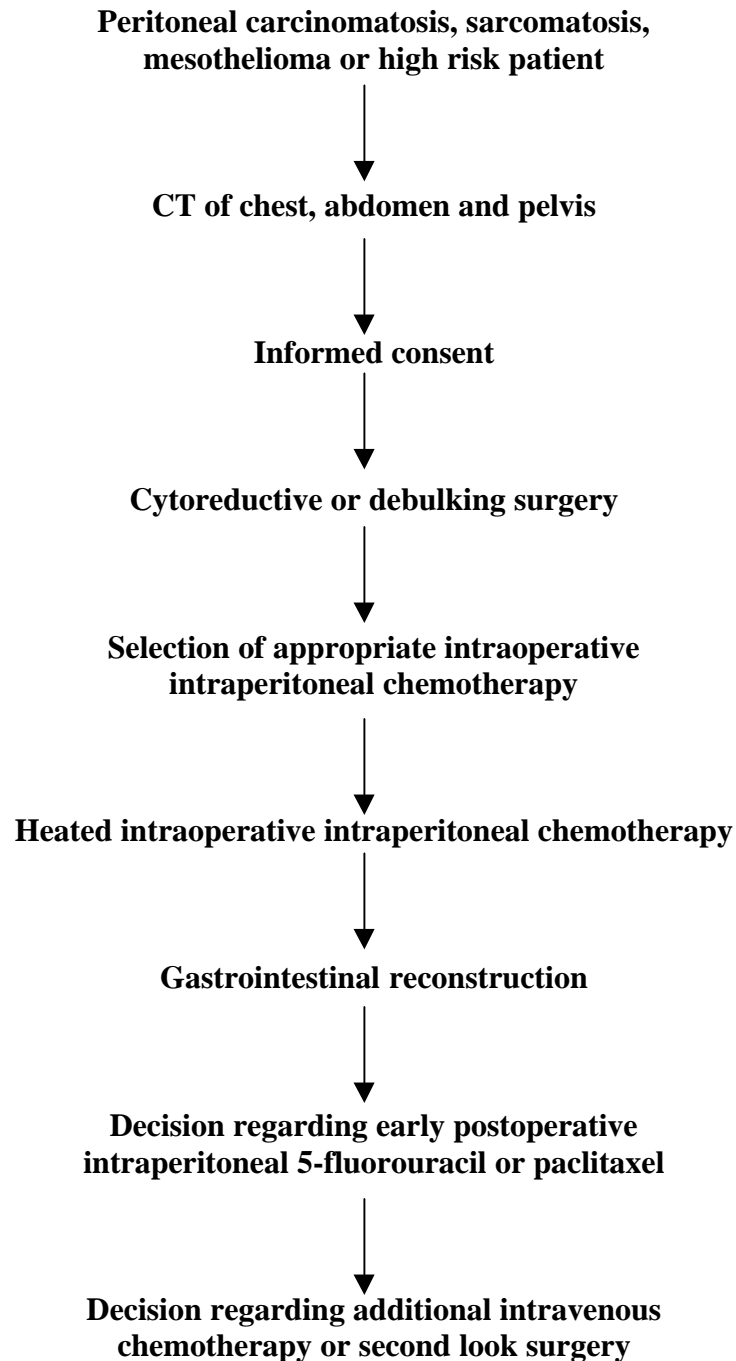
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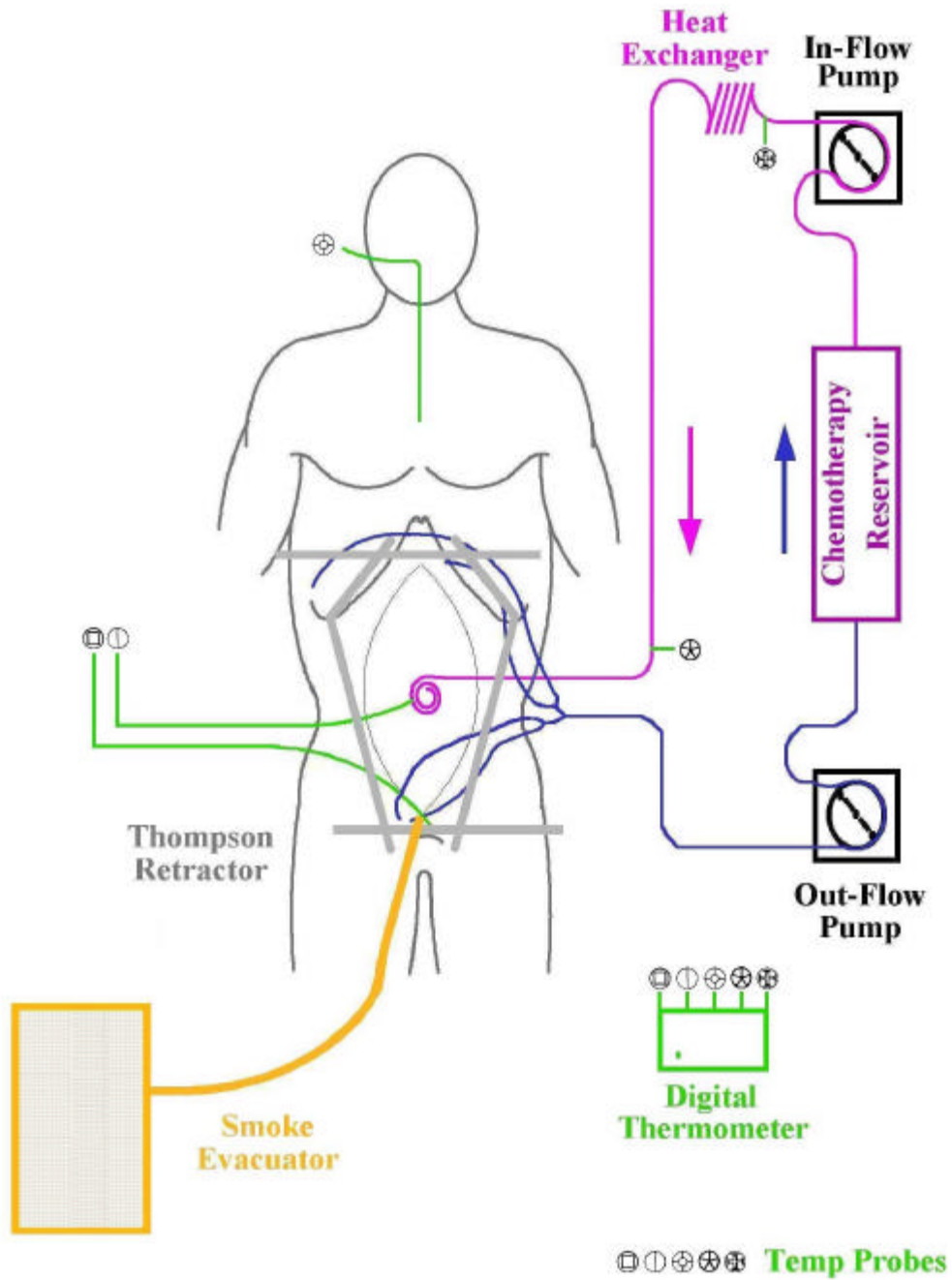
**Appendix A – Schema.**



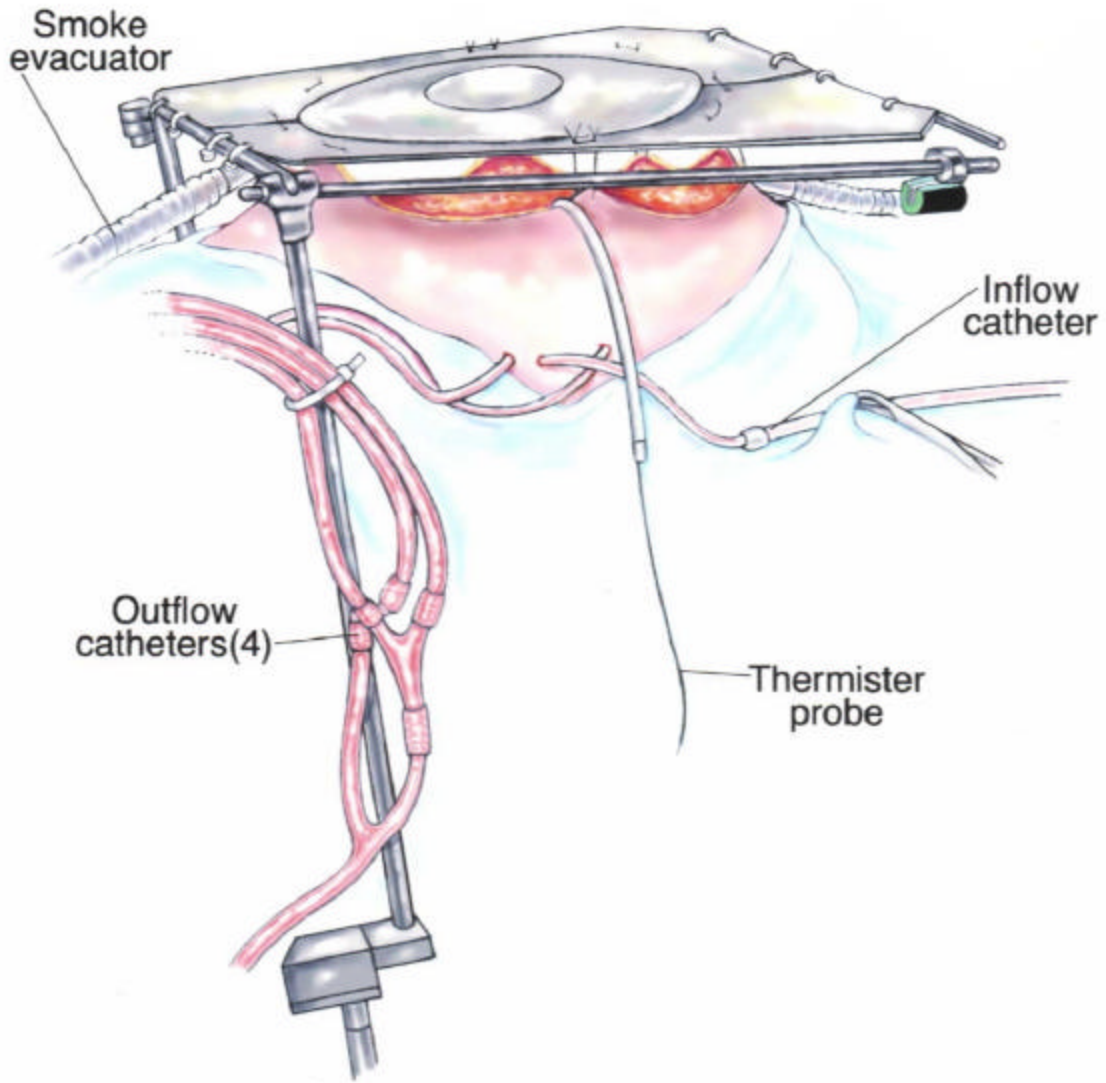
**Appendix B – Parts and price list for heated intraoperative intraperitoneal chemotherapy.**

<b>Item</b>	<b>Vendor</b>	<b>Cat#</b>	<b>Unit Price</b>	<b>Qty</b>	<b>Amount</b>	
Thermistor Thermometer	Cole-Parmer	08502-10	590.00	1	590.00	
Masterflex Rotary Pump (USA)	Cole-Parmer	P-07553-70	495.00	2	990.00	
Masterflex Pump Head (USA)	Cole-Parmer	P-77201-60	225.00	2	450.00	
Masterflex Rotary Pump (Europe)	Cole-Parmer	P-07552-75	495.00	2	990.00	
Masterflex Pump Head (Europe)	Cole-Parmer	P-77201-60	225.00	2	450.00	
Heating Circulator	LTD laboratory Equipment Div.	DC-10	1745.00	1	1745.00	
20" straight arm	Thompson Surgical Instruments	SN44120N	227.00	2	454.00	
Power rail clamp	Thompson Surgical Instruments	41950	550.00	2	1100.00	
Hinged rods 21" x 21"	Thompson Surgical Instruments	44733B	405.00	2	810.00	
Universal joint ½" x ½"	Thompson Surgical Instruments	42110N	285.00	4	1140.00	
HIIC Chemo Pack	Cobe	027606-210	195.00	1	195.00	
Heat Exchanger Holder	Cobe	050305000	247.00	1	247.00	
Reservoir Holder	Terumo	8CXHLVRA	450.00	1	450.00	
Mon-a-therm Temp Probe Cable	Mallinckrodt	502-0400	60.00	5	300.00	
Temperature probe @ heat exchanger	Lifestream	74868UG88U	257.00	1	257.00	
Closed Suction Catheter	Zimmer	2567-000-10	12.67	4	50.68	
Tenckhoff Catheter	Quinton Instrument Co.	11313-0009	61.51	1	61.51	
Esophageal Temp Probe	Respiratory Support Products	ES400-18	2.70	5	13.50	
#2 Nylon Suture 60"	Ethicon	825G	2.40	2	4.80	
Smoke Evacuator	-----	-----	-----	1	2000.00	Approx.
Biogel Gloves	Regent	-----	89.00	1	89.00	50/box
Perry X-tenda Cuff Gloves	Smith & Nephew Perry	-----	16.00	1	16.00	25/box
6-outlet electrical strip	Wiremold	WMUL206BD	28.5	1	28.5	
Stainless steel cart	Lakeside Manufacturing	331				
IV Pole	Automated IV Systems	6001	45.00	1	45.00	
IV Pole - cart clamps	Guild Medical Services	-----	5.00	2	10.00	
Stainless steel cart	Fisher Scientific	11-926-50	250.00	1	250.00	
Lock strap	FSI Fastening Solutions	MRV-124	5.27	1	5.27	
Water fitting	Cobe	050114-000	8.00	2	16.00	
Worm gear clamps	Gold Seal	MM 4 SS	0.50	8	4.00	
3/8 x 3/32 plastic tubing						
1/2 x 3/32 plastic tubing						
Adapter 1/2 to 3/8	Sea Fit	1856483	0.50	2	1.00	

**Appendix C – Perfusion circuit for heated intraoperative intraperitoneal chemotherapy.**

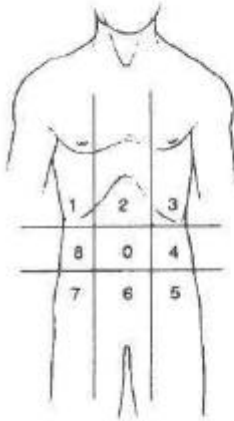


**Appendix D – Intraoperative intraperitoneal chemotherapy containment instrument.**



Appendix E – Peritoneal cancer index.

## Peritoneal Cancer Index



**Regions**

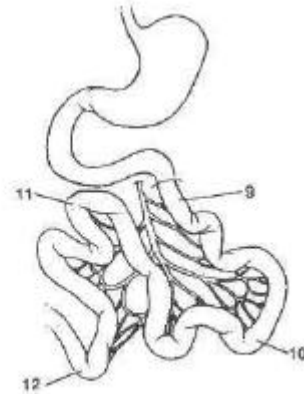
- 0 Central
- 1 Right Upper
- 2 Epigastrium
- 3 Left Upper
- 4 Left Flank
- 5 Left Lower
- 6 Pelvis
- 7 Right Lower
- 8 Right Flank
- 9 Upper Jejunum
- 10 Lower Jejunum
- 11 Upper Ileum
- 12 Lower Ileum

**Lesion Size**

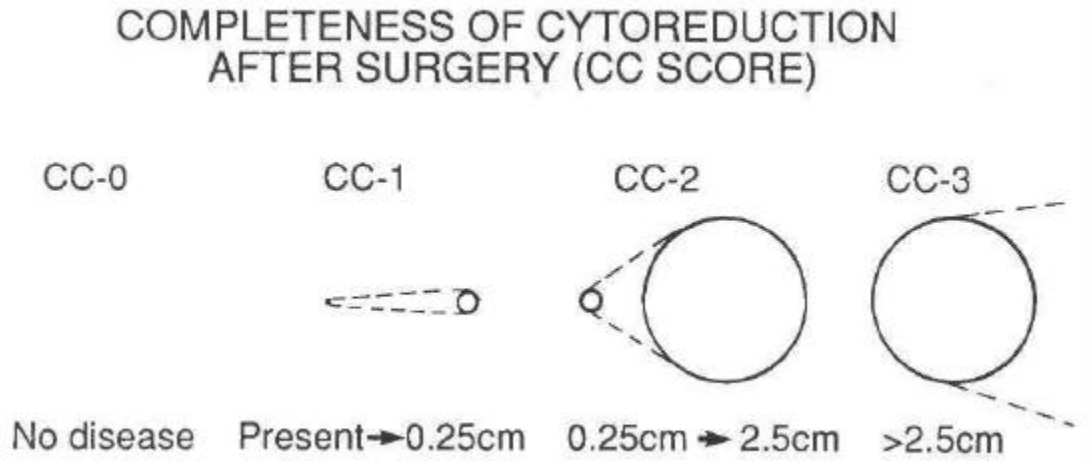
**Lesion Size Score**

- LS 0 No tumor seen
- LS 1 Tumor up to 0.5 cm
- LS 2 Tumor up to 5.0 cm
- LS 3 Tumor > 5.0 cm or confluence

**PCI**



**Appendix F – Completeness of cytoreduction score.**



**Appendix G – GI oncology morbidity/mortality database.**

<b>GRADE</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>
	<b>Asymptomatic diagnosis</b>	<b>Symptomatic minimal intervention</b>	<b>Invasive intervention</b>	<b>Major intervention, return to OR</b>
<b>GASTROINTESTINAL</b>				
Anastomotic Failure	Subclinical, no Tx, afebrile, radiologic DX	Antibiotics, febrile	Percutaneous drainage	Re-operation
Fistula	Subclinical, no Tx, afebrile, radiologic DX	Antibiotics, febrile	Percutaneous drainage	Re-operation
Pancreatic Fistula	Elevated enzymes in JP, no Tx required	TPN and Somatostatin	Non-operative invasive drainage	Re-operation
Pancreatitis	Elevated enzymes, (-) radiology, no systemic inflammation	Elevated enzymes, $\leq 3$ Ranson's score febrile, pain	Percutaneous drainage, organized collection, 4-6 Ranson's score	Re-operation
Bile Leak from Liver Surface	Bile only in JP, afebrile	Bile in JP, febrile	Percutaneous drainage	Re-operation
Hartmann Pouch Blow-Out	Afebrile, no Tx	Febrile	Percutaneous drainage	Re-operation
Enterostomy Tube Complication	Skin irritation at entrance site	Tube replaced on floor	Interventional radiology replacement, infection	Abscess formation
Oral	Soreness/erythema	Erythema, ulcers can eat solids	Ulcers; requires liquid diet only	Alimentation not possible
Nausea/Vomiting	Nausea	Transient vomiting	Vomiting requiring therapy	Intractable vomiting
Diarrhea	Transient < 2 days	Tolerable, but > 2 days	Intolerable, requiring IV therapy	Dehydration prolonged IV therapy
Ascites	Mild	Abdominal distention	Symptomatic, requiring tap	Compromising vital function
Other GI	I s c h e m i c B o w e l			

**Appendix G (continued)**

**GRADE**

**1**  
Asymptomatic  
diagnosis

**2**  
Symptomatic minimal  
intervention

**3**  
Invasive  
intervention

**4**  
Major intervention,  
return to OR

**PULMONARY**

Respiratory Distress	Mild symptoms; O <sub>2</sub> required only	Moderate symptoms Medications required (i.e. Lasix, Albuterol, etc.)	Transfer to ICU	Endotracheal Intubation
Pleural Effusion	Asymptomatic	Symptomatic, diuretic required	Thoracentesis required	Compromised respiratory function requiring chest tube
Pneumonia	Only antibiotics required	Antibiotics and Respiratory Therapy	Bronchoscopy	Intubation required
ARDS	Mild symptoms; supportive care required only	Respiratory failure requiring moderate respiratory support	Prolonged respiratory failure requiring return to ICU	Persistent respiratory failure requiring tracheostomy, chest tubes, and/or independent lung ventilation
Chest Tube Removal	Radiologic DX, no Tx required	Heimlich valve required	Chest tube required	Tension pneumothorax

**Appendix G (continued)**

<b>GRADE</b>	<b>1</b> Asymptomatic diagnosis	<b>2</b> Symptomatic minimal intervention	<b>3</b> Invasive intervention	<b>4</b> Major intervention, return to OR
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**CARDIOVASCULAR**

Rhythm	Sinus tachycardia, > 150 at rest	Arrhythmia, medical management	Interventions required	ICU care
Hypotension	Asymptomatic orthostatic	Responds to fluids	Requires & responds to pressors	Unresponsive to pressors
Ischemia	Ischemic EKG changes	Mild angina	Severe angina	Myocardial infarction
Pulmonary Embolism	(+) VQ scans,	Hypoxemia; ICU required	ICU required with intubation	Cardiovascularly, unstable
Thrombophlebitis	Cellulitis only	Cellulitis plus lymphangitis	Cellulitis plus bacteremia	Cellulitis plus septicemia
Venous Thrombosis	Swelling plus doppler evidence of clot	Extremity only	Extremity into trunk	Phlegmasia
Pulmonary Edema	Reduce fluids	Diuretic therapy	Abnormal blood gases, respiratory distress	Intubation
5-FU toxicity	D/C 5-FU	Diuretics and CV medications	CHF	Transfer to ICU
Hypertension	Asymptomatic	Diuretics and medications	Monitored medications	Transfer to ICU

## Appendix G (continued)

<b>GRADE</b>	<b>1</b> Asymptomatic diagnosis	<b>2</b> Symptomatic minimal intervention	<b>3</b> Invasive intervention	<b>4</b> Major intervention, return to OR
--------------	---------------------------------------	---	--------------------------------------	---

### GENITOURINARY

Urinary Tract Infection	Asymptomatic bacteriuria	Bacteriuria with symptoms	Bacteriuria with elevated temperature or WBC	Bacteriuria with positive blood cultures
Urine Leak	Asymptomatic	prolonged tube or stent placement	Percutaneous drainage	Return to OR

### HEMATOLOGICAL (Record most abnormal test results)

Hemoglobin	9.5 - 10.9	8.0 - 9.4	6.5 - 7.9	< 6.5
WBC/mm <sup>3</sup>	4000 - 3000	2999 - 2000	1999 - 1000	< 1000
Platelets (1000)	75 - 99	50 - 74	25 - 49	< 25
Post Op Hemorrhage	Blood in JP, no replacement	≤ 4 units	> 4 units	Re-operation

### NEUROTOXICITY

State of Communication	Transient lethargy	Somnolence < 50% of waking hours	Somnolence > 50% of waking hours	Coma
Orientation/Intellect	Oriented but with mild confusion	Mild disorientation but able to care for self	Disorientation requiring help with activities of daily living	Grossly disoriented, combative, psychotic
Stroke	TIA	RIND	Stroke, permanent disability	Stroke, systemic symptoms

### SKIN

Allergic	Urticaria	Bronchospasm; no parenteral therapy required	Bronchospasm; parenteral therapy	Anaphylaxis
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### INFECTION

Intraabdominal Infection	Minimal symptoms, intraabdominal accumulation	Prolonged antibiotics	Requires interventional radiology	Re-operation
Wound Infection	Cellulitis and swelling only	A few sutures removed	Open wound	Re-operation

**Appendix G (continued)**

**GRADE**

**1**  
Asymptomatic  
diagnosis

**2**  
Symptomatic minimal  
intervention

**3**  
Invasive  
intervention

**4**  
Major intervention,  
return to OR

**INTRAVENOUS  
CATHETER STATUS**

Line Sepsis	Entrance site only	Positive cultures, Elective line removal	Bacteremia requiring urgent line removal	Septic shock with cardiovascular collapse
Line Thrombosis	Swelling, minor	Swelling, moderate pain	Anticoagulation therapy required	Clot lysis required
Insertion Pneumothorax	Radiology (+) only; no Tx required	Chest tube required	Chest tube with persistent air leak ( $> 48^\circ$ )	Tension pneumothorax
TNA Intolerance	Mild	Moderate	Severe	Requires discontinuation

**INTRAPERITONEAL CATHETER**

Tenckhoff	Swelling, minor pain, or leakage	Moderate pain, infection	Removal required due to pain or infection	Skin loss or peritonitis
-----------	-------------------------------------	-----------------------------	---	-----------------------------

**TUBES/DRAINS**                      **Location**                      **Date In**                      **Date Out**                      **Morbidity (Yes, No)**

Nasogastric				
Endotracheal Tube				
Subclavian				
Jugular				
Chest Tube Right				
Chest Tube Left				
Foley				
Tenckhoff				
Other	Home on TPN			
Other				

**Appendix H – Intraoperative heat monitoring sheet.**

**HIIC Worksheet**

Patient: \_\_\_\_\_

Date: \_\_\_\_\_

Initials: \_\_\_\_\_

MR #: \_\_\_\_\_

Dose: \_\_\_\_\_

Height: \_\_\_\_\_

Weight: \_\_\_\_\_

BSA: \_\_\_\_\_ meter<sup>2</sup>

Minutes	1 LUQ	2 RUQ Tenckhoff	3 Midabdomen	4 Pelvis	5 Heating Circulator	Esophageal
0						
3						
6						
9						
12						
15						
18						
21						
24						
27						
30						
33						
36						
39						
42						
45						
48						
51						
54						
57						
60						
63						
66						
69						
72						
75						
78						
81						
84						
87						
90						

**Urine Volume**

15' \_\_\_\_\_  
 30' \_\_\_\_\_  
 45' \_\_\_\_\_  
 60' \_\_\_\_\_  
 75' \_\_\_\_\_  
 90' \_\_\_\_\_

**Total Urine  
Volume:**

\_\_\_\_\_

**Final Perfusate  
Volume:**

\_\_\_\_\_

## Appendix I – Standardized orders.

### Standardized orders for heated intraoperative intraperitoneal chemotherapy

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#### Mitomycin Orders

1. For pseudomyxoma peritonei and adenocarcinoma from appendiceal, colonic, and rectal cancer; add mitomycin \_\_\_\_\_ mg to 2 liters of 1.5% dextrose peritoneal dialysis solution. Dose of mitomycin for males 12.5 mg/m<sup>2</sup>; dose of mitomycin for females 10 mg/m<sup>2</sup>.
2. Use 33% dose reduction for heavy prior chemotherapy, marginal renal function, age greater than 60, extensive intraoperative trauma to small bowel surfaces, or prior radiotherapy.
3. Send 1 liter of 1.5% dextrose peritoneal dialysis solution to test the perfusion circuit.
4. Send 1 liter of 1.5% dextrose peritoneal dialysis solution for immediate postoperative lavage.
5. Send the above to operating room \_\_\_\_\_ at \_\_\_\_\_ o'clock.

#### Cisplatin and Doxorubicin Orders

1. For gastric and ovarian cancer, mesothelioma and sarcoma; add cisplatin \_\_\_\_\_ mg to 2 liters of 1.5% dextrose peritoneal dialysis solution. Dose of cisplatin 50 mg/m<sup>2</sup>.
2. Add doxorubicin \_\_\_\_\_ mg to same 2 liters of 1.5% dextrose peritoneal dialysis solution. Dose of doxorubicin 15 mg/m<sup>2</sup>.
3. Use 33% dose reduction for heavy prior chemotherapy, marginal renal function, age greater than 60, extensive intraoperative trauma to small bowel surfaces, or prior radiotherapy.
4. Send 1 liter of 1.5% dextrose peritoneal dialysis solution to test the perfusion circuit.
5. Send the above to operating room \_\_\_\_\_ at \_\_\_\_\_ o'clock.

**Appendix I (continued)**

Immediate postoperative abdominal lavage

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**Day of Operation:**

1. Run in 1000 ml 1.5% dextrose peritoneal dialysis solution as rapidly as possible. Warm to body temperature prior to instillation. Clamp all abdominal drains during infusion.
2. No dwell time.
3. Drain as rapidly as possible through the Tenckhoff catheter and abdominal drains.
4. Repeat irrigations every 1 hour for 4 hours, then every 4 hours until returns are clear; then every 8 hours until chemotherapy begins.
5. Change dressing covering Tenckhoff catheter and abdominal drain sites using sterile technique once daily and prn.

## Appendix I (continued)

### INSTRUCTIONS FOR EARLY POSTOPERATIVE INTRAPERITONEAL CHEMOTHERAPY

#### Post-op Days 1-5:

#### 5-FLUOROURACIL

1. 5-FU \_\_\_\_\_ mg ( $650 \text{ mg/m}^2 \times \text{_____ m}^2$ ) (maximum dose: 1400 mg), and 50 meq sodium bicarbonate in \_\_\_\_\_ cc 1.5% dextrose peritoneal dialysis solution via IP catheter on \_\_\_\_\_.  
Last dose \_\_\_\_\_.
2. Infuse as rapidly as possible via Tenckhoff catheter. Dwell for 23 hours and drain for one hour prior to next instillation.
3. Use 1 liter 1.5% dextrose peritoneal dialysis solution for body surface 1 - 2 m<sup>2</sup>, 1.5 liters for body surface > 2.0 m<sup>2</sup>.
4. Continue to drain abdominal cavity after last dose until Tenckhoff catheter is removed.
5. During initial 6 hours after chemotherapy infusion, patient's bed should be kept flat. The patient should be on the right side during infusion. Turn at ½-hour post infusion onto the left side and continue to change sides at ½-hour intervals for 6 hours.
6. Monitor with pulse oximeter during the first 6 hours of intraperitoneal chemotherapy.
7. Remove venous compression boots during first 6 hours after chemotherapy administration to facilitate turning.

#### PACLITAXEL

1. Paclitaxel \_\_\_\_\_ mg ( $20\text{-}40 \text{ mg/m}^2 \times \text{_____ m}^2$ ) (maximum dose: 80 mg) in \_\_\_\_\_ cc 1.5% dextrose peritoneal dialysis solution via IP catheter on \_\_\_\_\_.  
Last dose \_\_\_\_\_.
2. Infuse as rapidly as possible via Tenckhoff catheter. Dwell for 23 hours. Drain from Tenckhoff x 15 minutes before draining all catheters for one hour prior to next instillation.
3. Use 1 liter perfusate for body surface 1 - 2 m<sup>2</sup>, 1.5 liters for body surface > 2.0 m<sup>2</sup>.
4. Continue to drain abdominal cavity after last dose until Tenckhoff catheter is removed.
5. During initial 6 hours after chemotherapy infusion, patient's bed should be kept flat. The patient should be on the right side during infusion. Turn at ½-hour post infusion onto the left side and continue to change sides at ½-hour intervals for 6 hours.
6. Monitor with pulse oximeter during the first 6 hours of intraperitoneal chemotherapy
7. Remove venous compression boots during first 6 hours after chemotherapy administration to facilitate turning.

**Appendix J – Data Collection Sheet.**

**Gastrointestinal Oncology  
Patient Database**

ICD Database \_\_\_\_\_  
PTS Database \_\_\_\_\_

Name: \_\_\_\_\_

Medical Record #:

Op Date: \_\_\_ / \_\_\_ / \_\_\_

Primary or Recurrent Cancer?

Group:	1	2	3	4	5
MTG:	1	1.5	2	3	4
LS:	1	2	3		

Completeness of Resection : CC0 CC1 CC2 CC3

Site of Primary: \_\_\_\_\_, ICD · 9 · CM \_\_\_\_\_

Metastases: Yes No

Prior Surgical Score: \_\_\_\_\_

0	No prior surgery or biopsy only	
1	Exploratory laparotomy or minor cytoreduction (1 region only)	1.5 Expl Lap + HIIC
2	Moderate cytoreduction (2-5 regions)	2.5 Moderate Cyto + HIIC
3	Extensive cytoreduction (>5 regions)	3.5 Extensive Cyto + HIIC

IDC Induction Chemotherapy: \_\_\_\_\_ cycles

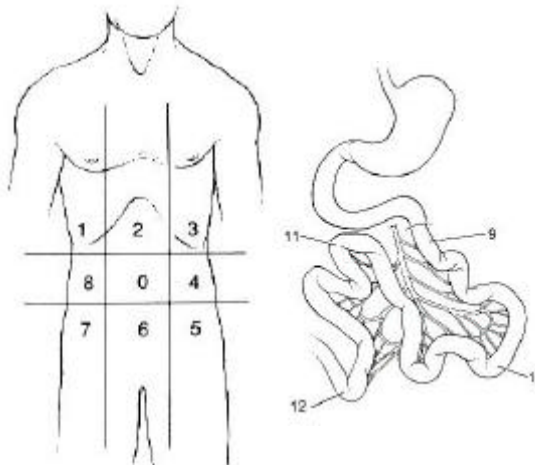
IOC Intraoperative Chemotherapy: HMC HPC HMP HPD HPAM  
Mitomycin C Cisplatin MMC+CDDP CDDP+Doxo CDDP+Doxo+MMC  
 HG HMTA  
Gemcitabine MTA

POC Postoperative Normothermic Chemotherapy: MMC + 5-FU, 5-FU, PD

HI\_\_: Postoperative Heated: CDDP + DOX\_\_\_cycl, 5-FU\_\_\_cycl, Gem\_\_\_cycl, MMC\_\_\_cycl

- Regions
- 0 Central
  - 1 Right Upper
  - 2 Epigastrium
  - 3 Left Upper
  - 4 Left Flank
  - 5 Left Lower
  - 6 Pelvis
  - 7 Right Lower
  - 8 Right Flank
  - 9 Upper Jejunum
  - 10 Lower Jejunum
  - 11 Upper ileum
  - 12 Lower Ileum

At Exploration



Regions Post Exploration

- 0 Central
- 1 Right Upper
- 2 Epigastrium
- 3 Left Upper
- 4 Left Flank
- 5 Left Lower
- 6 Pelvis
- 7 Right Lower
- 8 Right Flank
- 9 Upper Jejunum
- 10 Lower Jejunum
- 11 Upper ileum
- 12 Lower Ileum

PCI

PCI

Address:

City: \_\_\_\_\_ State: \_\_\_\_\_ Zip: \_\_\_\_\_

Home Phone:

Sex: \_\_\_\_\_ DOB: \_\_\_ / \_\_\_ / \_\_\_ Race: \_\_\_\_\_ Title: \_\_\_\_\_

## Appendix I (continued)

## International Classification Disease<sup>9</sup>

1. Use peritoneal carcinomatosis groups if possible.
2. Use XXX.9 for GI primary cancers when precise location is unknown.
3. If patient presents with multiple processes, choose the classification with the worst prognosis.

### 153.5 APPENDICEAL MALIGNANCY

#### Groups

00.0	Mucocoele
01.0	Pseudomyxoma peritonei, complete cytoreduction
02.0	Pseudomyxoma / carcinoma hybrid (MTG 1.5), complete cytoreduction
02.0	Carcinoma, no metastases, complete cytoreduction
03.0	Lymph node or liver metastases, complete cytoreduction
04.0	Incomplete cytoreduction
05.0	Distant disease
06.0	Inoperable peritoneal carcinomatosis
07.0	Adenocarcinoid
08.0	Carcinoid

### STOMACH

151.0	Gastric cardia
151.1	Pylorus
151.2	Pyloric antrum
151.3	Fundus of stomach
151.4	Body of stomach
151.5	Lesser curvature
151.6	Greater curvature
151.9	Site unknown

### SMALL INTESTINE

152.0	Duodenum
152.1	Jenunum
152.2	Ileum
152.3	Meckel's diverticulum

### COLON

#### Groups

01.0	carcinomatosis, complete cytoreduction
02.0	carcinomatosis, lymph node or liver metastases, complete cytoreduction
03.0	carcinomatosis, incomplete cytoreduction
04.0	carcinomatosis, extra-abdominal distant disease

153.0	Hepatic flexure
153.1	Transverse colon
153.2	Descending colon
153.3	Sigmoid colon
153.4	Caecum
153.5	Appendix
153.6	Ascending colon
153.7	Splenic flexure
153.9	Site unknown

### RECTOSIGMOID → ANUS

154.0	Rectosigmoid
154.1	Mid-rectum
154.2	Anal canal
154.9	Site unknown

### LIVER - GALL BLADDER - BILE DUCTS

155.0	Liver primary
155.1	Intrahepatic bile duct
156.0	Gallbladder
156.1	Hepatic duct
156.2	Ampulla of Vater

### PANCREAS

157.0	Head of pancreas
157.1	Body of pancreas
157.2	Tail of pancreas
157.3	Pancreatic duct

### PERITONEUM

158.8	Spec. part of peritoneum and origin not determined
158.9	Peritoneum unspecified, mesothelioma

### GYN

179.0	Uterus, unspecified
180.0	Cervix uteri
182.0	Corpus uteri
183.0	Ovary

### SARCOMA

171.0	Head, face, neck
171.2	Upper limb, shoulder
171.3	Lower limb, hip
171.4	Thorax
171.5	Abdominal wall
171.6	Pelvis

152.8	Sarcoma small bowel
151.9	Sarcoma stomach

158.0	Retroperitoneum
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### LIVER

197.4	Small bowel to liver
197.5	Colorectal to liver
197.6	Sarcoma to liver
197.8	Other GI to liver
155.0	Liver primary