Chapter

CYTOREDUCTIVE SURGERY AND HYPERThERMIC INTRAPERITONEAL CHEMOTHERAPy FOR MUCINOUS TUMORS OF THE GASTROINTESTINAL TRACT

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ABSTRACT

The peritoneal cavity is the largest potential space in the body. With its own lymphatic system and vascularization, it is critical to appreciate the biology of the peritoneum to better understand how disease may spread. For example, benign or low-grade malignancies may spread along the peritoneal surface by exploiting the lymphatic flow patterns of peritoneal fluid. Any pathological process involving the peritoneal cavity can easily disseminate throughout this space by means of unrestricted movement of fluid and cells. These varied mechanisms of disease spread necessitate a range of therapeutic options including intraabdominal chemotherapeutic options.

In the past, cancer dissemination to peritoneal surfaces (carcinomatosis) was universally a lethal condition with a very limited survival. Peritoneal cavity metastasis (carcinomatosis) constitutes 10-12% of colorectal cancer metastases, 40% of gastric cancer metastases and 75% of ovarian metastases. This chapter discusses the peritoneal surgical treatment options for peritoneal tumors and carcinomatosis. Cytoreductive surgery (CRS) entails removing all visible disease within the abdomen. This is followed by administration of hyperthermic intraperitoneal chemotherapy (HIPEC). CRS/HIPEC has become a well-recognized, standardized method in a select patient population for treatment of carcinomatosis. An approach to this treatment strategy is detailed in this chapter. Though CRS/HIPEC by experienced surgeons has increased survival for patients with primary peritoneal cancers and peritoneal metastases, multimodality options are continuing to evolve.
INTRODUCTION

The metastatic progression of malignant tumors of the gastrointestinal tract can occur by different mechanisms, including the hematogenous, lymphatic, and peritoneal surface routes. Benign or low-grade malignancies may also spread along the peritoneal surface by exploiting the flow patterns of peritoneal fluid. These varied mechanisms of disease spread necessitate a range of therapeutic options beyond the rote administration of systemic cytotoxic drugs. When cancers metastasize by the hematogenous and lymphatic routes, it is logical and intuitive to administer intravenous chemotherapies to achieve direct cytotoxic effects. However, when cancers progress exclusively or predominantly within the peritoneal cavity, the direct exposure of intravenous drug to tumor volume is limited; thus the cytotoxic effects are often suboptimal. Indeed, patients with predominance of peritoneal carcinomatosis, in contrast to visceral metastasis, often have poorer rates of overall survival because of the lower efficacy of systemic therapies in that setting [1]. Therefore, patients with peritoneal surface disease may benefit from a therapeutic approach that directly addresses its unique mechanism of disease progression.

In the 1970s a multidisciplinary approach to better manage intra-peritoneal cancer spread was developed [2-4]. This multimodal regimen consists of two major steps. In the first step, the surgical team performs operative resection to eradicate all sites of gross disease (i.e., cytoreductive surgery, CRS). In the second step, heated chemotherapy is instilled intraoperatively into the peritoneal cavity to eradicate all sites of microscopic disease (i.e., hyperthermic intraperitoneal chemotherapy, HIPEC). Although CRS and HIPEC are applied worldwide, there remains much debate and controversy regarding its indications, techniques, and efficacy. In this chapter we will examine CRS and HIPEC for mucinous gastrointestinal cancers while describing our experience on how to perform this complex multimodal treatment approach.

UNDERSTANDING THE PERITONEUM

It is critical to appreciate the biology of the peritoneum to better understand how disease may spread within the peritoneal cavity and how to optimally manage this disease. In its very simplest form, the peritoneum is the serous membrane supported by a thin layer of connective tissue that lines the abdominal cavity. It has both parietal and visceral components with the parietal peritoneum covering the inner surface of the abdominal walls, the diaphragm, and the pelvis; whereas the visceral peritoneum envelops the intraperitoneal organs and covers the anterior surface of retroperitoneal organs. The space between the parietal and visceral peritoneum is the peritoneal space; and within this space exists the fluid to lubricate the visceral surfaces. In its more complex form, the peritoneum doubles up to establish major extensions, including numerous mesenteries, the greater and lesser omentum, and complex ligamentous structures.
figure 1. Operative photograph of a patient with appendiceal mucinous adenocarcinoma. The surgeon is holding the "omental cake." The small intestine is spared of disease.

There is an intricate relationship between the circulation of peritoneal fluid, the major peritoneal extensions, and the intra-peritoneal organs. The peritoneal fluid, which is <100 mL under physiologic conditions, is constantly produced as a transudate and resorbed through major pores in the large surface area of the peritoneum to create a steady-state circulation [5]. The typical pattern of circulation occurs with peritoneal fluid flowing up the right para-colic gutter and leading up to the right hemidiaphragm [6]. Major pores under the right hemidiaphragm clear nearly 90% of peritoneal fluid. Not surprisingly, peritoneal surface disease may be frequently detected under the right hemi-diaphragm as tumor cells travel in the circulatory pattern of peritoneal fluid. The lesser and greater omentum also contribute to the steady-state peritoneal fluid circulation with sizeable pores throughout its large surface area [7, 8]. Thus, it is also a common location for both benign and malignant peritoneal disease spread. Massive replacement of the greater omentum by mucinous disease has been referred to as "omental cake" [8, 9]. Finally, under pathologic conditions (e.g., cirrhosis, malignant ascites, etc.) peritoneal fluid may accumulate in the dependent areas of the peritoneal cavity (e.g., pelvis and lateral abdominal gutters), which are also frequent locations for peritoneal disease. Overall, the circulation of peritoneal fluid may help predict the progression of peritoneal surface disease (Figure 2).

MUCINOUS PERITONEAL TUMORS

Epithelial mucin-producing cells are at the core of the problem with mucinous peritoneal surface neoplasms. Mucins belong to a family of proteins also known as MUC glycoproteins. Intrinsically, these secreted mucins provide a physical barrier for epithelial cells lining the gastrointestinal tract and they contribute to the immune defense system on the mucosal surfaces [10-13]. These secreted mucins can accumulate and form voluminous gels slowly over months or years leading to a chronic condition that may elude detection until advanced stages of disease.

Pseudomyxoma peritonei (PMP) has been the term traditionally applied to the intraperitoneal dissemination of mucinous ascites from perforated mucinous cystadenoma of
the appendix [14]. In this condition, epithelial mucin-producing cells proliferate within the appendix, leading to occlusion of the lumen and expansion and eventual rupture of the appendix. If the mucinous cystadenoma is detected prior to rupture, simple appendectomy is sufficient to permanently eradicate disease (Figure 3). Extreme caution should be taken when laparoscopic appendectomy is attempted with large mucinous cystadenoma to avoid inadvertent rupture (Figure 4). When the appendix does rupture, which is frequently without symptoms, then semi-solid mucin may eventually fill the entire abdominal cavity leading to ‘jelly belly’ and ‘omental cake.’

Figure 2. Typical locations of disease with peritoneal mucinous disease. Peritoneal surface disease from an appendiceal primary will follow the typical circulation of peritoneal fluid leading to disease under the hemi-diaphragms, omentum, and para-colic gutters. Gravity will also lead to disease in the pelvis.

Figure 3. Appendiceal mucinous cystadenoma from laparoscopic appendectomy. The pathologic specimen has been stained blue. The solid arrow points to the mucinous cystadenoma. The dashed arrow shows the diameter of the non-diseased appendix.
The biologic aggressiveness of peritoneal surface disease has been classified to designate benign and low-grade malignant conditions together as disseminated peritoneal adenomucinosis (DPAM). In this schema, lesions are categorized as low-grade when they have scant simple to focally proliferative mucinous epithelium with minimal or little cytologic atypia or mitotic activity. In contrast, moderate or high-grade lesions of peritoneal mucinous carcinomatosis (PMCA) include lesions with more aggressive biologic disease that are composed of abundant mucinous epithelium with architectural and cytologic features of carcinoma. PMCA is typical for appendiceal mucinous adenocarcinoma or mucinous colorectal cancers and gastric cancers that violate the peritoneal cavity either by direct extension or by viscus rupture. This disease then spreads along the peritoneal surface with epithelial mucin-producing cells forming metastatic nodules in the absence of visceral metastases. The response to systemic therapies is generally poor and optimal management of these patients may include CRS and HIPEC in combination with systemic therapies [3, 4, 15-24].

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

General Overview

Eradication of gross and microscopic disease by surgical resection and heated chemotherapy, respectively, are the principles of CRS and HIPEC. This treatment approach is ideally suited for disease processes that have peritoneal surface disease but lack visceral metastases; and generally excludes cancers that have metastasized outside the peritoneal cavity. Incomplete surgical resection of disease should be avoided since patients derive minimal to no survival benefit [1, 3, 16, 25-32]. As such, complete resection of all tumor volume to margin negative disease is the goal of CRS. The amount of disease burden may be estimated prior to surgical exploration with the Peritoneal Cancer Index (PCI). This scoring system separates the abdominal cavity into 13 distinct regions. The operator assigns tumor burden scores for each
of these regions based upon the Lesion Size (LS) of the tumor volume in each of those regions. The numerical value of these PCI scores have correlated with clinical outcomes; and patients with lower PCI scores generally fare better than patients with higher scores [33, 34].

**Morbidity and Mortality of the Treatment Approach**

Patients who undergo CRS and HIPEC may endure major physiologic stress from multi-visceral resection, rapid changes in fluid homeostasis, and alterations in body core temperature. Not surprisingly, there is considerable morbidity and mortality associated with this procedure with approximate rates approaching up to 50% and 5%, respectively [16, 21, 23, 24, 35-39]. Strategies to avoid unnecessary surgical steps and abandoning unsafe HIPEC protocols have improved the safety profile of these procedures without adversely impacting overall survival [40, 41]. In our practice we perform resection for grossly visible disease and generally avoid prophylactic or empiric resection except for the appendix and gallbladder. When disease is encountered on the surface of intra-peritoneal organs, we make concerted efforts to remove disease by stripping the peritoneal lining rather than resecting the entire organ en bloc. Finally, we avoid using D$_3$W in the hyperthermic perfusate, thus avoiding potentially serious electrolyte alterations.

**Technique for Cytoreductive Surgery**

For our cytoreduction procedures, we routinely use a generous midline incision with a Thompson retractor to provide full exposure. Once the peritoneal cavity is entered, mucin is typically removed with suction catheters. Tenacious, thick mucin may require manual removal using laparotomy pads. After initial exploration to rule out unresectable disease, we proceed with resection of all sites of gross disease. Regardless of detection of gross disease, we advocate mandatory resection of the greater and lesser omentum, appendix, and the gallbladder. We use a thermal energy device (Ligasure, Covidien) to remove the omentum by dividing the gastrocolic ligament close to the transverse colon from the hepatic to splenic flexures. The omentum is then divided along the greater curvature of the stomach while preserving the gastro-epiploic vessels. Appendectomy is performed using a linear stapling device, rather than using biodegradable suture to avoid its exposure to HIPEC. Similarly, titanium clips are placed on the cystic artery and duct during cholecystectomy.

For many patients, cytoreduction procedures will also require stripping of the right and occasionally left hemi-diaphragm. We use long Allis clamps to grasp the peritoneal lining of diaphragm and “strip” only gross disease. If the thoracic cavity is entered, we close the diaphragm around a red rubber catheter. A purse-string suture is placed around the catheter; and the catheter is removed and the suture tied down once the air in the thoracic cavity has been suctioned. Another common site of disease is on the liver surface. We have found that the bipolar hemostatic device (Aquamantys, Medtronic) is safe and effective for stripping Glisson’s capsule of the liver. Finally, the removal of intraperitoneal or retroperitoneal organs may sound contrary to the benign nature of low-grade malignancy; however, thick tenacious mucinous disease may coat the pelvis, rectum, lesser curvature of the stomach, antrum of the stomach, the liver surface, and the porta hepatis. Therefore, it is common to perform major multi-visceral
resection to completely remove disease even for patients with DPAM. Since mucinous disease tends to spare areas of active peristalsis, the small intestine is typically spared. In our experience we have identified lesions overlooked by other surgeons during combination operative resections. These examples of missed disease give us pause when considering laparoscopic HIPEC procedures.

![Open technique for hyperthermic intraperitoneal chemotherapy.](image1)

Figure 5. Open technique for hyperthermic intraperitoneal chemotherapy. Multiple sutures have been placed to suspend the skin to the retractor system. Inflow and outflow catheters have been placed through openings in the mesh. A smoke evacuator has been placed above the opening.

![Closed technique for hyperthermic intraperitoneal chemotherapy.](image2)

Figure 6. Closed technique for hyperthermic intraperitoneal chemotherapy. Inflow and outflow catheters have been placed into the abdominal cavity and the skin has been closed with a continuous running suture.
Administration of Heated Intraoperative Chemotherapy

The rationale to use intra-peritoneal chemotherapy is to eradicate microscopic disease with higher local concentrations of chemotherapy that may enhance cytoreduction, which may be further potentiated by the cytotoxic effects of heat [4, 15, 16]. Once gross resection of disease is completed and prior to anastomotic reconstruction, we perform HIPEC. Anastomoses should be delayed until after HIPEC is completed to avoid exposing the fresh anastomosis to the peritoneal dosage of chemotherapy. For colorectal and appendiceal tumors, we instill oxaliplatin or mitomycin C into our perfusion circuit, whereas cisplatin is used for gastric cancer. Mitomycin C may be the chemotherapeutic agent of choice for patients with peritoneal surface disease of colorectal origin with the American Society of Peritoneal Surface Malignancies (ASPSM) advocating its use for this disease [40-42].

HIPEC has been performed using an open platform, referred to as the coliseum technique (Figure 5), in which the abdomen is left open and the operator manually stirs the chemotherapy perfusate to ensure equal distribution throughout the abdominal cavity [16, 43, 44]. Because of institutional or state restrictions, the open technique has been abandoned in some centers. The alternate approach is the closed technique (Figure 6) [41, 43-47], which is our preferred technique. We employ the Genesis Medical system (Figure 7), which utilizes two inflow catheters connected by a Y connector to a single primary catheter; and a single outflow “lasso” catheter. In our experience this system rapidly achieves goal temperature when the catheters have been placed and the skin closed; and we have observed no interruptions in HIPEC secondary to system or catheter malfunction.

Once closed, the abdomen is warmed with hyperthermic saline to 41-42°C. Once the target temperature is reached, chemotherapy is infused into the circuit and perfused for 30-90 minutes. Once the perfusion has been completed, the hyperthermic chemotherapy fluid is drained from the abdomen. Next, the skin is reopened and the final anastomoses are performed or ostomies constructed.

CONCLUSION

Multimodal therapies for patients with primary peritoneal cancers and peritoneal metastases are continuing to improve and evolve. Instead of representing rapidly fatal disease as in the past, contemporary management of DPAM and PMCA with CRS and HIPEC has improved survival in the hands of experienced surgeons. Importantly, the implementation of standardized protocols and advances in HIPEC delivery systems has resulted in decreased rates of morbidity and mortality. We recommend adhering to the guidelines from The American Society of Peritoneal Surface Malignancies (ASPSM) on the use of HIPEC in our difficult to manage patients. This organization has provided HIPEC guidelines on chemotherapy administration, timing, and dosage and temperature settings to improve patient safety [41, 42, 48]. Despite these past improvements, additional investigational studies are needed to further improve the outcomes of patients with mucinous peritoneal disease.
Figure 7. The Genesis Medical system for hyperthermic intraperitoneal chemotherapy.

REFERENCES


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