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Gastrointestinal Fistulas after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: A 20-Year Retrospective Analysis

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Abstract

Introduction: The development of digestive fistulas is a common complication following Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC). This study aims to analyze the incidence, management, and outcomes of enterocutaneous fistulas over the past 20 years.

Methods: From 2005 to 2024, 1,350 patients with peritoneal metastases underwent CRS and HIPEC. HIPEC was administered in the operating room immediately following CRS, with 80% of cases with a closed abdomen and anastomoses performed before HIPEC.

Discussion: Of the 1,350 patients, 149(11.03%) developed a digestive fistula. Spontaneous closure was observed in 120 patients (80.53%), with a median closure time of 28 days (range: 14 to 94 days). For the 29 patients whose fistulas did not close spontaneously, 21(72.4%) required reoperation. There were 4 postoperative deaths (19%).

Conclusion: The incidence of digestive fistulas following CRS and HIPEC is increased a little compared to that of conventional digestive surgery.

Keywords: Gastrointestinal fistulas; Complications; CRS; HIPEC; Peritoneal metastasis.

Introduction

Peritoneal Metastasis (PM) has historically been considered a terminal condition, often managed only with palliative care. However, Cytoreductive Surgery (CRS) combined with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has emerged as the only potentially curative treatment for PM [1,2].

CRS with HIPEC, which involves peritonectomy procedures and multivisceral resections as described by Sugarbaker [3], is a high-risk, complex cancer surgery. It is characterized by prolonged operative time, hemodynamic alterations, potential toxicity of extended intraperitoneal chemotherapy, and prolonged ICU hospitalization. One of the most critical factors affecting outcomes is hospital volume and the surgical team's learning curve, which impacts the procedure's success [4,5].

A prevalent and serious complication of this procedure is the development of digestive fistulas. These can result from anastomotic leak [2] or bowel perforation away from anastomotic lines. Fistulas have been reported in 3.9% to 34% of patients undergoing this procedure [6-9].

Such figures are somewhat higher than the 5% reported for common elective surgeries [10].

Materials and methods

Aim: The aim of our study was to retrospectively evaluate our 20-year experience with CRS and HIPEC, focusing on the incidence, management, and outcomes of digestive fistulas.

Design of the study: Between 2005 and 2024, 1,350 patients with Peritoneal Metastasis (PM) underwent CRS and HIPEC. The goal of the procedure was to visibly eliminate all cancer cells from the abdomen and pelvis. Following CRS, all patients received HIPEC in the operating room. The primary endpoints of the study were the incidence of digestive enterocutaneous fistulas, along with the management and outcomes of this complication in CRS-HIPEC patients.

Table 1: Digestive fistulas after CRS and HIPEC.

Location	No. of patients	Percentage (%)
Gastric	6	4,02
Duodenal	12	8,05
Pancreatic	18	12,08
Biliary	10	6,71
Small Bowel	78	52,34
Colon	25	16,77

Table 2: Digestive fistula output.

Output level	No. of patients	Percentage (%)
Low (<200 ml/day)	73	48,99
Medium (200-500 ml/day)	42	28,18
High (>500 ml/day)	34	22.81

Table 3: Spontaneous closure according to output and time.

Output level	Spontaneous closure	Day of closure (Range)
Low Output	67/73(91.7%)	14.3±6.1 days
Medium Output	34/42(80.9%)	23.2±7.3 days
High Output	19/34(55.9%)	47±11.3 days

Table 4: Anatomic location and spontaneous closure rates.

Anatomic location	No. of patients	Spontaneous closure (%)
Gastric	6	5(83,3)
Duodenal	12	6(50,0)
Pancreatic	18	16(88,8)
Biliary	10	9(90,0)
Small Bowel	78	64(82,0)
Colon	25	20(80,0)

Discussion/conclusion

Over the 20-year period from 2005 to 2024, 1,350 patients were treated with CRS and HIPEC for peritoneal metastasis. Of these, 149 patients (11.03%) developed an enterocutaneous digestive fistula. The origins of the fistulas are presented in (Table 1).

All patients had received preoperative chemotherapy, and 60 of them (40%) were malnourished. The mean Peritoneal Cancer Index (PCI) among all patients was 20 (range: 12-29). The onset of fistula formation typically occurred on postoperative day 9 (range: 4-17 days).

(Table 2) presents the output levels of the digestive fistulas.

Spontaneous closure of the fistula was observed in 120 patients (80.5%).

(Table 3) demonstrates the spontaneous closure rates according to output levels and the day of closure after fistula onset.

All patients with digestive fistulas were managed with Total Parenteral Nutrition (TPN), subcutaneous octreotide, and antibiotics to control sepsis, correct dehydration, and restore electrolyte balance. Oral intake was restricted, and allowed only for patients with low-output or colorectal fistulas.

The median day of spontaneous closure between high-output and low- or medium-output fistulas was statistically significant ($p<0.001$).

(Table 4) demonstrates the percentage of spontaneous closure according to the anatomic location of the fistulas.

From the remaining 29 patients with non-spontaneous closure of their fistulas, the therapeutic management was as follows:

Of the 29 patients with non-spontaneous closure, after meticulous laboratory investigations including CT scans, MRIs, and fistulography, 21 patients (72.4%) underwent reoperation. There were 4 postoperative deaths (19%), including 3 in the high-output group and 1 in the medium-output group.

The main causes of death were:

ARDS: 1 patient.

Sepsis: 2 patients.

Bleeding: 1 patient.

Among the remaining 8 patients who refused re-operation, 6 of them continued conservative management with home total parenteral nutrition and sandostatin, one patient died due to disease progression and the other one patient lost from follow-up.

Conclusion

A digestive fistula is an abnormal communication between two epithelialized hollow spaces or organs. Enterocutaneous fistulas specifically connect the gastrointestinal tract to the skin and can be classified according to location, output volume, and etiology. The type of output and its volume can vary depending on the origin of the fistula, leading to differing degrees of electrolyte and nutritional loss.

High-output fistulas are difficult to heal spontaneously and these patients are at a higher risk for metabolic disturbances, fluid loss, and malnutrition. In our study, despite meticulous nutritional management, antibiotic therapy, and hormonal/metabolic interventions, we achieved a 56% rate of spontaneous closure after 2 months for these high-output fistulas.

The primary management tools included Total Parenteral Nutrition (TPN), adequate hydration, and the use of somatostatin analogs to reduce fistula output. Antibiotics were also employed to control potential infections and manage the fistula output effectively [11-16]. The pathophysiology of postopera-

tive complications, including digestive fistulas, is significantly associated with factors such as prolonged operative time, prior preoperative or postoperative systemic chemotherapy, radiotherapy, the number of anastomoses performed, and the patient's nutritional status [14].

Other studies have found that the extent of cytoreductive surgery and the use of intraperitoneal chemotherapy agents (e.g., oxaliplatin vs mitomycin vs CDPD) are independent risk factors for the development of digestive fistulas [15]. Additionally, the potential complications related to hyperthermia during HIPEC, in combination with simultaneous drug administration, raise questions. It is evident that this regional treatment can profoundly impact wound healing. Intestinal wall edema following CRS and HIPEC causes the loosening of intracellular tight junctions, facilitating bacterial translocation [16].

The role of somatostatin analogs, such as octreotide, in fistula management remains controversial. However, in cases of pancreatic and small bowel fistulas, these agents have been shown to reduce output and expedite spontaneous closure [17].

Nutritional support is essential in the management of gastrointestinal fistulas, with Total Parenteral Nutrition (TPN) being the best option for high-output fistulas or fistulas located in the upper gastrointestinal tract (e.g., duodenum, stomach). The second crucial step is infection control and the correction of electrolyte imbalances. Normal intestinal function and motility typically return once abdominal sepsis is controlled and fluid and electrolyte imbalances are addressed. These actions gradually contribute to the maturation of the fistula tract.

Enteral feeding can also be initiated, especially in low-output fistulas or colorectal fistulas. In our study, we started patients on an elemental diet while carefully monitoring fistula output [18].

In conclusion, patients with Peritoneal Metastasis (PM) often have a history of prior abdominal surgeries and multiple cycles of neoadjuvant treatments, which can lead to altered immunity, poor performance status and nutritional deficiencies. Undergoing CRS and HIPEC puts these patients at high risk for postoperative complications, contributing to significant morbidity and mortality. However, these risks can be mitigated in specialized centers dedicated to this procedure [19,20].

The decision to proceed with CRS and HIPEC requires careful consideration of the potential benefits and associated risks of therapy.

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