

Reduced Morbidity Following Cytoreductive Surgery and Intraperitoneal Hyperthermic Chemoperfusion

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Background: Cytoreductive surgery and intraperitoneal hyperthermic chemoperfusion (IPHC) are an aggressive treatment for patients with peritoneal based malignancies or those with peritoneal dissemination of select histology. Although promising, this therapeutic regimen has been associated with significant morbidity, long hospital stays, and, in some reports, moderate risk for perioperative mortality. Recent experience suggests that these outcomes may be improved.

Methods: Thirty-three patients underwent cytoreductive surgery and intraperitoneal hyperthermic perfusion during the period of December 1999 to July 2002. All patients underwent resection by a three-surgeon team, followed by IPHC with an open technique. Peritonectomy was performed with the goal of total gross excision of disease.

Results: Thirty-five procedures were performed in 33 patients (20 female) with a mean age of 49 years (range, 26–72). Complete cytoreduction was achieved in 22 cases (63%), and in 6 cases (17%) residual disease was <4 mm. There were nine major perioperative complications (27%) and no perioperative deaths. The median hospital stay was 11 days.

Conclusions: These results demonstrate that cytoreductive surgery and IPHC can be performed with morbidity and mortality rates in line with those of other major oncologic operations. Employment of a three-surgeon approach, limited peritonectomy, and an open technique may help to reduce the morbidity from this aggressive treatment. Continued investigation of this promising treatment regimen is warranted.

Key Words: Appendiceal carcinoma—Cytoreduction—Hyperthermia—Intraperitoneal chemotherapy—Peritoneal carcinomatosis.

Cytoreductive surgery combined with intraperitoneal hyperthermic chemoperfusion is a promising treatment regimen for select patients with peritoneal metastases and peritoneal-based malignancies. Such procedures are generally long and technically challenging, and it is not surprising that significant morbidity may result as major surgical resections are combined with cytotoxic chemotherapy.^{1–9} Major

morbidity and mortality rates of 27% to 56% and 0% to 11%, respectively, have been reported.^{10–14} A number of different techniques for the administration of intraperitoneal chemotherapy have been described, with variations in perfusate temperature, in chemotherapeutic drug and dosage, and in whether the abdomen remains open during the perfusion.^{2,11–14}

We performed cytoreductive surgery and IPHC with modifications of current techniques and strategies. In our practice, three surgeons (two surgical oncologists and one senior resident) performed the cytoreductive procedures to limit individual surgeon fatigue. Additionally, we performed involved field peritonectomies with the goal of resecting all gross tumor. Finally, we administered intraoperative intraperitoneal hyperthermic chemotherapy, employing an open technique. We present our experience to support the contention that cytoreductive surgery and IPHC can be performed with morbidity and

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mortality rates that are similar to those with other major surgical procedures.

METHODS

Patients

All patients treated with cytoreductive surgery and IPHC from 1999 to 2002 were identified from an institutional database and included in this review. Complete medical records were reviewed to examine demographic, clinical, pathologic, and outcome data. Twenty-seven patients were initially treated elsewhere and were referred to our institution on the basis of operative findings. Six patients were referred for treatment without prior operative intervention.

Preoperative evaluation included history and physical examination, review of outside pathology, computed tomography of the abdomen and pelvis, chest radiography, and laboratory evaluations. If patients had an adequate Zubrod performance status (≤ 2) and no evidence of extraperitoneal disease, they were deemed candidates for operation.

Cytoreductive Surgery and IPHC

All cytoreductive surgeries were performed through a midline laparotomy incision. A Thompson abdominal wall retracting system (Thompson Surgical Instruments, Traverse City, MI) was utilized for maximal exposure of the peritoneal cavity. The resections were performed by two attending surgical oncologists and one senior resident. This team approach was designed to minimize the effects of fatigue during the long operative procedures. Resections were performed with the goal of complete gross excision of tumor. Complete eradication of visible disease was categorized as R0 resections. If gross disease was left behind, these operations were categorized as incomplete resections (R1, ≤ 4 mm; R2, >4 mm).

Cytoreduction was performed by stripping all involved peritoneal surfaces, including subdiaphragmatic, porta hepatis, Glisson's capsule, lateral abdominal wall, pelvic sidewall, and limited visceral peritoneal surfaces. If visceral peritoneal surfaces were extensively involved, segments of hollow viscus or solid organs were resected as necessary. If the splenic surface was involved, a complete splenectomy was performed. The falciform ligament, gallbladder, and greater and lesser omentum were resected routinely.

Following surgical cytoreduction but prior to completion of gastrointestinal anastomoses, the peritoneum was treated with hyperthermic chemotherapy. The chemotherapeutic agents were instilled via inflow catheters at a temperature of 44°C. Core temperatures were monitored

by bladder and esophageal temperature probes. Intra-abdominal temperature probes were placed within the liver and within a single inflow and two outflow catheters located in separate quadrants of the peritoneal cavities. The patient's temperature was controlled by pre-cooling with cooling blankets to approximately 35°C. An open abdominal method (Coliseum technique) was utilized. The edges of a Silastic sheet (Dow Corning, Hemlock, MI) were incorporated into a running suture that suspended the skin and fascia of the abdominal wall on the Thompson retractor. In this way, further expansion of the peritoneal cavity was achieved, leading to an increased total-surface-area exposure of peritoneal surfaces to the perfusate. A central incision in the Silastic was made to allow access to the abdomen and pelvis for manual stirring of the heated chemotherapeutic agents. A smoke evacuation device was utilized to protect against the theoretical risk of aerosolized chemotherapy.

Chemotherapy was added to the perfusate once peritoneal surface temperatures exceeded 40°C. Chemotherapeutic agents were selected on the basis of the histological characteristics of the primary tumor. Mitomycin C (15 mg per liter of perfusate, to a maximum dose of 65 mg) was utilized to treat gastrointestinal malignancies. Mitomycin C was given as an initial 10-mg/L dose and was redosed midway through the perfusion with an additional 5 mg/L. A combination of cisplatin (50 mg/m²) and doxorubicin (15 mg/m²) was utilized to treat sarcoma, ovarian carcinoma, and primary peritoneal carcinomas. In addition, patients with gross residual disease following cytoreduction or debilitating ascites received intraperitoneal 5-fluorouracil (750 mg/m²/day) for 5 days following surgery. Some patients were later treated with systemic chemotherapy at the discretion of their medical oncologists.

In all cases, the total perfusion time was 90 minutes. After completion of the perfusion, excess fluid was drained from the abdominal cavity, which was then irrigated with 6 L of peritoneal dialysis fluid. Because of the expected prolonged ileus, a gastrostomy tube was inserted for gastric decompression, and selected patients had jejunostomy tubes inserted as well. Additionally, patients who underwent diaphragmatic stripping or resection underwent placement of a thoracostomy tube to treat expected postoperative pleural effusion.

Complications

Complications were identified by retrospective review of the medical records. They were categorized as major and minor complications. The major complications included pancreatic fistula (defined as abdominal fluid amylase levels two times greater than serum levels per-

sisting beyond the fifth postoperative day), pulmonary embolism, perforated gastric ulcer, intra-abdominal abscess, superficial femoral artery thrombosis, deep venous thrombosis, and neutropenia. Minor complications included ileus, wound infection, urinary tract infection, urinary retention, pleural effusion, and diarrhea.

RESULTS

From December 1999 to July 2002, 33 patients underwent 35 surgical cytoreductions with intraoperative IPHC. Twenty-seven patients (82%) had previous surgery at another institution. Of the 33 patients, 20 (61%) were women. The mean age of patients was 49 years (range, 26–72 years). The most common neoplasm was mucinous cystadenocarcinoma of appendiceal origin (n = 17), followed by appendiceal adenomucinosis (n = 5), colon carcinoma (n = 4), sarcoma (n = 3), gastric carcinoma (n = 2), ovarian carcinoma (n = 1), and primary peritoneal carcinoma (n = 1). Eighteen tumors (55%) were classified as high-grade malignancies, 10 (30%) were low-grade malignancies, and the remaining 5 (15%) were adenomucinosis.

Surgery

Cytoreductive surgery was performed with the goal of complete eradication of tumor in all 35 operations. Multiorgan resections were undertaken in 30 cases to achieve this end (Table 1). Solid and hollow viscus organs were resected when extensively involved with tumor and more conservative resection could not be achieved. Complete cytoreduction (R0) was accomplished in 22 cases (63%); additionally, there were 6 R1 resections (17%) and 7 R2 resections (20%). The mean operative time was 500 minutes (range, 248–886 minutes), which included 90

minutes for administration of perioperative chemotherapy. The estimated blood loss was 650 mL (range, 100–3300 mL). The average number of hollow and/or solid organs resected per patient was 3 (range, 1–8; Table 2).

Complications

There were nine major morbidities complicating the postoperative courses of eight patients. One patient with appendiceal cystadenoma had undergone splenectomy and hepatic wedge resection. During her immediate postoperative course, she was found to have a perforated gastric ulcer, necessitating re-exploration and repair. Her hospital course was then further complicated by a pulmonary embolism, which was successfully treated with anticoagulation.

Three patients developed fistulas. Two patients developed fistulae following distal pancreatectomy. These fistulas closed with drainage alone. The remaining patient had undergone two cytoreductive procedures with IPHC for mucinous adenocarcinoma of the colon and subsequently developed an enterocutaneous fistula. The fistula never closed, and the patient succumbed to recurrent tumor 16 months after his initial procedure.

One patient underwent cytoreductive surgery with IPHC for gastric adenocarcinoma. She developed fever and leukocytosis in the postoperative period, and the diagnosis was made on computed tomographic examination of the abdomen, revealing a subphrenic fluid collection. The fluid collection was treated with percutaneous drainage. Another patient with primary peritoneal carcinoma developed a subhepatic abscess, which was successfully treated with percutaneous drainage. A third patient developed an intra-abdominal fluid collection

TABLE 1. Range of operative resections

Surgical Resections	Patients (n)
Hollow viscus resection	
Colectomy	21
Small bowel resection	13
Gastrectomy	4
Cholecystectomy	17
Cystectomy	1
Hysterectomy	3
Solid organ resection	
Hepatectomy (wedge resection)	2
Pancreatectomy	2
Splenectomy	15
Salpingo-oophorectomy	6
Omentectomy	20
Peritonectomy*	28

* Stripping of undersurface of diaphragm, Glisson’s capsule, lateral walls of the peritoneal cavity and pelvis.

TABLE 2. Perioperative outcomes

Operative Parameters	Data
Cytoreductive procedures (n)	35
Cytoreduction (n)	
R0 resection	22
R1 resection	6
R2 resection	7
Number of organ resections*	
Mean	3
Range	(1–8)
Operative time (min)	
Mean	500
Range	248–886
Blood loss (mL)	
Mean	650
Range	100–3300
Length of stay (days)	
Median	11
Range	6–112

* Hollow viscus and solid organ resection.

after surgery for low-grade fibrosarcoma. This was successfully treated with percutaneous drainage, and cultures yielded only *Candida albicans*.

Limb-threatening ischemia of the right lower extremity was diagnosed in one case following treatment for a mucinous cystadenocarcinoma of the appendix. The patient had preexisting peripheral vascular disease and had undergone previous angioplasty of the superficial femoral artery (SFA). We hypothesize that fluid shifts contributed to decreased perfusion, leading to acute thrombosis of the superficial femoral artery. The patient was treated with thrombolytic therapy followed by patch angioplasty, which resulted in limb salvage.

The final major complication was a deep venous thrombosis in a patient treated for mucinous cystadenocarcinoma of the appendix. Ipsilateral leg swelling was noted in the postoperative period. Subsequent duplex scanning of the affected limb revealed a thrombus in the superficial femoral vein. The patient was successfully treated with anticoagulation.

There were a total of 22 minor complications, all successfully treated during the inpatient period. These included ileus ($n = 8$), urinary tract infection ($n = 4$), pleural effusion ($n = 3$), urinary retention ($n = 2$), central venous catheter infection ($n = 2$), wound infection ($n = 1$), prolonged diarrhea ($n = 1$), and pneumonia ($n = 1$).

The number of major and minor complications was independent of the number of solid/hollow organs resected (Fig. 1). Furthermore, the frequency of complications did not relate to the magnitude of the operation (P

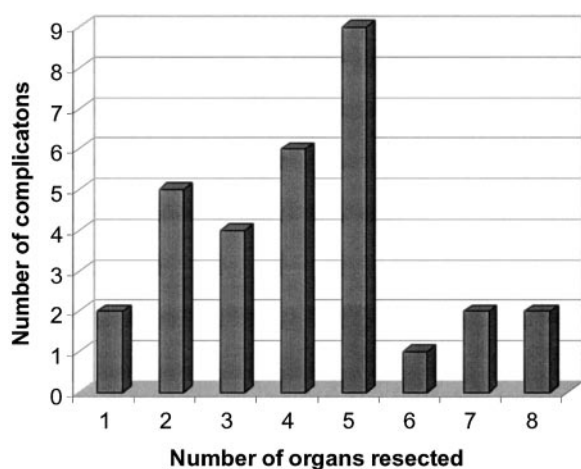


FIG. 1. The numbers of major and minor complications were independent of the number of solid and hollow organs resected. Thus, perioperative complications did not relate to the magnitude of the operation.

= NS). The median length of stay for all patients in the series was 11 days (range, 6–112 days).

Survival

By a median follow-up of 19 months (range, 1–44 months), 11 patients had died of recurrent disease. Six patients died of appendiceal carcinoma, three of colon carcinoma, one of recurrent gastric carcinoma, and one of recurrent sarcoma. Analysis of the subset of patients with appendiceal carcinoma demonstrated a survival difference between adenomucinoses, low-grade malignancy, and high-grade malignancy ($P < .05$). Kaplan-Meier survival curves were then analyzed and compared between each group (Fig. 2). There were no deaths in the adenomucinoses group and two in the low-grade malignancy group; four deaths occurred in the high-grade group.

DISCUSSION

Surgical cytoreduction and intraperitoneal hyperthermic chemoperfusion may improve survival for patients with peritoneal metastases or peritoneal-based malignancies.^{1–8} To date, only one prospective randomized trial has been performed to demonstrate the benefits of cytoreduction and hyperthermic intraperitoneal chemotherapy. Verwaal et al. demonstrated a survival advantage (median survival of 21.6 months versus 12.6 months; $P < .05$) for patients undergoing cytoreduction and hyperthermic intraperitoneal chemotherapy in comparison with a similar cohort of patients being treated with standard systemic therapy with or without palliative surgery.¹⁵ Cytoreductive surgery with IPHC has been associated with significant morbidity and occasional mortality. Recent series of Sugarbaker et al. and Wit-

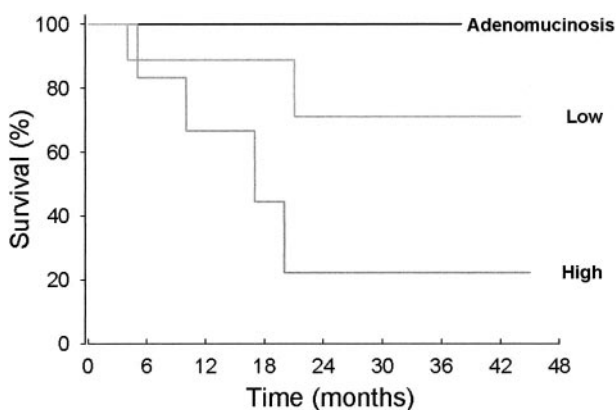


FIG. 2. Kaplan-Meier survival curve analyzing the subset of patients with appendiceal cancer, demonstrating differences in survival between patients with high-grade cancer, low-grade cancer, and adenomucinoses.

TABLE 3. *Morbidity and mortality in recent series of cytoreduction and intraperitoneal hyperthermic chemoperfusion*

Senior author	Technique	Primary tumor	No. of patients	Morbidity (most common major surgical complications)	Mortality (%)
Sugarbaker ⁸ (1999)	Open + postoperative	Appendix	155	27%—(pancreatitis, fistula)	2
Sugarbaker ¹ (1996)	Open + postoperative	Appendix, colon	60	35%—(anastomotic leak, bowel perforation, bleeding, bile leak)	5
Loggie ³ (2000)	Closed	Colon, appendix, stomach	84	30%—(bowel leak, wound leak, sepsis, prolonged intubation)	6
Cavaliere ²³ (2000)	Open	Ovary, colon, peritoneum, appendix	40	40%—(fistula, anastomotic leak, abscess, bleeding)	12.5
Zoetmulder ²⁴ (2001)	Open	Appendix, ovary	46	39%—(bowel perforation, fistula, pulmonary embolism, pneumonia)	9
Lowy (2003)	Open	Appendix, colon, stomach, sarcoma	33	27%—(abscess, pulmonary embolism, DVT)	0

kamp et al. had major morbidity rates of 27% and 39%, respectively. Perioperative mortality at these highly experienced centers has ranged from 0% to 9% (Table 3). Thus, while clinical benefit is suggested by these studies, morbidity and mortality are more certain. It is therefore even more critical than usual that efforts be made to minimize morbidity and mortality with this extensive procedure. Review of our early experience with cytoreductive surgery and IPHC demonstrates major morbidity and mortality rates of 27% and 0%, respectively, and median length of stay of 11 days.

Although a retrospective analysis cannot define the keys to improved outcomes, we speculate that several aspects of our treatment have helped to limit morbidity and mortality. Some authors have advocated the routine use of six peritonectomy procedures to achieve maximal cytoreduction.¹⁶ Extensive surgical cytoreduction beyond the limits of macroscopic evidence of disease may not be necessary and may lead to excessive morbidity. We perform surgical cytoreduction according to the extent of gross disease only and do not resect any peritoneal surfaces that are visibly free of disease.

The rationale behind this approach is that since all peritoneal surfaces are exposed to tumor but cannot be resected, the resection of additional parietal peritoneum that is visibly unaffected is unlikely to influence outcome. Resection of only grossly involved peritoneal surface serves to reduce the magnitude of the operation and its duration and thereby may help reduce the likelihood of postoperative complications. With use of this approach, complete cytoreductions were achieved in 63% (n = 22). Our mean operative time of 8.2 hours was shorter than that in other large series. In our series, there were nine major complications (27%) and no deaths

(Table 3). This outcome compares favorably with those of other large series involving similar histological characteristics.^{12–14}

Intraperitoneal hyperthermic chemoperfusion may be administered using different techniques. It was originally described as a closed peritoneal approach.¹⁷ The theoretical disadvantage of this approach is that it may result in uneven distribution of drug and hyperthermia within the peritoneal cavity. Hot spots may result in focal ileus or tissue damage resulting in impaired wound healing.¹⁸ We have utilized the open technique, popularized by Sugarbaker. This method has been shown to be safe for both patient and operating room personnel.^{19,20}

We prefer the open technique because it results in expansion and improved exposure of the entire seroperitoneal surface to the perfusate. We have also found this technique to be useful in controlling intraabdominal temperatures. Schanke et al. have shown the development of postoperative neutropenia to be associated with intraabdominal temperatures.²¹ Sugarbaker et al. have reported a 4% hematological complication rate with the open technique.¹² Similarly, in our series, only one patient—who had been heavily pretreated with systemic chemotherapy—developed postoperative neutropenia.

The median length of stay in our series was 11 days, which compares favorably with that noted in the existing literature.^{21,22} We believe several factors may have contributed to this finding. We routinely place prophylactic thoracostomy tubes to prevent symptomatic postoperative pleural effusions in patients undergoing diaphragmatic peritonectomy. The second factor for our short length of stay may have been related to the use of routine gastrostomy tubes. In our experience this allows for earlier discharge of patients who may still be experienc-

ing mild gastroparesis. We have also utilized a strategy of early postoperative feeding that has been shown to result in earlier discharge for patients following gastrointestinal surgery.²³

Surgical cytoreduction with intraperitoneal chemotherapy is a long and often physically demanding procedure. The fatigue engendered on a single surgeon may lead to suboptimal outcomes. We have employed a three-surgeon approach, which allows for breaks and thereby prevents fatigue and may contribute to shorter operative times. Although there are no controlled data to support this practice, we believe it is practical.

Surgical cytoreduction and IPHC is a promising treatment for patients with peritoneal metastases and peritoneal-based malignancies. The modifications that we have made may have contributed to shorter operative times, acceptable operative morbidity without mortality, short hospital stays, and survival consistent with that in other series. The development of cooperative trials among centers performing cytoreductive surgery and IPHC are needed to investigate the efficacy of this treatment paradigm as well as the technical details that may contribute to limiting morbidity.

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