

Delayed Presentation of Major Complications in Patients Undergoing Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy Following Hospital Discharge

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Introduction: Peritoneal surface malignancy is increasingly treated with cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC). This is associated with potentially high morbidity. We analyzed the incidence of delayed major complications following CRS plus HIPEC. **Methods:** Delayed events were chosen as those which occurred after discharge from the hospital following CRS plus HIPEC and prior to 90 days. Major complications included any adverse event requiring intervention or intensive care unit admission. **Results:** One hundred thirty six patients underwent 140 procedures. Eight patients (5.7%) developed delayed major complications. Complications were pancreatic pseudocyst/pancreatitis (n = 3), abdominal wall dehiscence (n = 2), gastric perforation (n = 1), and ureteral stricture with associated hydronephrosis (n = 2). All of the patients had undergone multivisceral resections. Seven patients achieved complete cytoreduction (cc 1). Mean peritoneal carcinomatosis index (PCI) was 15.25 ± 5.33 (6–22). Standard of care was met for the management of all the complications and all patients recovered following intervention without any further morbidity or mortality. **Conclusion:** There is a lack of report of the delayed major complications in patients undergoing CRS plus HIPEC in the literature. Awareness should be raised among health care providers regarding possible occurrence of such late complications given that many patients undergo CRS plus HIPEC remotely from their localities.

INTRODUCTION

The surgical treatment of peritoneal surface malignancies in the past was largely limited to palliation. With better understanding of the natural history of the disease, combining cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has been increasingly utilized. The procedure, however, is generally long and technically challenging. The potential for major morbidity is one of the many criticisms of the application of HIPEC to patients with peritoneal surface disease.

Multiple groups have assessed the risk factors for CRS plus HIPEC-related complications with reported morbidity and mortality rates of 12–52% and 0.9–5.8%, respectively [1–5]. These reports are limited to perioperative complications. To our knowledge, long-term complications following CRS plus HIPEC have not been described. Rather, immediate postoperative morbidity and mortality has been extensively addressed.

In general, delayed major complications following well-studied major abdominal surgeries, such as Whipple procedure, are underreported or have many limitations. For example, Epelboym et al. [6] found that in the American College of Surgeon National Surgical Quality Improvement Program (ACS NSQIP) database there is an inevitable tendency to misclassify the postoperative events following pancreatectomies on a 30-day and 90-day scale. They suggested a hepatopancreatobiliary-specific module to better capture and report the long-term outcome of the procedure, which our group thinks would be a valuable tool to establish for the CRS plus HIPEC patient population early on. Herein, we report our 'delayed' complications occurring after discharge from the hospital following CRS plus HIPEC.

MATERIALS AND METHODS

All patients receiving CRS plus HIPEC for peritoneal surface malignancies between August 2007 and April 2014 were included. Data for this retrospective analysis was retrieved from a prospectively-maintained database. Procedures were conducted by a single surgeon.

Our treatment consisted of tumor resection and removal of involved organs and peritoneum, as deemed safe by the operating surgeon per previous description [7]. We used Cavitational Ultrasonic Surgical Aspirator (CUSATM) (Tyco Healthcare Group LP, Valleylab, CO) and/ or Plasma JetTM (Plasma Surgical Inc., Roswell, GA) to cytoreduce tumors that were adherent to vital structures that could not be removed. Peritoneal Cancer Index (PCI) was used to score the extent of peritoneal involvement at the time of surgery.

At the completion of cytoreductive surgery, HIPEC was performed using the closed abdomen technique at 42–43°C. Inflow and outflow catheters were placed into the abdominal cavity. The abdomen was then closed at the skin level using running suture to prevent leakage of the perfusate. Temperature probes were placed at the inflow and outflow catheters just outside the exit sites from the abdomen.

We used 3 L Ringer's lactate as perfusate to establish a circuit with flow rates of approximately 800–1,400 ml/min managed by the perfusionist. Intraperitoneal chemotherapy regimens used included Mitomycin C (40 mg) for malignancies of GI origin, or the combination of Cisplatin (4 mg/L) and Doxorubicin (1 mg/L) for non-GI malignancies. The ThermoChemTM HT-1000 system (ThermaSolutions, White Bear Lake, MN) was used to establish the heated circuit prior to April 2013. We have been

utilizing the RecirculatorTM 8.0 (Eight Medical, Bloomington, IN) since April 2013. The main analysis included 'delayed' major postoperative complications defined as occurring after discharge from the hospital following CRS plus HIPEC and prior to 90 days postoperatively. They were reported according to the Clavien–Dindo grading system [8]. Grade III–IV complications were considered to be major and included any complication requiring endoscopic, radiologic, or surgical intervention or any life threatening postoperative condition requiring intensive care unit management.

RESULTS

One hundred thirty six patients underwent 140 procedures of CRS plus HIPEC. Eight patients (5.7%) developed delayed Grade III and IV complications based on the Clavien–Dindo classification. Complications were pancreatic pseudocyst/pancreatitis (three patients), fascial dehiscence (two patients), gastric perforation (one patient), and ureteral stricture with associated hydronephrosis (two patients) without recurrent disease.

All of the patients had undergone multivisceral resections along with the peritonectomy. PCI ranged from 6 to 22. In seven of these eight patients' complications complete cytoreduction (cc 1) was achieved. The Mean Length of Surgery (LOS) for this group was 496.25 ± 24.52 min; mean Length of Hospitalization (LOH) following CRS plus HIPEC was 13.75 ± 7.05 days. Seven patients were discharged home and one to a rehabilitation facility. A delay in the presentation due to the occurrence of the late complication ranged from postoperative day (POD) 17 to POD 81, with a mean of 45.13 ± 42.5 days. All patients recovered without added morbidity or mortality following optimal management of their complications, and they were subsequently discharged following readmission. A demographic and operative overview of the patients who developed delayed complications is summarized in Table I.

DISCUSSION

Peritoneal Carcinomatosis (PC) refers to the dissemination of tumor cells within the peritoneal cavity. Those tumors can originate from the peritoneal surface itself or from an intraabdominal organ. In either case, PC would escalate the staging of the cancer to stage IV which was regarded as terminal and non-operative with very poor prognosis. The EVOCAPE 1 group prospectively followed 370 patients and concluded in 2000 that the mean and overall median survival after establishing a diagnosis of PC from non-gynecologic malignancies are 6 and 3.1 months, respectively [9].

In the last two decades, the surgical approach for those terminal cases has dramatically changed since the introduction of the CRS plus HIPEC combination by Dr. Sugarbaker, and the significant improvement in survival that was reproduced by many surgeons in a variety of institutions. However, CRS plus HIPEC remains an aggressive means to achieve locoregional control of the metastatic disease. The macroscopic resection of all gross disease carries a risk of morbidity, both in the short and long term, postoperatively.

A systematic review by Chua et al. reported level II and III evidence studies between 2003–2008 on CRS plus HIPEC, in which they demonstrated that the perioperative mortality ranged between 0–17% overall. This was between 0.9–5.8% in high-volume centers. Moreover, the same review reported a mean major complication rate (grade III and IV) of 28.8% during a mean postoperative stay of 19 days [10]. Comparable rates were reproduced in a Dutch multicenter experience of CRS plus HIPEC with major complication and mortality rates of 34 and 3%, respectively [11]. Jafari et al. published their

report regarding the 30-day morbidity and mortality of CRS plus HIPEC [12]. They demonstrated that bleeding (17%), septic shock (16%), pulmonary complications (15%), and organ-space infections (9%) were the most prevalent immediate postoperative complications on analysis of the ACS NSQIP data between 2005 and 2011. The average length of stay was 13 days, with a 30-day readmission rate of 11%. The rate of reoperation was 10%, and overall mortality rate of 2%.

Based on these studies and supporting evidence in the literature, it was established that short term postoperative morbidity and mortality following CRS-HIPEC are improving with the advancement in technique and continuous breakthroughs in chemotherapy regimen and administration. Thus, an increasing number of centers are currently offering this approach for the management of peritoneal surface malignancies with improved outcomes.

However, most of the CRS plus HIPEC related literature has only addressed the procedure's short term morbidities which occur during the initial hospitalization. To the best of our knowledge, there is no description of the long term complications that can occur during follow up although disease-free and survival rates evaluation have been documented. Five-year survival rate was the primary outcome for most of the major CRS plus HIPEC reports for CRC and PMP [13–15].

In this study, we report that 5.7% of our patients were rehospitalized following discharge from the initial CRS plus HIPEC with grade III/IV complications that varied between gastric perforation (one patient), ureteral stricture (two patients), fascial dehiscence and evisceration (two patients), and pancreatic pseudocyst formation (three patients).

These complications were managed according to the standard of care and an optimal outcome was achieved in all the reported cases without significant added morbidity or any mortality. The late mean readmission date of POD 45 raises the concern for the possible occurrence of serious complications while patients are no longer being followed by the primary treating surgeon or institution. Therefore, in the authors' opinion, a longer period of immediate postoperative follow up must be considered. Also, education regarding the possible occurrence of late adverse events related to CRS plus HIPEC is warranted to care givers for early diagnosis and report of the adverse events.

Various studies were conducted in attempt to establish a clear set of factors that increases the risks of major morbidities in the perioperative period following CRS-HIPEC. Performance status, extent of carcinomatosis, duration of the surgery, number of peritonectomies and anastomoses, extent of cytoreduction, number of suture lines, and dose of chemotherapy were concluded as the factors associated with increased postoperative complications [1,16–18]. Interestingly, all the above listed factors are purely technical or operation-related factors.

It may be difficult to compare CRS plus HIPEC to other major intraabdominal procedures in terms of complications rate. Considering pancreaticoduodenectomy (PD) as an example, postoperative complications are common following this procedure and has been reported to range from 30% to 50% [19–21], with readmission rate ranging from 16% to 50% [22–25]. Sadot et al. [24] recently evaluated reasons for readmission following PD and the most common cause for 30-day readmission was procedure-related infection, while the most common cause for 31 to 90-day readmission reason was failure to thrive and chemotherapy-related symptoms.

Hoshal et al. [26] described the delayed complications of 134 Whipples completed during 28-year period by the same surgeon in a single institution. There was a noted variance in the type of delayed major complications compared to ours: three incisional hernias, three marginal ulcers bleeding, two jejunal strictures, one liver abscess, one choledocholithiasis, and one gastric perforation. However, the management of these delayed complications was not described.

One limitation of our study is that we did not assess whether there was a significant difference in demographics or operative characteristics among patients who developed delayed complications because of the small cohort of patients. We also did not address the overall emergency room visits nor the readmission rate given that this specific data reflects—in its majority—the occurrence of noninterventional postsurgical complications, whereas in our report the emphasis on major complications was our goal. Another limitation to our study is the inability of our data to show a pattern or predisposing factors to delayed complications that would help physicians anticipate such complications.

While we did not specifically explore all causes of readmission, we reviewed the literature reporting patients with stage III late complications and noted that they were all procedure related [26]. Lee et al. [25] showed an average of 11 days post discharge for readmission following PD. The reasons for readmission were: intraabdominal abscess, wound infection, sepsis, clostridium difficile infection, abdominal wall abscess, retained common bile duct stent, and abdominal pain of unclear origin. Hence, it is necessary to further investigate the long term complications of CRS plus HIPEC, and analyze the risk factors which would warrant closer and longer follow-up postoperatively.

In conclusion, the surgery-related major complications following CRS plus HIPEC can occur late in the postoperative period after discharge from the initial surgery. Given that patients are usually referred to institutions remote from their localities to receive the procedure, it is still possible that those delayed complications occur after they are no longer being followed or managed by the treating HIPEC institution. Therefore, the postoperative complications reported in the literature may not reflect the actual surgical morbidity, pertaining to long term follow up.

CONCLUSION

The authors of this article wish to raise the awareness of these delayed complications in our patient population, and educate care providers that CRS plus HIPEC can cause late major complications potentially requiring an intervention and ICU admission, and should always be reported to the primary treating institution. We also encourage surgeons and institutions to conduct longer follow up or communications with patients who undergo CRS plus HIPEC. The early establishment of a CRS plus HIPEC-specific module for longterm follow up or case tracking would probably be a useful tool to accurately apprehend the outcome and complications of this procedure.

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