Clinical Study
Gastrointestinal Complications in 147 Consecutive Patients with Peritoneal Surface Malignancy Treated by Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy

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Received 3 June 2011; Accepted 13 August 2011

1. Introduction

In the past, peritoneal carcinomatosis (PC) was considered as a final stage of unresectable cancer with a short duration of survival [1–3]. Since the mid 1990s, studies on CRS combined with perioperative intraperitoneal chemotherapy (PIC), hyperthermic intraperitoneal chemotherapy (HIPEC), and/or early postoperative intraperitoneal chemotherapy (EPIC) are considered a new treatment options for selected patients with peritoneal carcinomatosis [4–12].

As the surgical technology has improved and the regimens for administering chemotherapy have become safer, the complications associated with this treatment approach have decreased [13–18]. In a systematic review, Chua reviewed all the relevant studies reported before August 2008 and concluded that the morbidity and mortality of CRS and HIPEC were similar to other major gastrointestinal interventions [19]. An important concept, “the learning curve,” has been demonstrated to operate in the expanded application of CRS and HIPEC [20–22]. Smeenk et al. reported the results of 323 procedures over a 10-year time period; they showed a decrease in major morbidity from 71% to 34% [22]. Yan et al. demonstrated a reduction in the rate of severe morbidity, transfusion requirement, duration of operation, and length of intensive care unit stay over a similar period of time in 140 patients [21].

In recent publications overall grade III–IV morbidity rates are shown to be between 7 and 41% [23–26]. For gastrointestinal events, small bowel perforations and anastomotic leaks are the most common and clinically significant...
complications after CRS and PIC [23–27]. The aim of this study was to report the incidence of gastrointestinal events and identify the associated risk factors.

2. Materials and Methods

2.1. Patient Characteristics. All patients with appendiceal and colorectal carcinomatosis treated in a uniform manner at Washington Hospital Center, between January 1, 2006 and December 31, 2009 constituted the basis of the present study. Institutional Review Board approval was obtained to collect and analyze these data. All patients with appendiceal and colorectal malignancy who received CRS combined with a standardized treatment with PIC were included (Table 1). Patients who had an incomplete CRS combined with PIC were included in the study, patients who had an open and close procedure or palliative debulking were not included. The quantitative prognostic indicators were the histological grade, the prior surgical score (PSS), the peritoneal cancer index (PCI), and the completeness of cytoreduction score (CC) [28].

2.2. Cytoreductive Surgery and Perioperative Intraperitoneal and Systemic Chemotherapy. The goal of surgery in these patients was to visibly clear the abdomen and pelvis of cancer nodules. This required a series of peritonectomy procedures and visceral resections (Table 1). Normal peritoneum or normal visceral structures were not resected. A mechanical bowel preparation was used in all patients. Within one hour prior to the abdominal incision, patients received antibiotic prophylaxis. Prophylaxis for venous thrombosis and pulmonary embolus during the cytoreductive surgery was limited to sequential compression devices (SCD Response, Kendall Co., Mansfield, MA).

All patients received HIPEC in the operating room immediately after the CRS but before intestinal anastomoses or repair of seromuscular tears. A combination of two drugs was administered intraperitoneally: mitomycin C (15 mg/m²) and doxorubicin (15 mg/m²). The target temperature for the entire abdomen during HIPEC was 41.5 °C. Simultaneously, intravenous 5-fluorouracil (400 mg/m²) and leucovorin (20 mg/m²) were administered as a rapid infusion over 6–8 minutes. HIPEC was given using the Coliseum technique [29]. A heater circulator (Belmont Instruments Corporation, Billerica, MA) was used to maintain moderate hyperthermia within the abdomen and pelvis (41–43 °C). During the first 45 minutes, only manual distribution of the chemotherapy solution occurred. In the second 45 minutes of the 90-minute treatment, seromuscular tears were repaired, the anterior and posterior rectus sheath were brought together with a running 2-0 Vicryl suture (Ethicon, Cincinnati, OH), and chest tubes were positioned.

Esophago-jejunal and colorectal anastomoses were performed with a 28 mm or 33 mm diameter circular stapler, respectively (Ethicon, Cincinnati, OH). Esophago-jejunal anastomoses were reinforced with a layer of silk sutures. If the colorectal stapled anastomoses could be well visualized, a second layer of 3–0 silk sutures was used to plicate the anastomosis. If this double layer anastomosis was performed,

| Variable                                      | n  |
|----------------------------------------------|----|
| Total Patients                                | 147|
| Gender                                        |    |
| Male                                          | 68 (46%)|
| Female                                        | 79 (54%)|
| Age at the time of surgery (years)            |    |
| Mean ± 1 Standard Deviation                   | 49.9 (± 8.7) |
| Median                                        | 51 |
| Range                                         | 23–64 |
| Primary cancer diagnosis                      |    |
| Appendiceal cancer                            | 135 (92%) |
| Colorectal cancer                             | 12 (8%)  |
| Histological grade                            |    |
| Grade 1                                       | 61 (41.6%) |
| Grade 2                                       | 12 (8%)  |
| Grade 3                                       | 74 (50.4%) |
| Prior surgical score                          |    |
| 0–2                                          | 133 (90.5%) |
| 3                                            | 14 (9.5%)  |
| Peritoneal cancer index                       |    |
| 0–10                                         | 31 (21%)  |
| 11–20                                        | 40 (27%)  |
| 21–30                                        | 53 (36%)  |
| 31–39                                        | 23 (16%)  |
| Completeness of cytoreduction                 |    |
| Complete                                      | 125 (85%) |
| Incomplete                                    | 22 (15%)  |
| Peritonectomy procedures                      |    |
| Pelvic                                        | 123 (84%) |
| Right upper quadrant                          | 109 (74%) |
| Left upper quadrant                           | 72 (49%)  |
| Omental bursa                                 | 70 (48%)  |
| Anterior abdominal wall                       | 50 (34%)  |
| Peritonectomy procedures per patient          |    |
| zero                                          | 18 (12%)  |
| one                                           | 21 (14%)  |
| two                                           | 16 (11%)  |
| three                                         | 29 (20%)  |
| four                                          | 31 (21%)  |
| five                                          | 32 (22%)  |
| Visceral resections performed                 |    |
| Greater omentectomy                           | 144 (98%) |
| Splenectomy                                   | 84 (57%)  |
| Rectosigmoid colon resection                  | 70 (48%)  |
| Right colon resection                         | 57 (39%)  |
| Hysterectomy                                  | 47 (32%)  |

Table 1: Patients characteristics, quantitative prognosis indicators, peritonectomies, visceral resections, and intraoperative treatments.
Table 1: Continued.

| Variable                        | n   |
|---------------------------------|-----|
| Small bowel resection           | 29  (20%) |
| Transverse colon resection      | 20  (14%)  |
| Gastrectomy                     | 4   (3%)   |
| Visceral resections per patient |     |
| Zero                            | 2   (1.4%)  |
| One                             | 20  (13.6%) |
| Two                             | 34  (23.1%) |
| Three                           | 34  (23.1%) |
| Four                            | 32  (21.8%) |
| Five                            | 15  (10.2%) |
| Six                             | 8   (5.4%)   |
| Seven                           | 2   (1.4%)   |
| Anastomoses performed           |      |
| Esophageal                      | 2   (1.4%)   |
| Small bowel                     | 22  (15.0%) |
| Ileocolic                       | 29  (19.7%) |
| Colocolic                       | 3   (2.0%)   |
| Colorectal                      | 56  (38.1%) |
| Anastomoses performed per patient |      |
| Zero                            | 74  (50.3%) |
| One                             | 44  (29.9%) |
| Two                             | 21  (14.3%) |
| Three                           | 6   (4.1%)   |
| Four                            | 2   (1.4%)   |
| Ostomies performed              |      |
| Diverting ileostomy             | 30  (20.4%) |
| End ileostomy                   | 13  (8.8%)   |
| None                            | 67  (70.8%) |
| Blood replacement                |      |
| None                            | 39  (26.5%) |
| Blood 1–3                       | 68  (46.3%) |
| Blood 4–6                       | 35  (23.8%) |
| Blood > 6                       | 5   (3.4%)   |
| Fresh frozen plasma replacement |      |
| None                            | 80  (54.4%) |
| Plasma 1–4                      | 51  (34.7%) |
| Plasma >4                       | 16  (10.9%) |
| Time in operating room (hours)  |      |
| 0–6                             | 10  (6.89%) |
| 6–12                            | 124 (84.4%) |
| > 12                            | 13  (8.8%)   |
| Chemotherapy treatments         |      |
| HIPEC only                      | 82  (55.8%) |
| HIPEC plus EPIC                 | 65  (44.2%) |

no diverting ostomy was constructed. If the colorectal anastomosis was too low to place a second layer of silk sutures over the circular stapled anastomosis, a diverting ostomy was constructed. All small bowel, colo-colic and ileocolic anastomoses were double-layer hand sewn with an inner layer of running 3-0 Maxon (Davis and Geck, Danbury, CT) and interrupted outer layer of 3-0 silk.

2.3. Early Postoperative Intraperitoneal Chemotherapy (EPIC). The EPIC 5-fluorouracil (5-FU) was withheld in patients, who had a full course of oxaliplatin-based FOLFOX chemotherapy prior to CRS. The dose of EPIC 5-FU was 400 mg/m²/day for women and 600 mg/m²/day for men. It was infused via a Tenckhoff catheter over approximately 15 minutes with a 23-hour dwell time. After one hour of drainage, another administration of 5-FU occurred for 4 days after surgery.

2.4. Postoperative Management. Patients were transferred directly to a surgical intensive care unit for monitoring and extubation. An 18 French nasogastric tube (Silicone Salem Sump Tube, Kendall Co., Mansfield, MA) was placed intraoperatively in all patients and remained until the drainage of bile from the stomach has ceased and some enteric function per rectum or per ostomy had occurred. All patients received postoperative intravenous feeding through the intrajugular vein for the five postoperative days and then through a percutaneous central catheter (Vaxcel, Glen Falls, NY) until gastrointestinal function returned. Closed suction drains remained in place after surgery in all patients until drainage was below 50 mL per 24 hours from a single drain.

2.5. Database for Morbidity Assessment. The database was specially constructed to evaluate gastrointestinal complications in patients with peritoneal surface malignancy. The morbidity variables were prospectively recorded according to the Common Toxicity Criteria (version 3.0) of the National Cancer Institute [30]. It consisted of 11 gastrointestinal adverse events (anastomotic failure, fistula, pancreatic fistula, pancreatitis, bile leak, chyle leak, prolonged ileus, small bowel obstruction, nausea/vomiting, diarrhea and ascites). Types of gastrointestinal adverse events observed and the grade are listed in Table 2.

The following clinical variables were analyzed to assess factors predictive of gastrointestinal complications: gender, age (≤50 versus >51), primary cancer location, grade (grade 1 versus grade 2-3), prior surgical score (0–2 versus 3–5), peritoneal cancer index (0–10, 11–20, 21–30, 31–39, and 0–20 versus 31–39), completeness of cytoreduction (complete versus incomplete), peritoneectomy procedures (pelvic, right upper quadrant, left upper quadrant, omental bursa, and anterior abdominal wall), number of peritoneectomy procedures per patient (0–2 versus 3–5), visceral resections performed (omentumectomy, splenectomy, rectosigmoid colon resection, right colon resection, hysterectomy, small bowel resection, transverse colon resection, and gastric resection), visceral resections performed per patient (0–2 versus 3–7), types of anastomoses performed (esophago-jejunal, small bowel, ileocolic, colocolic, and colorectal), number
Table 2: The total number of gastrointestinal adverse events grade I through grade IV.

| Organ System                  | Grade I-Asymptomatic and self-limiting | Grade II-Symptomatic and medical treatment | Grade III-Invasive intervention | Grade IV-ICU care or return to operating room |
|-------------------------------|----------------------------------------|--------------------------------------------|---------------------------------|-----------------------------------------------|
| Gastrointestinal System       | N = 5                                   | N = 15                                     | N = 4                           | N = 11                                        |
| Anastomotic failure           | Sub-clinical, afibrile, radiologic diagnosis (0) | Antibiotics, febrile (0) | Percutaneous drainage (0) | Reoperation (3) |
| Fistula                       | Sub-clinical, afibrile, radiologic diagnosis (0) | Antibiotics, febrile (0) | Percutaneous drainage (0) | Reoperation (3) |
| Pancreatic fistula            | Elevated enzymes in drains (0)          | TPN and somatostatin (0)                  | Percutaneous drainage (0)      | Reoperation (1) |
| Pancreatitis                  | Elevated enzymes (4)                   | ≤3 Ranson’s score (4)                     | 4–6 Ranson’s score (0)         | Reoperation/ICU (1) |
| Bile leak                     | Bile only in drain (0)                  | Bile in drain, febrile (2)                | Percutaneous drainage (0)      | Reoperation (1) |
| Chyle leak                    | Transient (1)                           | Prolonged 1 week (0)                      | Cease prior to discharge (0)   | Persist past hospital discharge (0) |
| Prolonged ileus               | N/G (0)                                 | N/G > 2 weeks (1)                         | N/G >3 weeks (0)               | Persist past hospital discharge (0) |
| Small bowel obstruction       | Abdominal pain (0)                      | Abdominal pain, N/G reinsertion (0)       | Repeat radiologic studies (0)  | Reoperation (1) |
| Nausea/vomiting               | Transient vomiting (0)                  | Vomiting, anti-emetics (7)                | Vomiting, IV therapy (4)       | Vomiting with surgical intervention or ICU (1) |
| Diarrhea                      | Transient <2 days (0)                   | Tolerable, but >2 days (1)                | Intolerable, IV therapy (0)    | Dehydration prolonged IV therapy (0) |
| Ascites                       | Mild (0)                                | Fluid restriction (0)                      | Symptomatic, percutaneous tap (0) | Compromising vital function, ICU care (0) |

of anastomoses performed per patient (0–2 versus 3–5), ostomies performed (none, diverting ileostomy and end ileostomy), blood replacement (none, 1–3 units, 4–6 units, >6 units), fresh frozen plasma replacement (none, 1–4 units, >4 units), time in the operating room in hours (0–6, 7–12, >12), and chemotherapy treatment (HIPEC only versus HIPEC plus EPIC).

2.6. Statistical Methods. For univariate methods to assess the association between gastrointestinal complications and pre- and perioperative clinical characteristics, the Pearson Chi-square was used, or the Fisher’s exact test was used if there was sparse distribution. Those clinical characteristics that were significantly correlated to the outcome by univariate analysis (P-value < 0.05) were then fitted into the logistic regression model for multivariate analysis of variances to assess the strength of the risk factors.

All statistical analyses were conducted using SAS (SAS Institute Inc, Cary, NC, USA. SAS (r) Proprietary Software 9.2 (TS2M3)).

3. Results

3.1. Preoperative and Intraoperative Data. Between January 1, 2006 and December 31, 2009, a total of 147 patients (135 appendiceal cancer, 12 colorectal cancer) were treated. There were 68 men and 79 women. The mean age was 49.9 years (range, 23–64). Data on patient characteristics, quantitative prognosis indicators, peritonectomies, visceral resections, and intraoperative treatments are summarized in Table 1. In these 147 patients, 424 peritonectomy procedures were performed with a mean of 3 peritonectomies per patient (range 0 to 5). In 18 patients (12%), no peritonectomy procedures were performed and 32 patients (22%) had all 5 peritonectomy procedures. A total of 455 visceral resections were performed. The mean number per patient was 3.1 with a range of 0 to 7. Greater omentectomy was performed in 144 patients (98%) and 4 (3%) had a total or partial gastrectomy. In two patients (1%), there were no visceral resections. Thirty-four (23%) had 2 visceral resections and an additional 34 patients (23%) had 3 visceral resections. The total number of anastomoses in all patients was 112 with a mean of 0.76 per patient (range 0–4). The most common anastomosis was a colorectal anastomosis performed in 56 patients (38%). There was a total of 43 ostomies (29%) performed. Thirty (20%) were diverting ileostomies to protect a colorectal anastomosis and, 13 (9%) were permanent-end ileostomies following total abdominal colectomy.

In 39 patients (27%), no blood replacement in the operating room occurred. Only 5 patients had more than six units transfused. Sixty-seven patients (46%) received fresh frozen plasma and, 16 (11%) patients had more than four units. All 147 patients were treated with HIPEC and intravenous 5-FU in the operating room. In 65 patients (44%), EPIC was used in the postoperative period (Table 1).

3.2. Adverse Events. In these 147 patients, there was a single postoperative death (0.7%). This patient developed
Table 3: Univariate and multivariate analysis (gastrointestinal events).

|                      | Gastrointestinal events I–IV univariate analysis | Gastrointestinal events I–IV multivariate analysis |
|----------------------|-------------------------------------------------|---------------------------------------------------|
|                      | Yes \(N = 25\) | No \(N = 122\) | \(P\) Value/\(OR\) \((95\% \text{ CI})\) | Odds Ratio | \(P\) Value |
| Gender               |                       |                |                                      |            |              |
| Male                 | 12                     | 56             | 0.8480                                |            |              |
| Female               | 13                     | 66             | 0.9 (0.4, 2.2)                       |            |              |
| Age                  |                       |                |                                      |            |              |
| \(\leq 50\text{ year}\) | 14                     | 58             | 0.4408                                |            |              |
| \(>50\text{ year}\) | 11                     | 64             | 0.7 (0.3, 1.7)                       |            |              |
| Location             |                       |                |                                      |            |              |
| Appendix             | 22                     | 113            | 0.4297                                |            |              |
| Colorectal           | 3                      | 9              | 1.7 (0.4, 6.8)                       |            |              |
| Grade                |                       |                |                                      |            |              |
| Grade 1              | 5                      | 56             | 0.0166                                | 0.4 (0.1, 1.3) | 0.1345 |
| Grades 2-3           | 20                     | 66             | 0.3 (0.1, 0.8)                       |            |              |
| Prior Surgical Score |                       |                |                                      |            |              |
| 0–2                  | 23                     | 110            | 1.0000                                |            |              |
| 3–5                  | 2                      | 12             | 0.8 (0.2, 3.8)                       |            |              |
| Peritoneal Cancer Index (4 groups) |       |                |                                      |            |              |
| 0–10                 | 3                      | 28             | Reference                             |            |              |
| 11–20                | 6                      | 34             | 0.7220                                | 1.6 (0.4, 7.2) | NT   |
| 21–30                | 7                      | 46             | 0.7384                                | 1.4 (0.3, 5.9) | NT   |
| 31–39                | 9                      | 14             | 0.0100                                | 6.0 (1.4, 25.7) | NT   |
| Peritoneal Cancer Index (2 groups B) |       |                |                                      |            |              |
| 0–30                 | 16                     | 108            | 0.0049                                | 2.8 (0.9, 8.4) | 0.0586 |
| 31+                  | 9                      | 14             | 4.3 (1.6, 11.7)                      |            |              |
| Completeness of Cytoreduction |           |                |                                      |            |              |
| Complete             | 18                     | 107            | 0.0625                                |            |              |
| Incomplete           | 7                      | 15             | 2.8 (1.0, 7.7)                       |            |              |
| Peritonectomy Procedure |                  |                |                                      |            |              |
| Pelvic               | 21                     | 102            | 1.0000                                |            |              |
| Right Upper Quadrant | 19                     | 90             | 0.8166                                | 1.1 (0.4, 3.1) | NT   |
| Left Upper Quadrant  | 11                     | 61             | 0.5846                                | 0.8 (0.3, 1.9) | NT   |
| Omental Bursa        | 12                     | 58             | 0.9666                                | 1.0 (0.4, 2.4) | NT   |
| Anterior Abdominal Wall | 11                    | 39             | 0.2473                                | 1.7 (0.7, 4.0) | NT   |
| Peritonectomy Procedure per patient | |                |                                      |            |              |
| 0–2                  | 8                      | 47             | 0.5391                                |            |              |
| 3–5                  | 17                     | 75             | 1.3 (0.5, 3.3)                       |            |              |
| Visceral Resections Performed | |                |                                      |            |              |
| Omentectomy          | 24                     | 120            | 0.4308                                |            |              |
| Splenectomy          | 15                     | 69             | 0.7513                                |            |              |
| Rectosigmoid colon   | 14                     | 43             | 0.0524                                | 2.3 (0.98, 5.6) | NT   |
Table 3: Continued.

| Gastrointestinal events I–IV univariate analysis | Gastrointestinal events I–IV multivariate analysis |
|-----------------------------------------------|--------------------------------------------------|
| **Yes N = 25** | **No N = 122** | **P Value** | **OR (95% CI)** | **Odds Ratio** | **P Value** |
| Right colon resection | 15 | 55 | 0.1736 | 1.8 (0.8, 4.4) | NT |  |
| Hysterectomy | 4 | 43 | 0.0601 | 0.3 (0.1, 1.1) | NT |  |
| Small bowel resection | 9 | 20 | 0.0493 | 2.9 (1.1, 7.4) | 1.3 (0.4, 4.2) | 0.6202 |
| Transverse colon | 5 | 15 | 0.3377 | 1.8 (0.6, 5.5) | NT |  |
| Gastrectomy | 2 | 2 | 0.1343 | 5.2 (0.7, 38.9) | NT |  |
| Visceral Resections Performed per patient | - | - | - | - | - | - |
| 0–2 | 7 | 49 | 0.2539 | - | NT |  |
| 3–7 | 18 | 73 | 1.7 (0.7, 4.4) | - | NT |  |
| Anastomoses performed | - | - | - | - | - | - |
| Esophago-jejunal | 1 | 1 | 0.3122 | 5.0 (0.3, 83.4) | NT |  |
| Small bowel | 7 | 15 | 0.0605 | 2.8 (1.0, 7.7) | NT |  |
| Ileocolic | 7 | 22 | 0.2741 | 1.8 (0.7, 4.7) | NT |  |
| Colocolic | 1 | 2 | 0.4308 | 2.5 (0.2, 28.7) | NT |  |
| Colorectal | 14 | 42 | 0.0430 | 2.4 (1.0, 5.8) | 1.4 (0.5, 3.8) | 0.4986 |
| Anastomoses performed per patient | - | - | - | - | - | - |
| 0–2 | 21 | 118 | 0.0288 | 1.9 (0.3, 11.8) | 0.4616 |
| 3–5 | 4 | 4 | 5.6 (1.3, 24.2) | - | NT |  |
| Ostomies performed | - | - | - | - | - | - |
| None | 15 | 89 | reference | - | NT |  |
| Diverting ileostomy | 8 | 22 | 0.1172 | 2.2 (0.8, 5.7) | NT |  |
| End ileostomy | 2 | 11 | 1.0000 | 1.1 (0.2, 5.4) | NT |  |
| Blood replacement | - | - | - | - | - | - |
| None | 7 | 32 | reference | - | NT |  |
| Blood 1–3 | 8 | 60 | 0.3752 | 0.6 (0.2, 1.8) | NT |  |
| Blood 4–6 | 9 | 26 | 0.4178 | 1.6 (0.5, 4.8) | NT |  |
| Blood > 6 | 1 | 4 | 1.0000 | 1.1 (0.1, 11.8) | NT |  |
| Fresh frozen plasma replacement | - | - | - | - | - | - |
| None | 13 | 67 | reference | - | NT |  |
| Plasma 1–4 | 7 | 44 | 0.6953 | 0.8 (0.3, 2.2) | NT |  |
| Plasma > 4 | 5 | 11 | 0.1724 | 2.3 (0.7, 7.9) | NT |  |
a profound neutropenia followed by systemic inflammatory response syndrome and multiorgan failure. The overall incidence of gastrointestinal adverse events was 17%. Thirty-five gastrointestinal events occurred in 25 patients. Nine patients had more than one gastrointestinal event. All the gastrointestinal events observed grade I through IV are summarized in Table 2.

The incidence of grade III and IV events was 8% with 15 events observed in 12 patients. There were 5 grade I gastrointestinal events (4 pancreatitis and 1 chyle leak) that occurred in 5 patients. There were 15 grade II gastrointestinal events (4 pancreatitis, 1 prolonged ileus, 7 nausea/vomiting, and 1 diarrhea) that occurred in 11 patients. Four grade III gastrointestinal events (4 nausea/vomiting) occurred in 4 patients. Eleven grade IV gastrointestinal events (3 anastomotic failures, 3 fistulas, 1 pancreatic fistula, 1 pancreatitis, 1 bile leak, 1 small bowel obstruction, and 1 nausea/vomiting) occurred in 8 patients and all but two required a return to the operating room.

By univariate analysis, the following variables were proven to have a statistically significant correlation with gastrointestinal morbidity (Table 3): histological grade (\( P = 0.0166 \)), PCI (\( P = 0.0049 \)), small bowel resection (\( P = 0.0493 \)), performance of a colorectal anastomosis (\( P = 0.0430 \)) and the number of anastomoses performed per patient (\( P = 0.0288 \)).

On multivariate analysis using the logistic regression model, the PCI was shown to be the only independent risk factor for gastrointestinal complications (\( P = 0.0586 \)).

In patients who had HIPEC plus EPIC, an additional four treatments with intraperitoneal 5-fluorouracil were given on postoperative days 1–4. Thirteen of 52 patients (25%) had a grade I–IV complication. Ten of 69 patients (14%) who had HIPEC only were observed to have a grade I–IV complication. As shown in Table 3, this was not significant by a univariate (\( P = 0.2314 \)) or by the multivariate analysis.

4. Discussion

At our institution the management of peritoneal surface malignancy requires an integration of extensive surgery combined with intraperitoneal chemotherapy administered as a planned part of the surgical procedures [31]. The aim of this combined treatment modality is to remove all macroscopic tumor nodules and any adhesions between the bowel loops, in order to allow chemotherapeutic agents to be uniformly distributed within the peritoneal cavity to eradicate any microscopic tumor deposits. The potential advantages of using HIPEC compared to standard intravenous chemotherapy include an increased exposure to chemotherapeutic drugs at the peritoneal surface, an increase of drug penetration into the tissues, a synergistic effect of hyperthermia with systemic chemotherapy, and an independent cytotoxic effect of hyperthermia [32].

It is clear, however, that the effects of this regional chemotherapy are not limited to the peritoneal space. The profound effect that these treatments have on wound healing is shown by the increased incidence of gastrointestinal events. This paper represents the effort of our group to identify gastrointestinal events in patients with peritoneal surface malignancy and begin to understand their causes.

We found that our overall incidence of gastrointestinal events was 17% (grade I–IV), in that 35 gastrointestinal events occurred in 25 of the 147 patients. There was often more than one gastrointestinal event per patient. The incidence of grade III and IV gastrointestinal events was 8%.

Our data is compared to those reported by other authors in Table 4. We have calculated the incidence of gastrointestinal events (grades III-IV) in Glehen, Kusamura, and Hansson’s manuscripts by dividing the total number of events by the total number of patients. In Youssef manuscript and in our data, we were able to calculate the incidence of events per patient (Table 4). Glehen et al. conducted a study of 207 patients treated by CRS and HIPEC with the closed abdominal technique [23]. The overall postoperative morbidity rate including all grades III-IV was 24.5%. They had 25 digestive fistulas, 11 cases of prolonged ileus, and 5 intraperitoneal abscesses. The presence of digestive fistula was significantly associated with the duration of surgery and the number of anastomoses in the univariate analysis. Kusamura et al. conducted a study of 205 patients treated

**Table 3: Continued.**

| Gastrointestinal events I–IV univariate analysis | Gastrointestinal events I–IV multivariate analysis |
|-----------------------------------------------|--------------------------------------------------|
| Time in operating room (hours)                |                                                  |
| Yes N = 25                                    | No N = 122                                       |
| 0–6                                           | 2                                                |
| 7–12                                          | 18                                               |
| >12                                           | 5                                                |
| Chemotherapy treatment                        |                                                  |
| HIPEC only                                    | 10                                               |
| HIPEC plus EPIC                               | 13                                               |
| Unknown                                       | 2                                                |
| **P Value*/OR (95% CI)**                      |                                                  |
| 0–6                                           | reference                                        |
| 7–12                                          | 0.6445                                           |
| >12                                           | 0.450                                            |
| Chemotherapy treatment                        |                                                  |
| HIPEC only                                    | 0.7 (0.1, 3.5)                                   |
| HIPEC plus EPIC                               | 2.3 (0.4, 16.9)                                  |
| Unknown                                       | NT                                               |
| **Odds Ratio**                                |                                                  |
| 0–6                                           | NT                                               |
| 7–12                                          | NT                                               |
| >12                                           | NT                                               |

*: Pearson Chi-square, or Fisher’s exact test if sparse distribution. **: NT means Not Tested in multivariate modeling due to non significant univariate test.
Table 4: Comparison with other series with more than 100 patients.

| Author            | Institution | Year | Patient revised | Histology       | GI Events Revised                                                                 | GI Morbidity Grades III-IV | Risk Factor for GI Events                      | Statistical Analysis |
|-------------------|-------------|------|-----------------|-----------------|-----------------------------------------------------------------------------------|----------------------------|-----------------------------------------------|----------------------|
| Glehen et al. [23]| Lyon        | 2003 | 207             | Colon, PMP, ovarian | Digestive fistula (14) Prolonged ileus (11) Intraperitoneal abscess (5)          | *15% 30 events             | Carcinomatosis stage Duration of surgery Number of anastomosis | Univariate           |
|                   |             |      |                 |                 |                                                                                   |                            |                                               |                      |
| Kusamura et al. [24]| Milan     | 2006 | 205             | PM, PMP, ovarian | Anastomotic leak (17) Digestive perforations (6) Biliary fistula (1) pancreatic fistula (2) Ileus/gastric stasis (4) | *15% 30 events             | Extent of cytoreduction CDDP IPHP dose           | Multivariate         |
| Hansson et al. [25]| Uppsala    | 2009 | 123             | Colorectal, PMP, PM, ovarian | Anastomotic leak (7) Digestive perforation (11) Pancreatitis (1) Bile leak (1) Ileus (3) | *19% 23 events             | Stoma formation Duration of surgery Perioperative blood loss PCI | Multivariate         |
| Youssef et al. [26]| Basingstoke| NP   | 456 Just 441 had resections | PMP (appendix) | Anastomotic leak (7) Pancreatic complicate (5) Intestinal fistula (8) | 4.5% 20 events             | NA                                            |                      |
| Present series    | Washington  | 2011 | 147             | Colon, PMP (appendix) | Anastomotic failure (2) Fistula (4) Pancreatic fistula (1) Pancreatitis (1) Bile leak (1) Chyle leak (0) Prolonged ileus (0) Small bowel obst (1) Vomiting (5) Diarrhea (0) Ascites (0) | 8% 15 events                | Grade PCI Small bowel resection Colorectal anastomoses Number of anastomosis per patient | Multivariate         |

* Percentage calculated from total number of events/total number of patients.
NP: Not published. NA: Not available. CDDP: cisplatin, IPHP: intraperitoneal hyperthermic perfusion. PM: peritoneal mesothelioma. PMP: pseudomyxoma peritonei.
by CRS and HIPEC with the closed abdominal technique [24]. The overall postoperative morbidity rate including all grade III-IV was 12%. They had 17 anastomotic leaks, 6 digestive perforations, 1 biliary fistula, 2 pancreatic fistulas, and 4 ileus/gastric stasis. The most severe complications in their series were intestinal leakage due to anastomotic insufficiency and/or intestinal perforation. This morbidity constituted approximately 70% of all cases with major morbidity. The rate of fistula in the series was 11%. They found in the multivariate analysis that the extent of cytoreduction (levels 1 and 2 versus 3) and CDDP for IPHP dose ≥ 240 mg were independent risk factors for major morbidity.

Hansson et al. conducted a study of 123 patients treated by CRS and HIPEC and observed grade III-IV adverse events in 51 patients (41%) [25]. In multivariate analyses, grade III-IV adverse events were associated with stoma formation, duration of surgery, perioperative blood loss, and peritoneal cancer index. Among the gastrointestinal events, 7 anastomotic leaks, 11 digestive tract perforations, 1 pancreatitis, 1 bile leak, and 3 prolonged ileus occurred.

Youssef et al. conducted a study of 456 patients with pseudomyxoma peritonei syndrome of appendiceal origin [26]; grade III-IV morbidity was 7%. Seven anastomotic leaks, 5 pancreatic complications, and 8 intestinal fistulas were reported. An analysis of prognosis risk factors was not provided.

In our study, we found that the histological grade, PCI, small bowel resection, colorectal anastomoses performed, and the number of anastomoses performed per patient had a statistically significant correlation with gastrointestinal morbidity; by multivariate analysis only, the PCI was an independent risk factor for gastrointestinal complications. These data suggest that CRS combined with a standardized treatment with perioperative chemotherapy is a reasonable safe treatment for selected patients with peritoneal surface malignancy. There is an acceptable gastrointestinal morbidity as compared with modern series of pancreatic-duodenectomy, gastrectomy for cancer, or other multiorgan resections.

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