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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

# Natural History and Management of Small-Bowel Obstruction in Patients After Cytoreductive Surgery and Intraperitoneal Chemotherapy

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## ABSTRACT

**Backgroun.** Small-bowel obstruction (SBO) after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is a common complication associated with re-admission that may alter patients' outcomes. Our aim was to characterize and investigate the impact of bowel obstruction on patients' prognosis.

**Methods.** This was a retrospective analysis of patients with SBO after CRS/HIPEC ($n = 392$). We analyzed patients' demographics, operative and perioperative details, SBO re-admission data, and long-term oncological outcomes.

**Results.** Out of 366 patients, 73 (19.9%) were re-admitted with SBO. The cause was adhesive in 42 (57.5%) and malignant (MBO) in 31 (42.5%). The median time to obstruction was 7.7 months (range, 0.5–60.9). Surgical intervention was required in 21/73 (28.7%) patients. Obstruction eventually resolved (spontaneous or by surgical intervention) in 56/73 (76.7%) patients. Univariant analysis identified intraperitoneal chemotherapy agents: mitomycin C (MMC) (HR 3.2, $p = 0.003$), cisplatin (HR 0.3, $p = 0.03$), and doxorubicin (HR 0.25, $p = 0.018$) to be associated with obstruction-free survival (OFS). Postoperative complications such as surgical site infection (SSI), (HR 2.2, $p = 0.001$) and collection (HR 2.07, $p = 0.015$) were associated with worse OFS. Multivariate analysis maintained MMC (HR 2.9, $p = 0.006$), SSI (HR 1.19, $p = 0.001$), and intra-abdominal collection (HR 2.19, $p = 0.009$) as independently associated with OFS. While disease-free survival was similar between the groups, overall survival (OS) was better in the non-obstruction group compared with the obstruction group ($p = 0.03$).

**Conclusions.** SBO after CRS/HIPEC is common and complex in management. Although conservative management was successful in most patients, surgery was required more frequently in patients with MBO. Patients with SBO demonstrate decreased survival.

Patients with peritoneal metastasis have worse prognosis and limited treatment options compared with patients who have other sites of metastatic involvement. Systemic therapy has limited efficacy and treatment is often palliative. Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is an effective surgical



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treatment for selected patients with peritoneal malignancies, and is associated with a significant increase in overall survival, as noted in several randomized studies.[1–5]

One of the major drawbacks of the procedure is the high rate of postoperative morbidity,[6,7] which may result in prolonged hospitalization and increased utilization of healthcare resources. The rate of re-admission in these patients is high and occasionally requires invasive intervention or re-operation.[8]This can prohibit patients from receiving planned systemic therapy and may affect their oncological outcomes.

Several studies described the 30 days postoperative ileus and bowel obstruction rates after CRS/HIPEC. These rates reached 3.2%; however, this data was only limited to immediate postoperative complications.[3,9–11] Furthermore, bowel obstruction can be classified, based on the etiology of obstruction, into benign obstruction, secondary to adhesions or collections, and into malignant obstruction due to intra-abdominal malignant recurrence. Moreover, obstruction can also be classified according to obstruction timing into early obstruction or late obstruction (> 30 days after surgery).[12–14]

Bowel obstruction can be managed conservatively in mild cases. Management usually includes nil per os (NPO), intravenous (IV) fluids, and bowel drainage with nasogastric tube (NGT). In more severe cases where bowel viability is threatened, surgical intervention is promptly needed. For adhesive obstruction, several protocols have been described to assist the surgeon's decision making and choice of either surgical or conservative management.[14] However, there are no accepted guidelines to assist in the management of malignant bowel obstruction.[15–17]

CRS/HIPEC may be associated with higher rates of subsequent obstruction due to several factors including high rates of multi-visceral resection, administration of cytotoxic chemical agents, frequent history of previous abdominal surgeries and increased complication and reoperation rates. Most of these patients recur in the peritoneal cavity, and this frequently causes bowel obstruction.[18–21] The increased rates of both adhesive and malignant bowel obstruction in these patients confer a unique challenge in the management and in the assessment of the impact of the obstruction on patient outcomes.

We aimed here to study the occurrence and natural history of patients with bowel obstruction following CRS/HIPEC. We investigated the types of obstruction, different modalities of management, and surgical intervention. Further, we evaluated the impact of obstruction on long-term outcomes.

## METHODS

### *Patient Selection and Inclusion Criteria*

The Institutional Ethical Committee (IEC, Helsinki Committee) approved the study protocol. A retrospective analysis was made of a prospectively maintained database of peritoneal surface malignancy between 2014 and 2021. Analysis included patients with peritoneal malignancy who underwent CRS/HIPEC and had a final completeness of cytoreduction score (CC score) of 0 or 1, ($n$ = 366). Patients with residual disease (CC2) and patients with missing data ($n$ = 26) were excluded from the analysis. All patients with a re-admission due to bowel obstruction were collected as "bowel obstruction" group. The rest of the cohort was defined as the "non-obstruction" group for control (CONSORT chart—Fig. 1).

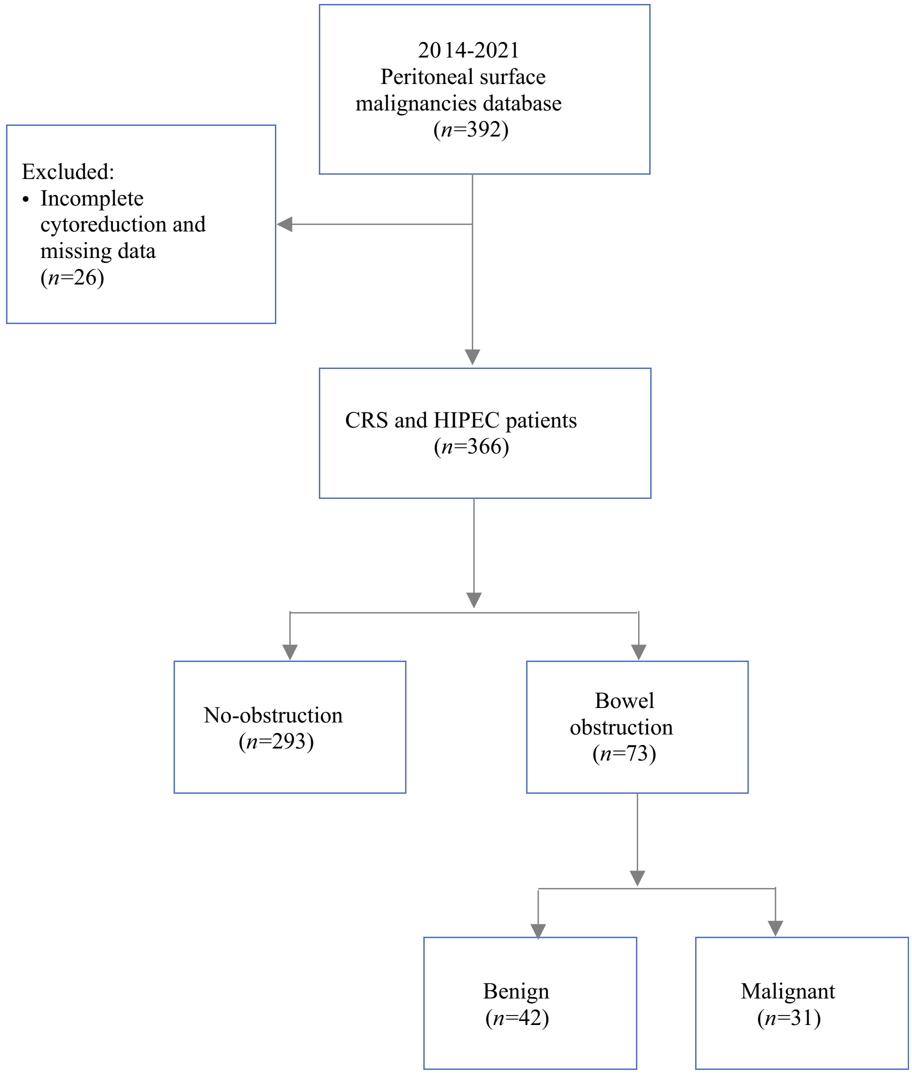
### *Patients' Data Analysis and Follow-Up*

The analysis included patient demographics: age, gender, body mass index (BMI), American Society of Anesthesiology score (ASA score) and co-morbid conditions (hypertension, diabetes, chronic heart disease, respiratory or renal dysfunction). Intraoperative assessment of the volume of peritoneal disease was performed using the peritoneal cancer index (PCI) score.[22,23] The extent of cytoreduction was evaluated by the following parameters: number of organs resected, number of peritonectomy procedures performed, number and type of anastomoses, and number and site of lesions resected. Complications were tracked and updated prospectively, and were classified according to the Clavien-Dindo classification (CD).[24]

All patients were followed up monthly for the first 3 months after discharge and thereafter every 6 months until loss to follow-up or death. The follow-up assessment included a physical examination, serum tumor markers, and cross-sectional imaging for evaluation of the disease status. Patients were divided into 3 groups based on their status: no evidence of disease (NED), alive with disease (AWD), and died of disease (DOD).

Overall survival (OS) was defined as the time interval from the procedure (CRS/HIPEC) to the date of last follow-up or death. Disease-free survival (DFS) was defined as the time interval from the time of CRS/HIPEC until the date of recurrence, death, or last follow-up. Disease recurrence was defined by the following: new lesions detected by cross-sectional imaging; elevated serum markers persistent in two consecutive tests 30 days apart without a lesion detected by cross-sectional imaging. In cases of equivocal imaging findings, biopsy was performed. Obstruction-free survival (OFS) was defined as the

**FIG. 1** Consort chart




time from operation (CRS/HIPEC) to an event of bowel obstruction requiring hospitalization.

*Bowel Obstruction Definition and Management*

Bowel obstruction was defined and diagnosed by one of the following parameters; *clinical*—by the absence of bowel movement or gas passing accompanied by vomiting, nausea, or abdominal distention; *radiological*—by abdominal X-ray showing distended bowel loops, air fluid levels or computed tomography (CT) showing similar elements with absence of passing oral contrast, or partially passing oral contrast; and *surgical*—presence of bowel obstruction due to adhesions, malignancy, or fluid collection/infection found during urgent surgical intervention.

Benign bowel obstruction was defined by the presence of adhesions, fluid collection, or intra-abdominal infection as an etiology of the obstruction. Malignant bowel obstruction (MBO) was defined as the presence of intra-abdominal lesions identified by a CT scan or intra-operatively as a cause for the obstruction. Patients with known recurrent disease in the abdominal cavity were considered to have MBO, even if there was no apparent lesion causing the obstruction.

During the bowel obstruction admission, data were collected that included initial assessment of the patient, type of imaging and method of diagnosis, the duration of hospital stay, the need for surgical intervention to resolve the obstruction, and whether the obstruction was resolved at the time of discharge.

*CRS/HIPEC Procedure and Choice of Chemotherapy*

All patients were operated on by the same surgical team using the same technique. Briefly, a midline xiphoid to pubis incision was made. Following initial inspection of the abdomen and pelvis with assessment of the operative PCI, any area of visible metastatic disease was resected and peritonectomy procedures were performed as described by Sugarbaker[22] with some modifications. All HIPEC procedures following CRS were performed according to established protocols using the closed abdomen technique as described before.[25,26] At the end of the CRS procedure, completeness of cytoreduction was assessed. HIPEC was added only in cases of complete CRS with (CC) score of 0 or 1. HIPEC was done using the Performer HT$^{TM}$ system (Rand-Biotech, Medolla, Italy).

### *Statistical Analysis*

Data analysis was performed using SPSS version 25 (Armonk, NY) software with a two-sided significance level of $\alpha = 0.05$. Descriptive statistics are presented using prevalence and percentage values for categorical variables. Although continuous variables are presented with means and standard deviation, skewed distributed variables are presented by median and range.

The correlations between obstruction and continuous variables were conducted using Pearson correlation: for non-continuous variables we used Spearman correlation. Univariate analysis was performed using a univariate binary logistic regression. Multivariate analysis, including only the univariate significance variables, was performed by binary logistic regression model with forward likelihood ratio method to exclude non-significant variables from the model. The binary logistic regression model was built using the model fit method. Survival analysis was performed using the Kaplan-Meier method with a log-rank test for significance.

## RESULTS

Of the 392 patients who underwent CRS/HIPEC in our center between 2014 and 2021, 366 patients met the inclusion criteria and were included in this study. We identified 73 (19.9%) patients that were re-admitted with bowel obstruction during the follow-up period. We divided the cohort into 2 groups for characterization and survival analysis: the bowel obstruction group ($n = 73$) and the non-obstruction group ($n = 293$). The bowel obstruction group was further subdivided according to the obstruction etiology into adhesive ($n = 42$) and malignant bowel obstruction ($n = 31$)

### *Group Characteristics, Operative, and Perioperative Details*

*Patient and Tumor Characteristics* Most of the patients' tumor characteristics and comorbid conditions were similar between the obstruction and non-obstruction groups. The median age was 57 years (range, 23–81) in the obstruction group and 61 years (range, 18–87) in the non-obstruction group ($p = 0.3$). The male to female ratio was 1:1.3 in the obstruction group and 1:1.6 in the non-obstruction group. Median BMI was 24.1 (range, 13.2–46) and 25.9 (range, 12.1–56.1) in the obstruction and non-obstruction groups, respectively, ($p = 0.015$).

The median ASA score was 3 (range 1–4) in the obstruction and 3 (range, 1–4) in the non-obstruction groups, ($p = 0.68$). There were no overall differences in comorbid conditions between the groups, ($p = 0.91$).

The primary tumor diagnosed was of colonic origin in 45 (61.6%) and 159 (54.2%), appendiceal in 13 (17.8%) and 53 (18.1%), rectal in 3 (4.15) and 8 (2.7%), gastric in 4 (5.4%) and 8 (3.7%), in the obstruction and non-obstruction groups, respectively. There was no difference in tumor origin between obstruction and non-obstruction groups.

Demographics, patients, and tumor characteristics of the groups are summarized in Table 1.

*Operative and Perioperative Details* All patients underwent CRS/HIPEC with a CC0 resection. The median PCI was 9 (range, 1–39) in the obstruction group and 8 (range, 1–39) in the non-obstruction group ($p = 0.13$). The mean operative (OR) time was 4.7 h ($\pm$ 1.6) and 4.5 h ($\pm$ 1.6) in the obstruction and non-obstruction groups, respectively ($p = 0.09$). Estimated blood loss was 467 cc ($\pm$ 310) and 504 cc ($\pm$ 439) ($p = 0.93$), and the use of packed cell units was 0.9 ($\pm$ 1.3) and 1.1 ($\pm$ 1.7) in the obstruction and non-obstruction groups, respectively ($p = 0.69$).

The rate of pelvic peritonectomy performed was higher in the obstruction group, 42 (57.5%), compared with the non-obstruction group, 116 (39.6%), ($p = 0.006$). Moreover, a diverting ileostomy was also used more frequently (17, 23.3% and 35, 11.9%) in the obstruction than in the non-obstruction groups, respectively, ($p = 0.01$).

We noted that the proportion of patients treated with mitomycin C (MMC) was higher in the obstruction group [66 (90.4%)] compared with 208 (71%) in the non-obstruction group, ($p = 0.001$). Whereas the use of both cisplatin and doxorubicin were associated with lower rates of obstruction (cisplatin: 5.5% in the obstruction group vs. 17.1% in the non-obstruction group, $p = 0.01$; doxorubicin: 4.1% in the obstruction group vs. 17.7% in the non-obstruction group, $p = 0.004$).

In the postoperative period, surgical site infections (SSI) were more frequently noted in the obstruction group [24 (32.8%)], compared with 50 (17.15%) in the non-obstruction group ($p = 0.003$). Other postoperative complications were not statistically significantly different between groups, including intra-abdominal collections in 14 patients (19.1%) in the obstruction group and 33 patients (11.2%) in

**TABLE 1** patients and tumor characteristics

| Variable | Obstruction group $n$=73 | Non-obstruction group $n$=293 | $P$ value |
|---|---|---|---|
| Median age in years, (range) | 57 (22–81) | 61 (18–87) | 0.3 |
| *Sex* | | | 0.51 |
| Male $n$ (%) | 31 (42.5) | 112 (38.2) | |
| Female $n$ (%) | 42 (57.5) | 181 (61.8) | |
| BMI mean (range) | 24.1(13.2–46) | 25.9 (12.1–56.1) | **0.015** |
| *Comorbidities prevalence* | | | |
| DM, $n$ (%) | 12 (16.4) | 49 (16.7) | 0.95 |
| HTN, $n$ (%) | 16 (21.9) | 94 (32.1) | 0.09 |
| CRF, $n$ (%) | 1 (1.4) | 6 (2) | 0.99 |
| IHD, $n$ (%) | 3 (4.1) | 23 (7.8) | 0.27 |
| COPD, $n$ (%) | 1 (1.3) | 6 (2.0) | 0.99 |
| *ASA score* | | | |
| Median (range) | 3 (1–4) | 3 (1–4) | 0.68 |
| ASA 1, $n$ (%) | 2 (2.7) | 5 (1.7) | 0.56 |
| ASA 2, $n$ (%) | 11 (15.1) | 52 (17.7) | 0.59 |
| ASA 3, $n$ (%) | 57 (78.1) | 230 (78.5) | 0.94 |
| ASA 4, $n$ (%) | 3 (3.2) | 6 (2.1) | 0.31 |
| *Primary tumor type* | | | |
| Colon, $n$ (%) | 45 (61.6) | 159 (54.2) | 0.26 |
| Rectum, $n$ (%) | 3 (4.1) | 8 (2.7) | 0.54 |
| Stomach, $n$ (%) | 4 (5.4) | 8 (2.7) | 0.24 |
| Appendix, $n$ (%) | 13 (17.8) | 53 (18.1) | 0.96 |
| Ovary, $n$ (%) | 3 (4.1) | 17 (5.8) | 0.57 |
| Mesothelioma, $n$ (%) | 2 (2.7) | 24 (8.1) | 0.1 |
| Small bowel, $n$ (%) | 2 (2.7) | 5 (1.7) | 0.56 |
| Sarcoma, $n$ (%) | 1 (1.3) | 7 (2.3) | 0.59 |
| PCI score, median (range) | 9 (1–39) | 8 (1–39) | 0.13 |

*P* values of statistical significance are given in bold

*DM* diabetes mellitus, *HTN* hypertension, *CRF* chronic renal failure, *IHD* ischemic heart disease, *COPD* chronic obstructive pulmonary disease, *PCI* peritoneal carcinomatosis index

the non-obstruction group ($p$ = 0.7) and gastro-intestinal leaks in 8 (10.9%) in the obstruction group compared with 29 (9.8%) in the non-obstruction group ($p$ = 0.94).

Operative and peri-operative information about the two groups is summarized in Table 2.

*Presentation and Management of Bowel Obstruction*

The median time to bowel obstruction post CRS/HIPEC was 7.7 months (range, 0.5–60.9). All patients presented with one or more obstruction complaints (vomiting, nausea accompanied with complete/near complete lack of passing bowel movements or gas).

At presentation, heart rate (HR) was elevated (> 100 bpm) in 24 (32.8%) patients, although only 7 (9.5%) patients presented to the emergency department (ER) with signs of grade II shock or higher. Furthermore, leukocytosis (> 12 K/µl) was noted in 26 (35.6%) patients and 51 (69.8%) patients showed increased CRP (> 5 mg/l). Lactate levels where elevated (> 18 ml/dl) in 30 patients and creatinine level was abnormal (> 0.95 mg/dl) in 5 (6.8%) patients.

All patients completed an imaging study and 56 (76.7%) were diagnosed with bowel obstruction via CT scan and 17(23.2%) by an abdominal X-ray alone.

All patients were admitted to our department, received IV fluids, and were kept nil per os (NPO). Nasogastric tube (NG tube) insertion was necessary in 63 (86.3%) cases. During their hospital stay, 21(28.7%) patients required surgical intervention and 27 patients (36.9%) received Total parenteral nutrition (TPN). The median length of hospitalization was 6 days (range, 1–180). Eventually, 56/73 (76.6%) patients were discharged with complete resolution of their bowel function (either spontaneous or by surgical intervention).

**TABLE 2** Operative and perioperative information of for both groups

| Variable | Obstruction group *n*=73 | Non-obstruction group *n*=293 | *P* value |
|---|---|---|---|
| *Perioperative* | | | |
| EBL, (cc) mean (SD) | 467.1 (310.8) | 504.7 (439.9) | 0.93 |
| PC, (units) mean (SD) | 0.9 (1.3) | 1.1 (1.7) | 0.69 |
| Duration of surgery (hHours.), mean (SD) | 4.7 (1.6) | 4.5 (1.6) | 0.097 |
| *Organs resected* | | | |
| Colon, *n* (%) | 31 (42.5) | 110 (37.5) | 0.44 |
| Small bowel, *n* (%) | 28 (38.4) | 104 (35.5) | 0.65 |
| Anterior resection, *n* (%) | 18 (24.7) | 46 (15.7) | 0.07 |
| Stomach, *n* (%) | 2 (2.7) | 18 (6.1) | 0.39 |
| Spleen, *n* (%) | 15 (20.5) | 44 (15.0) | 0.25 |
| Pancreas, *n* (%) | 1 (1.4) | 5 (1.7) | 0.99 |
| Liver, *n* (%) | 16 (21.9) | 60 (20.5) | 0.79 |
| Pelvic pPeritoneum, *n* (%) | 42 (57.5) | 116 (39.6) | **0.006** |
| Ileostomy, *n* (%) | 17 (23.3) | 35 (11.9) | **0.013** |
| *Type of IP chemotherapy* | | | |
| MMC, *n* (%) | 66 (90.4) | 208 (71) | **0.001** |
| Oxaliplatin, *n* (%) | 3 (4.1) | 29 (9.9) | 0.12 |
| 5FU, *n* (%) | 54 (74) | 185 (63.1) | 0.082 |
| Leucovorin, *n* (%) | 54 (74) | 185 (63.1) | 0.082 |
| Cisplatin, *n* (%) | 4 (5.5) | 50 (17.1) | **0.013** |
| Doxorubicin, *n* (%) | 3 (4.1) | 52 (17.7) | **0.004** |
| Gemzar, *n* (%) | 0 | 4 (1.4) | 0.59 |
| Melphalan, *n* (%) | 0 | 2 (0.7) | 0.99 |
| *Complications* | | | |
| SSI, *n* (%) | 24 (32.8) | 50 (17.1) | **0.003** |
| Collection, *n* (%) | 14 (19.1) | 33 (11.2) | 0.07 |
| Leaks, *n* (%) | 8 (10.9) | 29 (9.8) | 0.94 |

*P* values of statistical significance are given in bold

*EBL* estimated blood loss, *PC* packet cells, *MMC* mitomycin C, *5FU* Fluorouracil, *SSI* surgical site infection

*Adhesive Versus Malignant Obstruction*

The bowel obstruction group was further subdivided based on the obstruction etiology into either adhesive ($n = 42$) or malignant bowel obstruction groups ($n = 31$).

There were more patients with a colonic primary in the malignant group [25/31 (80.6%) compared with the adhesive group 21/42 (50%), ($p = 0.007$)]; appendiceal primary tumors presented only with adhesive obstruction 13/42 (31%) ($p = 0.001$). There was no difference in chemotherapy regimen used for the HIPEC procedure between the groups. Adhesive obstructions presented earlier in postoperative course with a median of 4.58 months (range, 0.5–39.2), while malignant obstructions presented later in the disease course, median 13.9 months (range, 2.5–60.9), ($p = 0.001$).

A total of 63/73 (86.3%) patients had surgery prior to CRS/HIPEC; 38/42 (90.4%) in the adhesive group; 25/31 (80.6%) in the malignant group ($p = 0.22$). Adjuvant treatment post CRS/HIPEC was given in 52/73 (71.2%) of all obstructed patients; 21/58 (36.2%) in the adhesive group; 31/58 (53.4%) in the malignant group, ($p = 0.001$). Adjuvant therapy was given to the patients according to their treating oncologist and in the context of the primary tumor origin, pathological results of CRS/HIPEC and patient's functional capability. Malignant obstruction occurred later in the disease course and thus did not interfere with patients' planned adjuvant therapy. Out of 42 patients in the adhesive group, a total of 21 (50%) patients were not planned for adjuvant therapy; most of these patients were low-grade mucinous of appendix (LAMN) in 9 (42%) patients; colon adenocarcinoma in 8 (38%) patients; adenocarcinoma of the appendix in 3 (14.2%) patients; and ovarian adenocarcinoma in 1 (4%) patient. The remainder of patients in the adhesive group $n = 21$ (50%) received planned adjuvant chemotherapy within

6 months from CRS/HIPEC. Only 4/42 (9.5%) patients had a delay in their scheduled treatment due to obstruction.

A Kaplan-Meier curve of overall survival of adhesive versus malignant bowel obstruction is presented in Supplementary Fig. 2.

Surgical intervention was needed in 5/42 (11.9%) patients in the adhesive group and in 16/31 (51.6%) in the malignant group, ($p = 0.001$). Bowel obstruction resolved eventually (either spontaneously or by surgical intervention) in 40/42 (95.2%) patients in the adhesive group and in 19/31 (61.3%) in the malignant group ($p = 0.001$).

Table 3 summarizes both groups' characteristics.

*Management of Malignant Bowel Obstruction*

*Conservative Management* Of the 31 patients in the malignant group, 15/31 (48.4%) were treated conservatively; of whom, 7/15 (46.6%) had a spontaneous resolution of their bowel obstruction. Two 2/7 (28.5%) had a subsequent obstruction event and were also successfully treated conservatively. Six of the 7 (85.7%) patients received systemic therapy after the obstruction event; 2/6 (33.3%) showed mild improvement under systemic therapy; (4/6, 66.6%) showed disease progression. Due to this outcome, treatment was discontinued. Out of the 15 patients in the conservative group, 8 (53.3%) did not resolve their bowel obstruction and 5 (33.3%) received TPN support. All 8 patients were discharged to a hospice/palliative care facility. A trial of systemic chemotherapy was given in 3/8 (37.5%) patients; unfortunately the disease progressed.

*Surgical Management* Surgical intervention was needed in 16/31 (51.6%) patients in the MBO group. Three of the 16 (18.7%) patients were initially diagnosed with adhesive obstruction, and at time of surgical exploration, intra-abdominal recurrence was identified.

Upon surgical exploration, burden of disease and sites of obstruction were evaluated. In 9/16 (56%) of the surgical interventions there were good outcomes with resolution of bowel obstruction. These patients had low PCI at exploration, small and large intestine were amenable to mobilization, and obstruction was noted only in one or two sites. In cases where distal obstruction was identified, end ileostomy was performed ($n = 6$). In one case of proximal obstruction, a gastro-jejunal bypass was performed. Three patients were urgently operated on; 2 with concomitant small- and large-bowel obstruction who underwent Hartmann's procedure; and 1 with bowel ischemia who underwent resection with end ileostomy. In the postoperative period, all resolved patients (9/16, 56.2%) needed TPN support perioperatively. Seven of 9 (77.7%) continued receiving systemic chemotherapy after the obstruction event. On long-term follow up, 3/9 (33.3%) patients died of disease and 6/9 (66.6%) were alive with disease (median 142 days: range, 39–566).

The opposite was noted in patients for whom surgical intervention did not yield favorable outcomes: 7/16 (43.7%). Dense adhesions and higher burden of disease were noted upon exploration. Bowel mobilization was difficult, and sites of obstruction were multiple. Inadvertent enterotomies occurred in 2 patients at the time of exploration. One patient was managed with a colostomy and another 2 with a diverting proximal jejunostomy. All patients received perioperative TPN support. Moreover, 2/7 (28.5%) received an attempt of systemic chemotherapy that was aborted due to poor performance status. Six of 7 (85.7%) patients died of disease and 1/7 (14.2%) patient was alive with disease at the end of follow-up and was discharged to home care facility or hospice (median follow-up of 140 days: range, 74–417).

Supplementary Fig. 3 illustrates the different group stratifications.

*Univariant and Multivariant Analysis of Factors Associated with Obstruction-Free Survival*

We investigated factors associated with obstruction-free survival (OFS). Univariant analysis identified intraperitoneal chemotherapy agents such as mitomycin C (MMC) (HR 3.2, $p = 0.003$), cisplatin (HR 0.3, $p = 0.03$) and doxorubicin (HR 0.25, $p = 0.018$) to be associated with OFS. Resected organs such as pelvic peritonectomy (HR 1.86, $p = 0.009$) and diverting ileostomy (HR 1.9, $p = 0.014$), and postoperative complications such as surgical site infection (SSI), (HR 2.2, $p = 0.001$) and collection (HR 2.07, $p = 0.015$) were also associated with worse OFS.

Further, multivariate analysis was performed to identify independent factors associated with OFS. Chemotherapy agents such as mitomycin C (MMC) (HR 2.9, $p = 0.006$), pelvic peritonectomy (HR 1.89, $p = 0.000$) and postoperative complication of SSI (HR 1.19, $p = 0.001$) and collection (HR 2.19, $p = 0.009$) were associated with bowel obstruction. Univariate and multivariate results are summarized in Table 4.

To further identify factors associated with OFS of different tumor origins, a separate univariant and multivariant analysis was performed for colorectal and appendiceal tumors.

Univariant analysis of colorectal origin identified BMI (HR 0.94, $p = 0.034$) and SSI (HR 1.2, $p \leq 0.001$) to be associated with OFS. On multivariate analysis BMI (HR 0.94, $p = 0.023$), pelvic peritonectomy (HR 1.8, $p = 0.03$) and SSI (HR 1.2, $p \leq 0.001$) were associated with OFS.

**TABLE 3** Bowel obstruction characteristics and management

| Variable | All obstruction $n$=73 | Benign $n$=42 | Malignant $n$=31 | $P$ |
|---|---|---|---|---|
| Median age in years, (range) | 57 (22–81) | 60 (22–81) | 55 (26–75) | 0.28 |
| *Primary tumor type* | | | | |
| Colon, $n$ (%) | 46 (61.6) | 21 (50) | 25 (80.6) | **0.007** |
| Rectum, $n$ (%) | 3 (4.1) | 3 (7.1) | 0 | 0.26 |
| Stomach, $n$ (%) | 4 (5.4) | 1 (2.4) | 3 (9.7) | 0.31 |
| Appendix, $n$ (%) | 13 (17.8) | 13 (31) | 0 | **0.0004** |
| LAMN, $n$ (%) | 9 (12.3) | 9 (21.4) | 0 | |
| HAMN, $n$ (%) | 1 (1.3) | 1 (2.4) | 0 | |
| Adenocarcinoma, $n$ (%) | 3 (4.1) | 3 (7.1) | 0 | |
| Ovary, $n$ (%) | 3 (4.1) | 2 (4.8) | 1 (3.2) | 0.99 |
| Mesothelioma, $n$ (%) | 2 (2.7) | 0 | 2 (6.5) | 0.18 |
| Small bowel, $n$ (%) | 2 (2.7) | 2 (4.8) | 0 | 0.51 |
| *Type of IP chemotherapy* | | | | |
| MMC, $n$ (%) | 66 (90.4) | 38 (90.4%) | 28 (90.3%) | 0.98 |
| Oxaliplatin, $n$ (%) | 3 (4.1) | 3 (7.1%) | 0 | |
| 5FU, $n$ (%) | 54 (74) | 28 (66.6%) | 26 (83.8%) | 0.09 |
| Leucovorin, $n$ (%) | 54 (74) | 28 (66.6%) | 26 (83.8%) | 0.09 |
| Cisplatin, $n$ (%) | 4 (5.5) | 1 (2.3%) | 3 (9.6%) | 0.17 |
| Doxorubicin, $n$ (%) | 3 (4.1) | 1 (2.3%) | 2 (6.4%) | 0.38 |
| Gemzar, $n$ (%) | 0 | 0 | 0 | |
| Melphalan, $n$ (%) | 0 | 0 | 0 | |
| Neoadjuvant treatment, $n$ (%) | 48 (65.7) | 21 (50) | 27 (87.1) | **0.001** |
| Adjuvant treatment, $n$ (%) | 52 (71.2) | 21 (50) | 31 (100) | < **0.0001** |
| Prior Surgery[#], $n$ (%) | 63 (86.3) | 38 (90.4) | 25 (80.6) | 0.22 |
| Days to obstruction, Median median (range) | 233 (8–1827) | 137.5 (8–1176) | 418 (47–1827) | < **0.0001** |
| *Imaging* | | | | |
| X-ray, $n$ (%) | 17 (23.3) | 13 (31) | 4 (12.9) | 0.07 |
| CT, $n$ (%) | 56 (76.7) | 29 (69) | 27 (87.1) | 0.07 |
| *Treatment* | | | | |
| NG tube, $n$ (%) | 63 (86.3) | 33 (78.5) | 30 (96.7) | **0.037** |
| IV-fluids, $n$ (%) | 73 (100) | 42 (100) | 31 (100) | 1 |
| Surgery, $n$ (%) | 21 (28.7) | 5 (11.9) | 16 (51.6) | **0.001** |
| Length of stay, median (range) | 6 (1–180) | 5 (1–65) | 10 (2–180) | **0.027** |
| Obstruction resolved, $n$ (%) | 56 (76.6) | 40 (95.2) | 16 (51.6) | < **0.0001** |

*P* values of statistical significance are given in bold

*DM* diabetes mellitus, *HTN* hypertension, *CRF* chronic renal failure, *IHD* ischemic heart disease, *COPD* chronic obstructive pulmonary disease, *PCI* peritoneal carcinomatosis index

[#]Surgeries other than CRS/HIPEC

Univariant analysis of appendiceal origin identified recto-sigmoid resection (HR 5.23, $p = 0.035$) and intra-abdominal collection (HR 5.5, $p = 0.003$) to be associated with OFS. However, multivariate analysis showed only intra-abdominal collections (HR 5.5, $p = 0.003$) to be associated with OFS. Univariate and multivariate analysis of different origins is summarized in Supplementary Tables 3, 4.

### *Survival Analysis*

The median time of follow-up from CRS/HIPEC was 16.83 months (0.13–173.3 months).

Overall survival (OS) was better in the non-obstruction group compared with the obstruction group ($p = 0.03$). In the obstruction group, the estimated median OS was 75.6 months. In the non-obstruction group, a median was not reached.

**TABLE 4** Cox regression analysis of factors associated with obstruction- free survival

| Variable | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | CI | $p$ | HR | CI | $p$ |
| BMI | 0.96 | 0.92–1.009 | 0.1 | | | 0.077 |
| HTN | 0.61 | 0.35–1.07 | 0.084 | | | 0.071 |
| PCI | 1.016 | 0.99–1.04 | 0.18 | | | 0.66 |
| *Chemotherapy agent* | | | | | | |
| MMC | 3.26 | 1.49–7.12 | **0.003** | 2.984 | 1.36–4.09 | **0.006** |
| Oxaliplatin | 0.46 | 0.14–1.46 | 0.19 | | | 0.47 |
| 5FU | 1.48 | 0.88–2.49 | 0.14 | | | 0.99 |
| Leucovorin | 1.48 | 0.88–2.49 | 0.14 | | | 0.99 |
| Cisplatin | 0.33 | 0.12–0.9 | **0.03** | | | 0.73 |
| Doxorubicin | 0.25 | 0.08–0.79 | **0.018** | | | 0.39 |
| Melphalan | 0.05 | 0.00–847.5 | 0.54 | | | 0.64 |
| Gemzar | 0.05 | 0.00–1550 | 0.57 | | | 0.61 |
| *Resected organ* | | | | | | |
| Anterior resection | 1.47 | 0.86–2.49 | 0.16 | | | 0.53 |
| Pelvic peritonectomy | 1.86 | 1.17–2.96 | **0.009** | 1.89 | 1.18–3.03 | **0.008** |
| Ileostomy | 1.99 | 1.15–3.42 | **0.014** | | | 0.48 |
| *Complications* | | | | | | |
| SSI | 1.21 | 1.09–1.33 | < **0.001** | 1.19 | 1.08–1.33 | < **0.0001** |
| Collection | 2.07 | 1.16–3.73 | **0.015** | 2.19 | 1.22–3.95 | **0.009** |

*P* values of statistical significance are given in bold

*BMI* body mass index, *HTN* hypertension, *PCI* peritoneal carcinomatosis index, *SSI* surgical site infection, *MMC* mitomycin, *5FU* 5 Fluorouracil

However, there was no significant difference in disease-free survival (DFS). Estimated median DFS was 14.03 months (10.3–17.8 months) in the non-obstruction group and 12.37 months (6.2–18.5) in the obstruction group ($p = 0.6$).

Kaplan-Meier curves of both overall and disease-free survival are presented in Fig. 2.

## DISCUSSION

We have demonstrated that, with long-term follow up, rates of SBO following CRS/HIPEC surgery are as high as 20%. Most of these cases were benign or adhesive in nature (12%) compared with malignant obstruction (8%). Both the obstruction and the non-obstruction groups were similar in primary tumor origin and patient characteristics. However, we noted a higher occurrence of SBO in patients receiving MMC and lower rates in patients receiving cisplatin and doxorubicin. Further, patients undergoing more aggressive surgery where pelvic peritonectomies and ileostomies are performed, and patients complicated by SSIs had higher rates of SBO. We further noted that benign obstruction occurred earlier in the postoperative course at a median of 20 weeks, while malignant SBO occurred at a median of 60 weeks. Colonic primaries were associated with malignant SBO whereas appendiceal tumors were exclusively benign. Most adhesive SBOs were treated conservatively and only 12% needed surgical intervention. In contrast, 52% of malignant bowel obstruction needed surgery. Disease-free survival was similar in the obstruction and non-obstruction groups; however, overall survival was better in the non-obstruction group.

There is a paucity of data in the literature about the rates of SBO following CRS/HIPEC. Most of these studies reported outcomes after short-term follow-up that ranged between 30 and 90 days post CRS/HIPEC. They included mainly postoperative ileus and small-bowel obstruction of an adhesive nature. The rates described reached 6.2%.[9–11,27–29] In a multi-institutional study, Glehen et al. reported an SBO rate of 1.5%.[9] In another large study that included 1304 patients, Gamboa et al. (2020) reported rates of 5.3%.[29] Moreover, Lee et al., in a study of 2372 patients, showed a re-admission rate of 15.9%, of which 67 patients (2.8%) presented with SBO.[8] In our study, we followed up the patients for a median of 17 months and reported both adhesive and malignant obstruction. This comparatively long-term follow-up unveiled much higher rates of intestinal obstruction that reached 20%. These rates are similar to published data for SBO following major abdominal and open colorectal surgeries.[30–33]

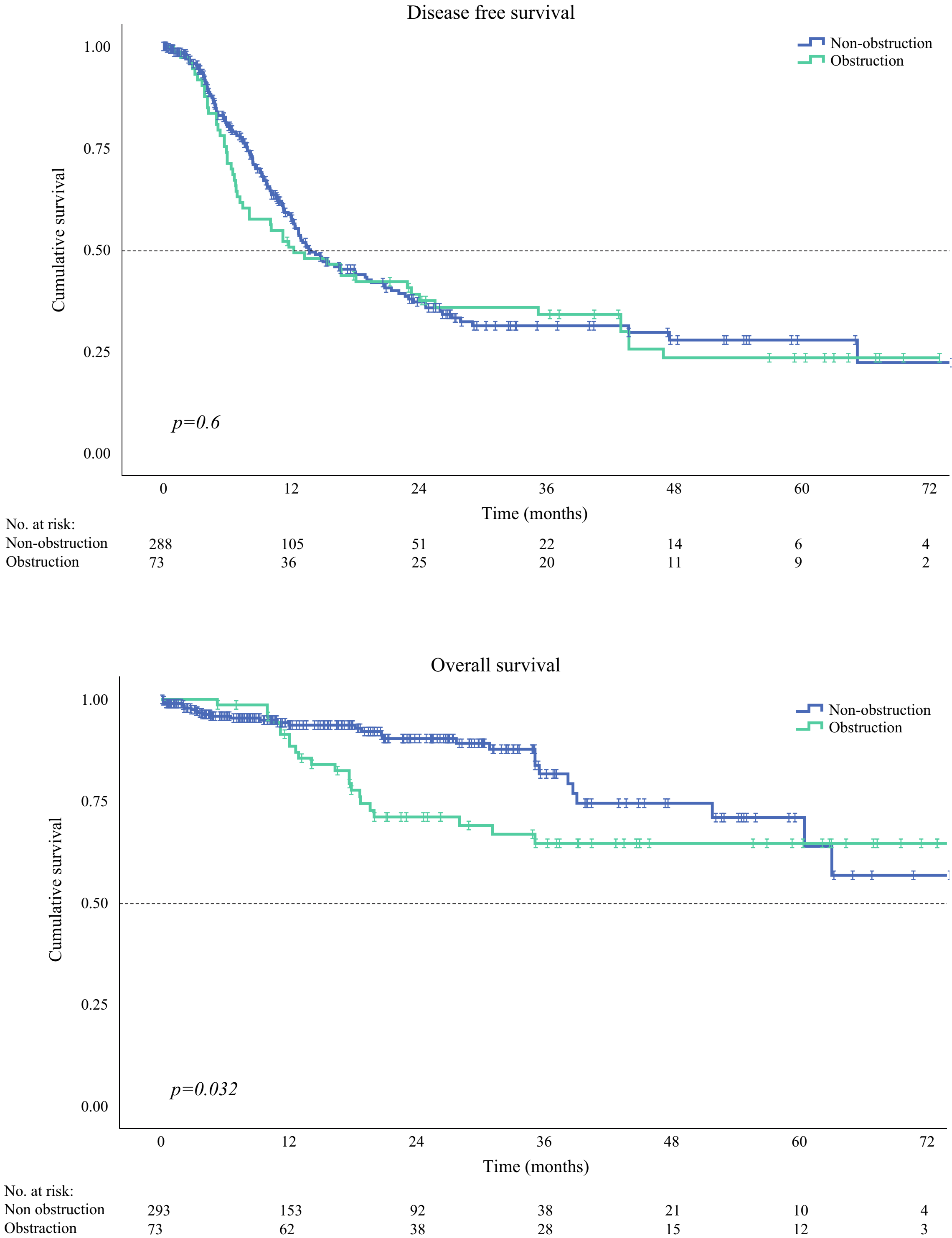



**FIG. 2** Disease free and overall survival

The concept of obstruction-free survival (OFS) has been recently introduced as an endpoint for measuring the effectiveness of surgical intervention on patients with MBO, whether the intervention is with curative intent, like CRS/HIPEC, or palliative, like pressurized intraperitoneal aerosol chemotherapy (PIPAC).[34,35] It evaluates the incidence and the interval to obstruction after surgical intervention. In our study, we utilized this concept to assess prognostic and predictive factors associated with and influencing OFS after CRS/HIPEC. The use of intraperitoneal MMC, pelvic peritonectomy, and diverting ileostomy were found to be independent factors associated with worse OFS on multivariate analysis.

Two preclinical studies have investigated the effect of chemotherapeutic agents like MMC on adhesion formation in rats.[36,37] Interestingly, both studies reported lower rates of adhesion formation; nevertheless, only one showed statistical significance. In the study of PRODIGE7, performing HIPEC with oxaliplatin did not increase the 60-day postoperative obstruction rate when compared with patients who did not receive intraperitoneal chemotherapy (1.52% vs. 1.53%, $p = 0.9$).[38] In our study, the use of MMC for the HIPEC procedures was associated with SBO. This, perhaps, is not due to the local effect of MMC on adhesion formation. However, it could possibly be explained by the utility of MMC as the primary line of intraperitoneal chemotherapy used for colorectal and appendiceal tumors. Colorectal cancer primaries tend to recur and cause more cases of malignant bowel obstruction. Further, these surgeries tended to be more complex with multiple lesions resected. Supporting these findings, we also noted that patients who underwent pelvic peritonectomy, diverting ileostomy, or who suffered postoperative complications such as SSI or collections had higher rates of obstruction.

The etiology of the obstruction factors tremendously in managing patients with SBO. Benign SBO may be managed frequently by a conservative approach. According to the Bologna guidelines, SBO due to adhesion, with no signs of peritonitis or sepsis, may be managed conservatively for up to 72 h.[14] In our study most of the benign SBOs resolved with conservative management alone. Surgical intervention, when needed, also rendered satisfactory results allowing $\sim$ 95% of patients to be discharged home with SBO resolution. In contrast to benign SBOs, there are no universal recommendations or guidelines for the management of MBOs. Some studies suggested that surgical intervention should be delayed if possible, due to a high failure rate.[39–42] Most of these patients suffered from a low quality of life and increased hospital stay. Surgical intervention was reserved for emergency situations or in cases with prolonged failure of conservative treatment.

Decisions regarding the management of MBO are complex and influenced by many factors. Primarily, the patient's general health status is a crucial factor when considering surgical options. However, often these patients may be in poor condition due to prolonged malnutrition or chemotherapy treatment. The patient's age could, in some instances, influence decision making. For instance, often a palliative surgical approach is chosen for younger patients even with aggressive disease. Disease related factors also affect decision making, such as the disease's biological behavior and aggressiveness. Patients with more aggressive disease, rapid recurrences, and progression under chemotherapy should seldom be offered surgical exploration. Decision making, and surgical exploration, should only be performed by experienced peritoneal surface malignancy surgeons as the variables may be complex and the surgery highly morbid. Additionally, although not readily quantifiable, the relationship between the patient and the treating surgical oncologist who managed the patient through the long and arduous journey of CRS/HIPEC may be significant. His/her decision-making may be swayed by an emotional burden from seeing his/her patient's anguish. Therefore, it is more advantageous that such decisions be undertaken by a team approach where surgical exploration is agreed upon by consensus. CT scans are usually used to evaluate disease burden and obstruction causality; however, they can be misleading and often underestimate the actual disease burden. The presence of a single site of clear transition usually favors surgical exploration for management.

Based on our experience with these patients, we suggest a treatment algorithm that may help surgeons in similar situations (Supplementary Fig. 5). First, if the patient presents with severe obstruction where intestinal viability is threatened, or in cases of perforation due to obstruction, we usually offer surgical exploration as a last resort after counseling the patient and his family regarding outcomes. Second, if the patient's condition is stable, we admit them for conservative management. All patients should get a trial of conservative management regardless of their disease condition. In many instances they recover with no need for surgical exploration. There are no time limits for the period of conservative management where surgical exploration is deemed necessary. All patients are evaluated with contrast CT scans, in order that the tumor burden and the site of obstruction be evaluated as accurately as possible. Surgical exploration should be offered only for patients with a mild to moderate tumor burden; a non-diffuse intestinal involvement that renders mobilization technically challenging; and a single site of obstruction clear in a CT scan. Patients that fail conservative management and are considered for surgical exploration should be given a period of perioperative TPN to enhance their recovery. Even after successful surgical exploration, the return of bowel function and oral intake is usually delayed. In summary, there is no one clear pathway in deciding to operate on malignant obstruction. Although not readily measurable, sound clinical judgment based on experience and thorough understanding of the surgical and oncological principles determines who may benefit from surgery. We operated on 52% of patients with MBO and only in 56% of these patients did we successfully manage their obstruction, and this often required a diverting ostomy or bypass.

The use of TPN in MBO has been controversial; Bozzetti et al. suggested that only in selected patients with more indolent disease can TPN palliate and prolong patients' survival from weeks to months.[43] We adapted the same policy to manage patients with MBO. In this current study, 68% of patients with MBO received TPN, especially those who underwent surgical intervention. Despite many limitations, we did not observe a difference in survival between those who received TPN compared with those who did not: the median survival from obstruction was 4.5 months (range days, 3–566) in patients who received TPN compared with a median of 4.3 months (range days, 74–494) in those who did not ($p = 0.79$).

The correlation between postoperative complications and worse long-term oncological outcomes after CRS/HIPEC is well documented.[6,7,11] Currently, there are no reports that link SBO to oncological outcomes in these patients. In this study, we show that in patients re-admitted with SBO, of both benign and malignant etiologies, the patients had similar disease-free but worse overall survival ($p = 0.03$).

This study has several limitations. Despite our prospectively maintained database, collection of data regarding SBO and operative details was retrospective in nature, yielding potential reporting bias. The patient population was too small to perform subgroup analysis of different SBOs or management approaches. Furthermore, the study included patients with various primary tumors, with different biology and survival potential that may alter the effect of bowel obstruction on oncological outcomes.

This study represents, to our knowledge, the longest follow-up of patients after CRS/HIPEC experiencing bowel obstruction. We describe the true incidence of SBO after CRS/HIPEC. Benign or adhesive SBO can be managed based on the Bologna guidelines and surgery is seldom required. MBO, on the other hand, is complex and decision making relies heavily on clinical judgment. Surgical interventions are accompanied by a high failure rate. We have provided some observations that may help guide clinicians in navigating these complex decisions. Prospective trials are needed to evaluate the actual role of surgery in MBO. Small-bowel obstruction appears to predict worse overall survival in patients after CRS/HIPEC.

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