



Obstruction-Free Survival Following Operative Intervention for Malignant Bowel Obstruction in Appendiceal Cancer

Joel M. Baumgartner, MD, MAS, Rebecca Marmor, MD, Athena Hsu, BS, Jula Veerapong, MD, Kaitlyn J. Kelly, MD, and Andrew M. Lowy, MD

Department of Surgery, University of California, San Diego Moores Cancer Center, La Jolla, CA

ABSTRACT

Background. Patients with peritoneal metastases from appendiceal cancer are at high risk of malignant bowel obstruction (MBO), which is associated with significant morbidity and mortality. There are no definitive treatment guidelines regarding operative intervention for MBO. We sought to evaluate the efficacy and safety of operative intervention in this population.

Methods. We identified patients with peritoneal metastases from appendiceal cancer who underwent surgery for MBO at our institution between 2011 and 2018. Baseline characteristics, postoperative complications, and follow-up data were collected. The primary endpoint was obstruction-free survival (OFS). Other endpoints were postoperative recovery of bowel function, 60-day Clavien–Dindo (CD) morbidity, and overall survival (OS).

Results. Twenty-six patients underwent operative treatment for MBO, of whom 14 had high-grade (HG) histology and 12 had low-grade (LG) histology. Seven (25.9%) patients had severe (CD grade 3 or higher) 60-day complications, including one (3.8%) postoperative death. All remaining patients had return of bowel function and resumed oral intake during hospitalization. Six (23.1%) patients had repeat admissions for MBO after surgery. Median OFS was 17.0 months (95% confidence interval [CI] 2.3–31.8), and median OS was 18.5 months (95% CI 3.6–33.3) following surgery.

Conclusion. In this carefully selected group of patients with peritoneal metastases from appendiceal cancer,

surgery for MBO provided durable palliation with acceptable morbidity.

Management of malignant bowel obstruction (MBO) in the setting of peritoneal metastases remains a frequently encountered yet challenging condition for patients and surgeons. As many as 29% of gastrointestinal cancer patients develop MBO, which is commonly considered a preterminal event.^{1,2} Treatment of MBO is primarily directed at palliation of symptoms. There are little data to guide patient and clinician decision making about the management of MBO and no randomized trials to compare management strategies that may include surgery, medical management and interventional procedures such as endoscopic stenting.

Many prior studies of MBO have utilized heterogeneous interventions, and studied varying histologies and patients with markedly disparate disease burdens, making it difficult to understand how interventions impact outcomes.^{1,3–5} Importantly, patients who have undergone surgery for MBO represent a carefully selected group, and analyses that combine patients who have undergone surgery with those who were not deemed surgical candidates may be biased. Prior work has demonstrated that patients who undergo operations to treat MBO have increased survival when compared with patients who do not undergo surgery.⁶

When determining the appropriate management for MBO, the patient's prognosis, functional status, treatment goals, and options for future cancer treatment must be considered.^{7,8} Consultation with palliative care may be helpful.⁹ Less than half of patients with MBO ultimately undergo surgical intervention.¹⁰ Patients treated operatively experience more complications than those undergoing nonoperative management,^{11,12} but surgical intervention can be more definitive, extending obstruction-free survival (OFS) in select patients.^{3,5}

Peritoneal metastasis is a risk factor for poor outcomes after surgery for MBO. Although 33–100% of patients with peritoneal metastasis-related MBO resume a diet or have resolution of obstructive symptoms after surgery, only 32–71% remain symptom-free at 60 days, 7–44% have serious complications, and the perioperative mortality rate is 6–32%, with an average median survival of < 9 months.^{11,13}

Appendiceal cancers are rare malignancies that give rise to peritoneal metastases in up to 75% of cases.¹⁴ Outcomes in patients with peritoneal metastases from appendiceal cancer vary widely, from 10 to 91% 5-year survival, depending on the extent of disease, completeness of resection, and histologic grade.¹⁵ MBO is a common problem encountered in these patients, although the exact incidence remains unknown.

We sought to investigate the safety and efficacy of operative management for patients with MBO secondary to peritoneal metastases from appendiceal cancer at our institution.

METHODS

Design

This was an Institutional Review Board-approved single-institution, retrospective cohort study to investigate the outcomes of operative management for patients with MBO secondary to peritoneal metastases from appendiceal cancer.

Eligibility

Participants were patients ≥ 18 years of age admitted to our institution between June 2011 and August 2018 with concomitant diagnoses of non-carcinoid appendiceal cancer, peritoneal metastasis, and MBO. Patients who underwent palliative operative intervention for their MBO during the study period were also included. Patients were excluded if they underwent emergent surgery for bleeding or perforation, had obstruction due to purely benign etiology (i.e. benign adhesions, internal hernia), underwent a curative-intent procedure (i.e. all peritoneal metastases were removed), or had non-therapeutic procedures (i.e. exploration without surgical intervention of MBO or gastrostomy tube only). Patients were divided into high-grade (HG) and low-grade (LG) histology based on the 2010 World Health Organization and 2016 Peritoneal Surface Oncology Group International consensus criteria,^{16,17} with LG histology defined as peritoneal metastases with LG mucinous carcinoma peritonei or well-differentiated mucinous adenocarcinoma, and HG histology defined as

peritoneal metastases with moderate or poorly differentiated mucinous adenocarcinoma and/or signet ring cell histology.

Data Collection

We performed a detailed chart review of each eligible patient to capture demographic, baseline health, and prior oncologic treatment data. We also gathered data on all admissions for MBO, regardless of whether an operation was performed. If an operation was performed for MBO, we collected operative data, including procedures performed, operative complications, time to return of bowel function, and length of stay. Sixty-day postoperative complications were calculated per the Clavien–Dindo (CD) classification.¹⁸

The primary long-term outcome of interest was duration of OFS, defined as the time from operation for MBO to recurrent bowel obstruction requiring hospitalization or death. The secondary long-term outcome was overall survival (OS), defined as the time from operation for MBO to death.

Statistics

Chi square tests were performed for categorical data, and Student's *t*-tests were used for continuous variables. OFS and OS were analyzed using the Kaplan–Meier method, and the Cox proportional hazards model was used to identify variables associated with OFS and OS. All statistical analyses were performed using SPSS software version 25 (IBM Corporation, Armonk, NY, USA).

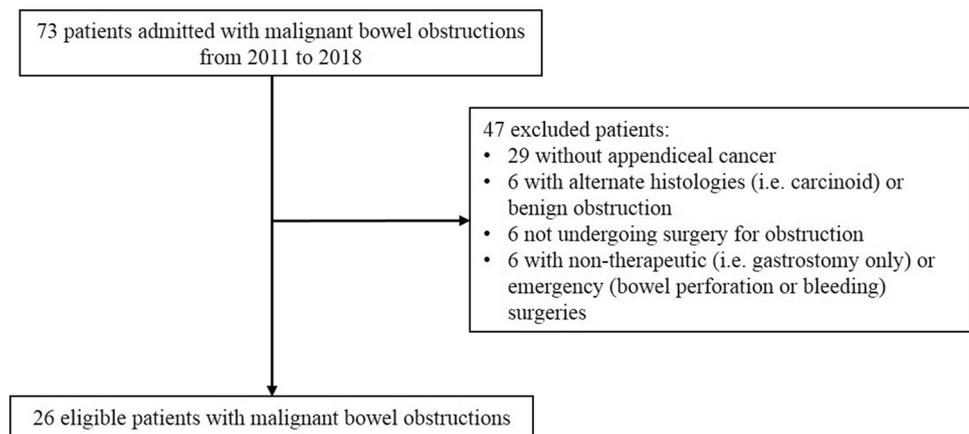
RESULTS

Baseline Data

Twenty-six patients met the eligibility criteria and were included in the study (Fig. 1). Baseline data are shown in Table 1. Of the 14 patients who received chemotherapy, 10 had HG disease (71.4% of all HG patients) and 4 had LG disease (33.3% of all LG patients). The median time from last chemotherapy/biologic therapy to MBO surgery was 3.1 months (range 1.4–22.1), and seven patients received chemotherapy/biologic therapy within 3 months of surgery.

Operative Data

Preoperative cross-sectional imaging was available for review in 17 patients, and revealed the following: median Peritoneal Cancer Index score of 8 (range 0–39), ascites in

FIG. 1 Patient eligibility**TABLE 1** Baseline characteristics of patients admitted with MBO undergoing operative intervention

Variable	
Age, years	55 (36–84)
Female	16 (61.5)
Grade	
LG	12 (46.2)
HG	14 (53.8)
Prior abdominal surgery	25 (96.2)
Two or more prior abdominal surgeries	21 (80.8)
Prior CRS/HIPEC	11 (42.3)
Prior chemotherapy	14 (53.8)

Data are expressed as *n* (%) or median (range)

LG low-grade, HG high-grade, CRS/HIPEC cytoreductive surgery/hyperthermic intraperitoneal chemotherapy, MBO malignant bowel obstruction

11 patients (42.3%), multifocal transition point in 4 patients (15.4%), and small bowel thickening and/or mesenteric disease in 5 patients (19.2%). All 26 patients underwent operative intervention for MBO; 18 (69.2%) had surgery on their first admission for MBO and the remainder had surgery on a subsequent MBO admission. Nine (34.6%) patients presented to the emergency department during their operative admission, 11 (42.3%) were semi-electively admitted, three (11.5%) were admitted urgently from clinic, and three (11.5%) were transferred to our facility. Six (23.1%) patients had admission albumin levels < 3.5 g/dL. Operative details are shown in Table 2. Nine patients (34.6%) had focal obstructions and 17 (65.4%) had multifocal obstructions discovered intraoperatively. All patients had restored gastrointestinal continuity at the conclusion of the operation. Twenty-five patients (96.2%) had gastrostomies placed, 24 (92.3%) underwent lysis of adhesions, 13 (50.5%) underwent bowel resection,

five (19.2%) underwent bowel bypass, five (19.2%) underwent bowel diversion (ostomy), and 13 (50.0%) underwent palliative tumor debulking. Of the five bowel bypass procedures, one was jejunum-to-transverse colon, three were ileum-to-transverse colon, and one was stomach-to-jejunum. Of the five patients with ostomies created, two were end colostomy/mucus fistulas, two were diverting loop ileostomies (one distal ileum, one mid-ileum), and one was an ileal conduit for urinary diversion.

There was one inpatient death on postoperative day 22. All the remaining patients had return of bowel function after surgery and were discharged home tolerating a diet. The median time to first flatus or bowel movement (earlier of the two) after surgery was 5 days (range 2–12). Eight (30.8%) patients were discharged home with total parenteral nutrition (TPN) for nutritional support; three (37.5%) of these patients were receiving TPN prior to admission. Of those patients discharged with TPN with available follow-up records, TPN was continued for a median of 10 weeks after discharge (range 3–17). Additional postoperative details are shown in Table 3.

Postoperative systemic therapy was received by nine patients (34.6%) and was unknown in six patients (23.1%). In those who received postoperative systemic therapy, six had HG disease and three had LG disease.

Complications

Three patients were readmitted within 60 days of surgery—one for dehydration and poor oral intake (in a patient with a urostomy), one for wound infection, and one for intra-abdominal abscess. Six (23.1%) patients had no 60-day CD complications; however seven (26.9%) patients had severe (CD grade 3 or higher) 60-day morbidity. This included five (19.2%) patients with 60-day grade 3 complications, which included myocardial infarction requiring angiography without stent or revascularization (one patient), percutaneous drainage of an intra-abdominal fluid

TABLE 2 Operative details

Variable	All [<i>n</i> = 26]	HG [<i>n</i> = 14]	LG [<i>n</i> = 12]
MBO admission ^a			
First	18 (69.2)	10 (71.4)	8 (66.7)
Second	5 (19.2)	2 (14.3)	3 (25.0)
Third	1 (3.8)	1 (7.1)	0 (0)
Fourth	1 (3.8)	1 (7.1)	0 (0)
Fifth	1 (3.8)	0 (0)	1 (8.3)
Admission albumin, g/dL	3.9 (2.5–4.8)	4.2 (3.2–4.8)	3.7 (2.5–4.3)
Hospital day of operation	2 (0–9)	4 (0–7)	0 (0–9)
Operative time, min	193 (76–587)	222 (98–587)	144 (76–257)
EBL, cc	75 (5–400)	88 (10–250)	75 (5–400)
Procedure			
Bowel resection	1 (3.8)	1 (7.1)	0
LOA and G-tube	2 (7.7)	0	2 (16.7)
Bowel bypass and G-tube	1 (3.8)	1 (7.1)	0
Bowel diversion (ostomy), LOA, G-tube	2 (7.7)	1 (7.1)	1 (8.3)
Palliative tumor debulking, LOA, G-tube	3 (11.5)	0	3 (25.0)
Bowel resection, LOA, G-tube	3 (11.5)	2 (14.3)	1 (8.3)
Bowel bypass, LOA, G-tube	3 (11.5)	3 (21.4)	0
Bowel resection, debulking, LOA, G-tube	7 (26.9)	3 (21.4)	4 (33.3)
Bowel resection, diversion, LOA, G-tube	1 (3.8)	1 (7.1)	0
Bowel bypass, debulking, LOA, G-tube	1 (3.8)	1 (7.1)	0
Bowel diversion, debulking, LOA, G-tube	1 (3.8)	0	1 (8.3)
Bowel diversion, resection, debulking, LOA, G-tube	1 (3.8)	1 (7.1)	0

Data are expressed as *n* (%) or median (range)

MBO malignant bowel obstruction, EBL estimated blood loss, G-tube gastrostomy tube, LOA lysis of adhesions, HG high-grade, LG low-grade

^aMBO admission on which surgery was performed

TABLE 3 Postoperative details

Variable	
Time to return of flatus (POD)	5 (2–10)
Time to return of BM (POD)	7 (2–15)
D/C diet	
Nil per mouth	1 (3.8)
Clear liquid	1 (3.8)
Full liquid	4 (15.4)
Solid	20 (76.9)
LOS (days)	14 (5–36)
D/C on TPN	8 (30.8)

Data are expressed as *n* (%) or median (range)

POD postoperative day, BM bowel movement, D/C discharge, LOS length of stay, TPN total parenteral nutrition

collection (three patients), and thoracentesis of a pleural effusion (one patient). Three of these complications occurred during the index MBO surgery admission, and

two occurred on subsequent admissions. One (3.8%) patient had a grade 4 complication with acute respiratory distress syndrome requiring mechanical ventilation in the intensive care unit (ICU; the patient also had an intra-abdominal abscess requiring percutaneous drainage).

There was one (3.8%) 60-day postoperative mortality in this series, in a patient who died during hospitalization on postoperative day 22. This patient had high-volume LG disease and underwent extensive lysis of adhesions, palliative debulking, cholecystectomy, and gastrostomy tube placement. Postoperatively, the patient developed an intra-abdominal abscess requiring percutaneous drainage, an enterocutaneous fistula, and respiratory failure requiring mechanical ventilation. The patient's family opted to make the patient comfort care and the patient expired.

Obstruction-Free and Overall Survival

The median follow-up time in the cohort was 12.6 months (range 0.3–50.3). Six (23.1%) patients had repeat admissions for MBO. The median OFS was

17.0 months (95% confidence interval [CI] 2.3–31.7): 18.5 months for HG patients (95% CI 0.0–37.5) and 9.6 months for LG patients (95% CI 0.0–29.3; $p = 0.347$ by log-rank test) [Fig. 2a]. Median OS was 18.5 months (95% CI 3.6–33.3): 18.5 months for HG patients (95% CI 0.0–37.4) and 17.0 months for LG patients (95% CI 4.1–29.9; $p = 0.586$ by log-rank test) [Fig. 2b].

DISCUSSION

The management of MBO in the setting of peritoneal metastases is complex. As with other palliative interventions, carefully defining the risks and benefits of surgical management of MBO are essential for informed decision making.¹⁹ However, due to the heterogeneity in this population and the paucity of data on outcomes, weighing the risks and benefits of various management strategies is problematic. Successful management of MBO is multifaceted, with a primary goal of alleviating obstructive symptoms, and secondary goals of restoring gastrointestinal function, improving performance status, and potentially enabling additional oncologic interventions to improve survival and quality of life.

We generally use the following criteria when considering operative intervention for MBO:

1. *Technical aspects:* Is there a transition point or other operative target? Does the number or type of prior operations or the overall disease burden make surgical intervention too high risk? Is the abdominal wall diffusely firm?
2. *Prehospitalization performance status:* We generally consider an Eastern Cooperative Oncology Group (ECOG) score ≤ 2 to be appropriate for consideration for surgery.
3. *Prognosis:* Is the life expectancy from the underlying disease 6 months? Are there reasonable treatment options available if the obstruction resolves?

The decision to offer operative intervention for MBO is thus inherently patient-specific. For example, patients with a poor performance status (ECOG > 2) or short life expectancy are only offered an operation if the operative risks are thought to be low (i.e. focal transition point, low disease burden, limited prior operations, soft abdominal wall, etc.) and all non-surgical options have been explored. In contrast, patients with a good performance status and long life expectancy (i.e. LG disease) might be candidates for more extensive operations (i.e. those who have multifocal transition points, higher disease burden, more significant surgical history, etc.).

The surgical procedure performed is also dictated by patient- and/or disease-related factors to optimize efficacy and minimize morbidity, and includes lysis of obstructing adhesions, resection of obstructing tumor(s) or obstructed segment of bowel, bypass of an obstruction, proximal diversion of the obstruction, or some combination thereof. Ventilating gastrostomy tubes are often utilized in conjunction with these procedures, and gastrostomies can be used alone to alleviate nausea and/or vomiting, although, when used alone, they do not alleviate the obstruction itself. Palliative tumor debulking in the setting of MBO is primarily performed in LG patients who have partial obstructions with elective procedures, with the goal of relieving additional symptoms (abdominal distension, pain, etc.) or to avoid future complications (i.e. removal of additional mesenteric/bowel disease to prevent future bowel obstruction). In cases of HG histology, complete obstructions, and more urgent procedures, debulking is generally only performed to resolve the active obstruction or to prevent additional impending obstruction(s).

Guidelines on goals of therapy, surgical candidacy, and surgical procedures are perhaps more generalizable than the specific details of the presented cohort. However, our study provides an in-depth analysis of a series of appendiceal cancer patients with MBO secondary to peritoneal metastases who underwent operative intervention, offering

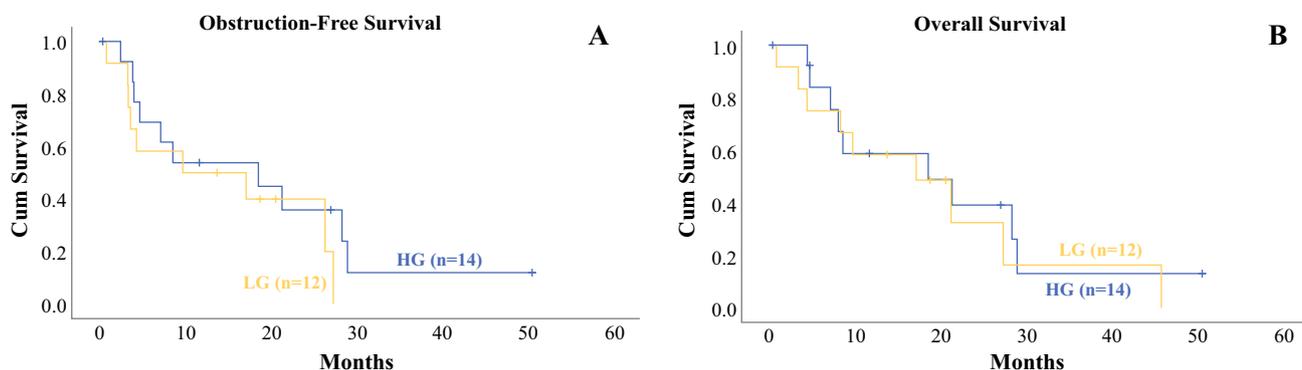


FIG. 2 a Obstruction-free survival and b overall survival for HG and LG patients following surgery for malignant bowel obstruction. Cum cumulative, HG high-grade, LG low-grade

insight into their postoperative and long-term outcomes. We have shown that in a selected group of patients, operative management of MBO can be efficacious, with acceptable risks. Twenty-five of the 26 patients had return of bowel function and left the hospital, and > 75% were able to tolerate a regular diet by the time of discharge. Only six patients (23.1%) were readmitted with obstructive symptoms during the period of observation, demonstrating that operative intervention provided durable palliation. These results are similar to those from other published reports of surgical management of MBO.^{10,11} The median OFS was 17.0 months in our series. OFS is not a metric reported in other studies and we feel it is a useful composite measure of the competing risks of recurrent obstruction and disease-related mortality.

However, the symptomatic relief provided by these operations does not come without risk. Approximately one-quarter of patients in this series had a serious complication within 60 days following their operation, including one death. This complication rate is partially attributed to the complexity of this patient population, most of whom had undergone prior open abdominal operations and treatment for their primary cancer. Additionally, many patients were malnourished—most patients received parenteral nutrition at some point during their hospital course and nearly one-quarter had a low preoperative albumin level. The morbidity and mortality in our series is similar to or lower than those published in other studies, with serious complications reported in 7–44% of patients and mortality of 6–22% in a large systematic review of surgical intervention for MBO in patients with peritoneal metastases.¹³

OS in our series was a median of 18.5 months. These findings are in contrast to previous work that found the life expectancy of patients with MBO from peritoneal metastases to be approximately 2–8 months.¹³ These discrepancies may be explained, in part, by the large proportion of patients with LG appendiceal cancers in our series—cancers known to have a relatively indolent course, with an average survival from time of diagnosis to approximately 6 years.²⁰ Additionally, all patients in our series were selected for surgery, and were deemed healthy enough to undergo operative intervention. Regardless, patients with HG appendiceal cancers also had longer survival than previously reported, which may be due to additional post-obstruction oncologic therapies and follow-up. Finally, we believe these data can be of use during discussions with patients admitted for MBO secondary to appendiceal cancer as the data can help to quantify the potential benefits and risk of surgery, i.e. nearly 1.5 years of OFS.

Limitations

Our conclusions must be viewed in the context of a retrospective small sample-size study. This limited sample size made it impossible to conclusively determine differences in outcomes between HG and LG patients. Additionally, as a tertiary referral center for patients with peritoneal metastasis, many patients in this series were from outside our region, and despite all attempts made to obtain information from referring institutions, these patients may have had additional admissions for obstructions that were not fully captured. Perhaps most significantly, this study represents highly selected patients who ultimately underwent surgery for MBO. By design, this group has improved medical and/or functional status compared with patients who were not offered an operation. We were unable to compare outcomes with nonoperative management in a similar population, although a randomized controlled trial in surgical versus nonsurgical management of MBO is ongoing.²¹ Time to return of bowel function is potentially confounded by the presence of ostomy in some patients, which may reduce the time to passage of flatus or stool into the ostomy.

CONCLUSIONS

This study examines operative management of MBO in patients with peritoneal metastases from appendiceal cancer. We have demonstrated that carefully selected patients can achieve a durable palliation for obstructive symptoms with surgery. This did not vary according to tumor grade in this series. Further studies with a larger dataset are required to study OFS among patients with MBO from appendiceal cancer treated with other modalities.

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