Unanswered Questions in Malignant Bowel Obstruction

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INTRODUCTION

Ms. M. is a 57-year-old woman with a one-year history of stage IV ovarian cancer for which she was treated with surgery for staging and debulking followed by carboplatin and paclitaxel. She was doing well and still able to work part-time, but over the course of a month, she became progressively fatigued and experienced gradually increasing abdominal distension. She continued to eat normally and was active for more than half her waking hours. However, she called her outpatient palliative care doctor to report two days of nausea with five episodes of bilious emesis per day. She had been unable to tolerate any oral intake during those two days, vomiting food and drink shortly after ingesting it. Her last bowel movement had been three days prior and was normal. She denied having a history of constipation.

Malignant bowel obstruction (MBO) is defined as a bowel obstruction beyond the ligament of Treitz in patients diagnosed with intra-abdominal cancer with incurable disease or non-intra-abdominal primary cancer with clear intraperitoneal disease (1). Not all bowel obstructions that occur in people with cancer are considered MBOs by this definition, but we will focus on those that are.

Malignant bowel obstruction is a common problem, occurring in up to half of patients with ovarian cancer and up to a quarter of patients with colorectal cancer (2). In one observational study, 15 percent of people who died on an inpatient palliative care unit had MBO (3). Given the prevalence of this problem, improving its management could have a substantial impact on our patients. Decreasing its incidence would be even more meaningful. To date, preventing or delaying bowel obstruction has not been a primary aim of oncologic trials, and it deserves further study.

After discussing Ms. M.’s symptoms with her, her doctor suspected that she might have MBO. Taking into account her preferences, her doctor recommended that Ms. M. present to the emergency department for urgent diagnosis and treatment. Her husband accompanied her there. In the emergency department, she underwent a computed tomography (CT) scan, which showed multiple sites where there was partial narrowing of the intestine, most prominently in the proximal jejunum, with air-fluid levels. The CT also showed moderate ascites and possible peritoneal seeding.

INTERVENTIONAL MANAGEMENT OF MALIGNANT BOWEL OBSTRUCTION

Treating MBO may involve surgery, nonsurgical interventions (such as stenting), and medical management. A systematic review of surgery for MBO in advanced gynecologic and gastrointestinal cancer showed a high rate of symptomatic improvement (42-80 percent); definitions of symptomatic improvement varied between studies, from being able to resume a normal diet postprocedure to having no symptoms of obstruction for at least 60 days. However, 30-day postoperative mortality varied widely (5-32 percent), as did rates of reobstruction (10-50 percent) (2). The variation in mortality rates was likely related to patient selection (that is, whether the patients who were operated on were sicker, and thus less able to tolerate the procedure or benefit from it) rather than to the technical proficiency of the procedures themselves.

A Cochrane review initially published in 2000 and updated in 2008 sought to determine when interventional approaches would be preferable to medical management alone for MBO in ovarian cancer (4). However, because of the retrospective, observational design of the studies reviewed, the authors were unable to draw any firm conclusions. Though it is likely that patients with single-level obstructions would benefit from surgery in a different way from patients with multilevel obstructions, questions remain about how, precisely, surgery alters the natural history of MBO.
and which patients would predictably benefit from surgery.

Furthermore, multiple surgical approaches exist, including intestinal resection or bypass, tumour debulking, diversion, and lysis of adhesions. Here, too, “without enough strong data to suggest one procedure is better than another in terms of morbidity, mortality, or quality of life, it remains up to the discretion of the surgical team to determine the course of action” (5, p. 578). In general, the main objective in the surgical treatment of MBO is to minimize the operation and incision as much as possible. However, few patients are candidates for a laparoscopic approach — most require open procedures, which are associated with increased postoperative pain and higher rates of wound complications. It is important to emphasize that it is not uncommon to abort an operation due to unanticipated intraoperative findings such as multiple levels of obstruction. Every effort should thus be made to place a venting gastrostomy tube during surgery to avoid the need for a long-term nasogastric tube or a separate procedure to place a venting gastrostomy tube in the future.

While neither the site of the obstruction nor the operative technique employed have been found to be significantly associated with outcomes, generalized carcinomatosis was identified as a preoperative predictor of a low likelihood of benefit from surgery (6). There are likely multiple reasons for this association, including: carcinomatosis can lead to blockages of the bowel at multiple levels and abnormal intestinal motility due to bowel wall infiltration or compromise of visceral nerves; blockages are typically partial and intermittent, rarely causing bowel strangulation, so symptoms may resolve with bowel rest and frequently recur; when patients with MBO from carcinomatosis are treated surgically, they have frequent complications, including reobstruction; and 30-day postoperative mortality rates are very high (6).

However, given that some patients with carcinomatosis have distressing symptoms despite maximal medical treatment, a recent literature review reexamined the question of palliative surgery for MBO in the setting of carcinomatosis (7). In 17 observational studies involving 868 patients, the authors found that surgery can improve symptoms and allow for oral intake as well as discharge home, but the duration of symptom relief was short (fewer than 60 days, on average), 30-day mortality was high (6 to 32 percent), complications were common, and patients spent a substantial portion of their remaining life in hospital (11 to 61 percent). In four of the five studies that compared palliative surgery to medical management alone for patients with MBO and carcinomatosis, survival and symptoms improved with surgery, but, importantly, patients with poor prognostic features prior to surgery had a median survival comparable to that of similar patients who were managed medically. These findings illustrate the limitations of observational studies; healthier patients were more likely to have surgery than sicker patients, contributing to the improved outcomes seen after surgery.

We appreciate this reexamination of the question of how patients with carcinomatosis fare after surgery for MBO, but the important question remains of which patients with carcinomatosis are likely to be on the low versus the high end of the risk scale. Several grading systems have been proposed to help oncologic surgeons predict outcomes following an attempt at curative resection (8-10). As might be expected, all of these different grading systems indicate that limited peritoneal disease is associated with a more favourable long-term outcome than diffuse carcinomatosis.

Ms. M. and her husband were seen by the general surgery team in the emergency department. The surgeons explained the risks, benefits, and expected outcomes of surgery in detail, but Ms. M. and her husband could only reply with tears. This information was devastating to them, and it did not feel relevant, as Ms. M. had recently felt well and had been able to do what she enjoyed, including preparing and sharing meals with her family. They wanted to know how she could return to that state.

**PSYCHOSOCIAL SUPPORT AND PATIENT-CENTRED OUTCOMES**

Psychosocial support for patients and their families is a critical component of care. This issue is especially important given that MBO causes a heavy burden of symptoms, carries a poor prognosis, and can be associated with a powerful grief reaction in patients and caregivers related to the patient’s inability to eat. Furthermore, making decisions, particularly about whether to proceed with surgery, can be highly stressful. It is made all the more difficult by gaps in the existing data, including a lack of information about how various treatments affect patients’ and caregivers’ experience. Future studies should focus more attention on patient-centred outcomes (such as quality of life, function, and comfort), family-centred outcomes (caregiver burden and emotional distress), and healthcare utilization metrics (hospital length of stay and readmission rate), in addition to the disease-centred outcomes with which we are familiar (survival and symptom control) (11). It is
important to remember that MBO is rarely a surgical emergency, as bowel strangulation is uncommon (12). Thus, there is time to monitor patients, determine their initial trajectory after institution of medical therapies, and consider patient and family preferences. If surgery is required, there is adequate time to optimize the management of comorbid conditions in order to maximize the likelihood of a successful surgical outcome.

After further discussion with admitting providers and palliative care consultants, Ms. M. and her husband expressed a preference to avoid operative management if Ms. M.’s symptoms could be relieved with medical treatments. She was starting to understand that her future was uncertain, so she wanted to prioritize symptom relief, after which she hoped to return home to her family.

MEDICAL MANAGEMENT

Medical management is a cornerstone of treatment for multilevel MBO, whether or not a patient is deemed also to benefit from interventional management. However, rigorous evidence indicating which medications to use and whether these medications will change the course of MBO is lacking. Medical management of partial MBO is based almost entirely on case studies, observational studies, and expert opinion. In theory, treatment is aimed at normalizing gut function, although slowing and resting the bowel may be necessary in the case of a complete and refractory MBO.

Opioid analgesics are typically given to patients with significant pain because no other class of analgesic can provide the same degree of analgesia. Antispasmodic drugs such as hyoscine butylbromide are widely used for colicky pain.

Commonly, a combination of antiemetics is needed to control nausea. No empiric evidence exists regarding which agents are preferable, and expert consensus has not even been reached. For partial obstruction, classes of medication sometimes recommended include prokinetics (such as metoclopramide), serotonin antagonists (such as ondansetron), and dopamine antagonists (such as haloperidol) (13). However, metoclopramide primarily works on the stomach and proximal intestine and therefore could not be expected to assist with all cases of MBO (14). Serotonin antagonists may be effective against nausea in MBO, but constipation is a known side effect, so these medications must be used with caution in partial MBO (15). When obstructions are complete or refractory, prokinetics are typically stopped, which is a practice based on pathophysiology rather than empirical evidence. Further study is needed to better define ideal, evidence-based practice.

Somatostatin analogs (such as octreotide and lanreotide) reduce gastric and intestinal secretions, peristalsis, and splanchnic blood flow (13). A 2012 review of three randomized controlled trials (involving 18, 17, and 68 patients, respectively) that examined the effects of octreotide compared to those of scopolamine butylbromide in patients with MBO showed improved symptom control with octreotide (16-19). Subsequently, a multicentre, randomized French study of 64 patients treated with octreotide or placebo showed that a greater percentage of patients treated with octreotide had symptomatic improvement, but the study was underpowered, and the null hypothesis could not be rejected (20). Another multicentre, randomized European trial, this one involving 80 patients with carcinomatosis treated with lanreotide or placebo, showed a trend toward improvement in patients’ self-reported symptoms that was not statistically significant (21). Finally, a multicentre, randomized trial of adding higher-dose octreotide (roughly twice the dose used in the previous two studies) or placebo to ranitidine and dexamethasone showed that in a population of 275 patients, there was no significant difference in the primary outcome of days free of vomiting, but there was a reduction in the number of episodes of vomiting in the octreotide arm (22). However, even where statistically significant benefits have been found, the clinical significance of these benefits is uncertain. This question of clinical significance is all the more important because somatostatin analogs are expensive and require continuous, thrice-daily intravenous or subcutaneous administration or a long-acting depot formulation that takes weeks to reach therapeutic levels. We also have little evidence as to whether these costly and inconvenient medications should be continued after the resolution of symptoms.

Anticholinergic medications (such as scopolamine and glycopyrrolate) also reduce gastrointestinal secretions and decrease motility (13). Scopolamine was shown to be inferior to octreotide when used alone, but little is known about its added benefit when used in conjunction with octreotide (18, 19).

Corticosteroids have both antiemetic and anti-inflammatory effects; it is hypothesized that by decreasing tumour swelling they can relieve malignant obstructions. A 1999 Cochrane review showed that corticosteroids are associated with improvement in bowel obstruction symptoms, a trend toward improved rate of resolution of obstructions that was not statistically significant (odds ratio, 0.51; 95 percent confidence interval, 0.19-1.42), and no significant difference in survival
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DISCUSSION

An understanding of malignant bowel obstruction is essential to those of us who work in the field of palliative care for several reasons: MBO is common in our patient population; it can cause great suffering when left unchecked; and its management is almost always palliative, as its clinical onset often marks a terminal event. We have taken some small steps toward changing the face of this morbid condition for many of our patients. However, a number of important questions remain unanswered, and from them we can draw lessons applicable not only to this topic but also to other areas of palliative care (Table 1).

First, nearly all of our data about MBO are observational; this is particularly true of the evidence related to surgical treatments. We need to work with our surgical and interventional radiology colleagues to develop a shared commitment and a unified system to collect high-quality prospective data sets that are randomized or large enough to enable robust adjustment to mitigate concerns about confounding. This approach could clarify many questions, including whether surgical treatments — or simply the preexisting characteristics of patients who are managed surgically — account for improved outcomes. However, there are well-recognized challenges to enrolling patients in palliative care studies, including high rates of incapacity due to severe illness, substantial loss to follow-up, and concerns about the burden of the scientific process when comfort is a priority (27). Advance or proxy consent for at-risk patients could help with enrollment. Using a factorial design for a randomized controlled trial could make it possible for us to answer multiple clinical questions based on data derived from a

Table 1 / Unanswered Questions about Malignant Bowel Obstruction (MBO)

<table>
<thead>
<tr>
<th>Question</th>
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<tr>
<td>Resulting from insufficient randomized or controlled data:</td>
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<td>• Which patients benefit from surgical or nonsurgical interventional approaches rather than medical management alone?</td>
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<td>• Which surgical approach is best?</td>
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<tr>
<td>• Which patients with carcinomatosis benefit from surgery?</td>
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<tr>
<td>Resulting from insufficient study of patient- and family-centred outcomes:</td>
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<td>• How do MBO and its treatments affect the experience of patients and their families as well as their quality of life?</td>
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<td>• How can we best provide psychosocial support to patients facing MBO and their families?</td>
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<td>Resulting from lack of a unified treatment algorithm for medical management:</td>
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<td>• How should medical therapies for MBO be sequenced and combined?</td>
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<td>• How long should medical therapies for MBO be continued and how should they be tapered?</td>
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<tr>
<td>Resulting from insufficient study of MBO as an outcome in oncologic studies:</td>
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<td>• Could MBO be prevented through particular active treatment regimens?</td>
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The team supported Ms. M.’s decision to avoid exploratory surgery, particularly as there were several factors in her case that predicted a high complication and mortality rate with minimal long-term benefit. She was managed medically and discharged home on hospital day six with opioids, haloperidol as needed, corticosteroids, and ranitidine. She was largely comfortable for several weeks, though she took little by mouth, and she died peacefully at home with her husband at her side.
single population of accrued participants. Multicentre trials are critical to ensure adequate recruitment and power. Even when randomization is not feasible, by collaborating across sites to collect a common set of data on each patient with MBO, we may gather sufficient data to adequately control for confounders — through propensity score-matching, for example. Many cooperatives, such as the Palliative Care Clinical Studies Collaborative and the European Palliative Care Research Collaborative, have demonstrated how obstacles to sufficiently powered prospective trials can be overcome in the face of rare conditions (28-30). These efforts will only be possible with adequate funding, however. While pharmaceutical companies are unlikely to be the primary source of funding for palliative care studies (as our patients’ high rates of morbidity and mortality may increase the reporting of adverse events), public institutes in many countries are interested in funding palliative care studies because a high proportion of medical care is ultimately paid for by public programs, creating an incentive to define appropriate and high-value care.

Second, given that MBO management is inherently palliative, we need to consider how our treatments and practices affect patient- and family-centred outcomes. While survival is an important outcome, for many patients with MBO, factors such as being able to eat, being able to spend days at home, quality of mood, quality of life, and degree of caregiver stress may be as or more important. Many validated survey instruments have been developed for this purpose — including the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C15-PAL), the Functional Assessment of Cancer Therapy (FACT) questionnaire, and the Steinhauser spiritual assessment — but they are not yet used routinely in oncology studies (31-33).

Third, we have substantial data about the effects of various medical treatments on MBO, but much of what we do is still determined by local culture and practice patterns (1). Several consensus groups have used the existing evidence to do the important work of developing treatment guidelines, even while acknowledging the limits of the evidence (6, 26). As a next step, we should conduct rigorously designed studies to empirically test the effects of these treatment algorithms and strive to determine how best to sequence, combine, and taper medical treatments. Again, large, multicentre trials or registries will be critical for this aim. Pharmacovigilance studies, including aggregate reporting, could also be used to monitor adverse drug reactions, though they are difficult to administer and currently limited by under-reporting (34, 35).

The rewards for the work we describe here are well within our collective reach, and they could have a profound effect on the substantial proportion of our patients who are at risk for MBO. Furthermore, by demonstrating the power of coordinated collaboration to enable robust, patient-centred research, we could have an impact on the broader field of palliative care and beyond.

REFERENCES


