ORIGINAL ARTICLE

Management of malignant bowel obstruction in advanced gynecologic malignancies: A proposed algorithm

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INTRODUCTION

Malignant bowel obstruction (MBO) is common in women with gynecologic cancer and is considered as a major clinical challenge due to the significant burden on patients, caregivers, and health systems [1]. Of all the gynecologic malignancies, ovarian cancer is the predominant cause of MBO and the deadliest malignancy. MBO is an important cause of morbidity and mortality of ovarian cancer, and its early detection may improve patient outcomes [2]. Although MBO may be the first manifestation in 20% of patients with gynecologic or gastrointestinal malignancies, in most cases, it is a sign of incurable recurrent disease [1, 3]. Among gynecologic cancers, MBO is more common in women with cancers of the ovaries, fallopian tubes, and peritoneum, and eventually affects up to 20% of patients. MBO has also been described as an end of life condition in 3 to 11% of patients with uterine cancer [4]. In retrospective studies, up to 51% of women with recurrent ovarian cancer developed MBO and their median survival after diagnosis of MBO ranged from 45 to 159 days. This rate was 124 to 408 days in patients who underwent palliative surgical intervention [1]. However, most cases of MBO in ovarian cancer are diagnosed when the bowel is involved at several levels and therefore are not a good candidate for surgical treatment [2].

MBO can be partial or complete and can occur at single or multiple sites of the bowel. Small bowel obstruction is more common than large bowel obstruction. The majority of MBO occurs due to external compression or functional occlusion of the gastrointestinal tract from peritoneal carcinomatosis or tumor infiltration of bowel muscle/nerves and in some cases, it may be due to nonmalignant causes such as adhesions from previous surgery, intraperitoneal chemotherapy, radiation enteritis, or opioids [1, 3]. However, other differential diagnosis should also be considered (Table 1) because it is estimated that approximately 25% of patients with peritoneal carcinomatosis have secondary MBO due to nonmalignant etiologies [3].

Diagnosis: Depending on the level and the degree of obstruction, patients usually present with colicky abdominal pain, anorexia, nausea, and vomiting [3]. Presentation of MBO is usually subacute with symptoms such as nausea, vomiting, pain, abdominal distention, and constipation and/or obstipation. Symptoms such as flatulence, stomach discomfort and noises, diarrhea, loss of appetite are nonspecific symptoms and may be due to the biological relationship between these symptoms and the cancer progression process itself. Symptoms of MBO in the partial type may be intermittent. Patients may also experience diarrhea due to bacterial liquefaction of nutritional content and increased intestinal secretions [1, 2, 5]. Inability to excrete gas and stool (obstipation) indicates complete obstruction, while paradoxical diarrhea and fecal incontinence (overflow diarrhea) indicate partial obstruction [3].

The diagnosis of MBO is established on clinical grounds and confirmed with abdominal imaging. Typical findings on abdominal radiographs seen in the upright position include distention of bowel loops with air-fluid levels in the segment proximal to the occlusion, as well as reduction in gas and stools in the segment distal to the occlusion (Figure 1). Plain abdominal radiographs have moderate sensitivity, ranging 40–80%, for detecting small bowel obstruction. The absence of radiologic findings despite clinical symptoms suggestive of obstruction does not rule out the diagnosis as patients may have functional bowel obstruction secondary to disseminated infiltration of the mesentery. Contrast computed tomography (CT) is more valuable and in addition to identifying the site, etiology, and extent of obstruction, it can confirm complications such as superimposed ischemia and intestinal perforation [1, 2, 6]. In order to get the benefits of CT scan, it has been suggested to perform a CT scan with IV and oral contrast agent [1, 3]. Due to the absorbability of iodinated contrast agents, the use of these substances (such as gastrografin) instead of barium as a contrast agent in a CT scan with an oral contrast agent, is recommended [1]. The use of biomarkers in the diagnosis of MBO is still limited, and although the CA-125 biomarker

has been approved as an indicator of disease activity and a guide to ovarian cancer management, for example in the ESMO study, CA-125 doubling has been seen in only less than half of patients before radiological confirmation of MBO, indicating insufficient sensitivity to doubling of CA-125 level in MBO assessment. Due to the lack of significant changes in the level of CA-125, despite the hidden activity of the disease and the possibility of MBO due to this activity, it is recommended that the cardinal symptoms (abdominal pain, nausea, vomiting, constipation) be examined at each follow-up visit of ovarian cancer patients [2]. The criteria to define MBO are [1] clinical evidence of bowel obstruction (history/physical/radiological examination), [2] bowel obstruction beyond the ligament of Treitz, [3] diagnosis of intra-abdominal cancer with incurable disease, or [4] a diagnosis of non-intra-abdominal primary cancer with clear intraperitoneal disease [1, 2].

Treatment options

Surgery: Surgical intervention can be successful in reestablishing bowel function for selected patients who have functional levels and good treatment options for underlying cancer [1, 3, 4]. As large bowel obstruction and acute complications (such as volvulus, ischemia) are associated with significant morbidity and risk of intestinal perforation and death, supportive care is usually not appropriate for it and requires surgical intervention. [1, 3]

Surgical approaches consist of diverting stoma, resection with anastomosis and bypass [1, 3]. Unlike MBO due to gastrointestinal carcinoma, which intestinal resection with anastomosis or internal bypass is preferred [3], in the large bowel obstruction due to gynecologic cancer, the predominant surgical approach is diverting stoma [1, 7]. Patients may need more than one surgical intervention [3]. Small bowel obstruction without strangulation is mainly treated with conservative measures as it often relates to multifocal small bowel involvement secondary to peritoneal carcinomatosis and only a few cases become candidates for small bowel resection with anastomosis or internal bypass [1].

It is very important and critical that discussions about realistic goals and limitations of surgery occur as it confers significant risk, with the operative mortality rate ranging from 6 to 32% and morbidity rate ranging from 7 to 44%, depending on type and setting (emergency versus elective) of the surgery [1]. There is also a considerable risk of re-obstruction (6–47%), hospital readmission (38–74%), and hospitalization for surgery which may consume a substantial portion of the patient's remaining life (11–61%) [1]. Counseling with patients and their families about palliative care is complicated and depends on the patient functional status, personal values, and physician opinions. In order to help patients, it is necessary to make decisions in line with their desires and to consider the reality of their disease status and possible consequences [4]. A Cochrane review examined the role of surgery in MBO secondary to advanced gynecologic and gastrointestinal cancer and included data from 43 studies with a total of 265 participants, no firm conclusion could be drawn due to the wide variability comparing different surgical procedures, the diverse definition of clinical outcome, heterogeneous clinical practice, and selection bias within these studies [1]. Therefore, the role of palliative surgery remains controversial and should be considered for selected patients with certain clinical characteristics including good performance status, longer treatment-free interval, absence or small volume ascites, single-site disease, and albumin level [1, 7, 8]. This is also in concordance with the recommendation by the European Association for Palliative Care (EAPC) that surgery should not be undertaken routinely in patients with poor performance status, intra-abdominal carcinomatosis, and massive ascites [1]. Although the median survival in patients with uterine cancer with MBO was less than half that of patients with ovarian cancer with MBO (57 vs. 131 days), Hoppenot et al. study [4] showed that the survival rate of those uterine cancer patients undergoing surgery is closer to the ovarian cancer group (182 vs. 210 days) [4].

Less invasive approaches using self-expandable metallic stent (SEMS) for gastric outlet obstruction and left-sided colonic obstruction may be feasible in some cases of MBO [1]. This procedure, especially in the presence of single obstruction site [3], has less morbidity when compared to open surgery and is able to restore bowel function without the need of creating a stoma [1]. The benefit of SEMS as a palliative procedure or as bridge to surgery has been well described with a lower overall morbidity and lower stoma [1]. It was also recognized that the procedural success rate relied heavily on operator expertise and facility resources, and the overall complication rate can be as low as 3.4% for the risk of perforation and 0.5% for the risk of major bleeding [1]. Therefore, it is recommended that this procedure be performed in frequently visited centers with advanced endoscopic facilities and surgical support [3] so that in case of complications (such as perforation), appropriate action can be taken to improve the outcome.

For inoperable but symptomatic patients, venting gastrostomy may be placed to avoid the prolonged use of a nasogastric tube for GI decompression, particularly in patients with protracted vomiting as their dominating symptom [1, 7]. Gastrostomy can be performed endoscopically, either with the guide of interventional radiology or surgery [3]. Placement of venting gastrostomy is shown to be feasible despite the inherently added risk of complications in patients with ascites [1] which can be performed surgically [3]. Prompt venting gastrostomy insertion can be advantageous in reducing the polypharmacy burden to control visceral symptoms, avoiding repeated hospital admissions for medical/nasogastric tube interventions, allowing consumption of modified diet for comfort, and facilitating sustained discharges to home or palliative care centers [1]. In the management of MBO in women with advanced recurrent disease, options such as endoscopic gastroscopy or surgery should be decided in an individualized way [7].

Chemotherapy: The role of chemotherapy in MBO is to treat the underlying disease and requires careful consideration of the anticipated response and tolerability. There are very limited data in scientific texts about effects of chemotherapy on MBO because patients with MBO are typically excluded from clinical trials. In addition, the majority of patients with MBO receive multiple lines of chemotherapy and thus are unlikely to mount a clinically

meaningful response resulting in the resolution of MBO [1]. The type of chemotherapy administered for patients with advanced gynecologic cancers and MBO may include platinum-, taxane-, or gemcitabine-based regimens [9]. Consideration of dose modification or a weekly regimen is common as patients with MBO are at higher risk of toxicity and complications due to their poor nutritional state [1].

Overall, the currently available data in scientific sources to support the use of chemotherapy in patients with advanced gynecologic cancers who developed MBO is still limited [1, 9], and caution should be exercised when using the results of large studies which mostly involving non-gynecological patients [1].

Total Parenteral Nutrition (TPN): Studies examining the use of TPN in patients with advanced gynecologic cancer and MBO reported short median overall survival of 40–93 days [1, 9]. In these studies, the rate of complications were highly variable, ranging from 4 to 54%, and they included predominantly catheter-related infections and less commonly deep venous thrombosis (DVT) and TPN-related liver disease [1, 9]. Despite all these studies, there is a subgroup in patients who survived more with using TPN (24% survival in the sixth month and 8% survival over one year), possibly due to TPN and disease stability [1, 9]. It is reasonable to postulate that certain disease histology/biology (such as low-grade ovarian cancer) and the absence of cancer spread to visceral organs may correlate with better survival [1]. Bozzetti et al. suggested that the Glasgow prognostic score (GPS) of zero (Table 2) [10], Karnofsky performance status (KPS) more than 50 (Table 3) [11], and tumor spread (local-loco regional disease) were prognostic factors of survival beyond 3 months following TPN [12]. Combining these three clinical variables may lead to the identification of a subgroup that has a 6-month survival of 43% vs. 5%. A nomogram based on these parameters was developed enabling estimation of 3- and 6-month survivable probability [13] (Figure 2). To use the nomogram, the score of each risk factor is determined using the scoring scale at the top of the nomogram, and then the location of the total scores is determined on the overall score scale. A line is drawn perpendicular to this score to estimate the median survival time (months), 3- and 6-month survivable probability, respectively [13]. In-depth discussions and realistic expectations must be set with patients and family members early on to emphasize the limitations of TPN use in MBO and possible economic impacts (cost-effectiveness) and situations when TPN should be discontinued [1].

Pharmacological Management: Medical management in MBO is directed at reducing inflammation and endoluminal pressure and secretions as well as relief of pain and distressing symptoms [1]. Combination of glucocorticoids, opioid analgesics, antiemetic, and anti-secretory drugs can achieve good symptomatic control for MBO. Most patients with MBO cannot tolerate oral medications; therefore, alternative methods of drug administration are considered such as intravenous, subcutaneous, and transdermal. Doses and choice of drugs are highly personalized and variable [1, 14]. It is also necessary to adjust the medication regimen periodically depending on the trajectory of MBO and treatment response [1] in order to prescribe the minimum medication required. Overall, there is a trend to support the use of steroids in MBO, and the side effects are generally well tolerated. Concerns regarding prolonged use of glucocorticoids in this setting include infection risk, gastric ulceration, and mood swings and therefore should be rapidly discontinued if minimal response is observed [1].

There is low-level evidence of benefit with somatostatin analogues in the symptomatic treatment of MBO [15]. Nonetheless, somatostatin analogues appeared to be well tolerated by the patients [1]. Olanzapine (Zydis ODT) is the only available orally dissolving drug that can be prescribed even to patients with nausea and vomiting, and its potential efficacy in relieving nausea in incomplete bowel obstruction has been proposed [16].

Opioid analgesia is an effective medication used to palliate pain in advanced cancers, as supported by the WHO guidelines [11]. Pain in MBO can be colicky or continuous in nature. The optimal analgesic agent for MBO is not determined; however, experts favor the use of opioid analgesia given that it can be administered bypassing the oral route (intravenous, subcutaneous, sublingual, or transdermal) and also the decreasing effect on bowel motility may relieve colicky pain [1].

Quality of Life (QOL): Data on QOL and cost analysis does not exist in the scientific texts for MBO. The resolution of MBO can be used as a marker for improved QOL. Bowel function recovery, and its measure for QOL, has been evaluated among patients undergoing stent or diverting colostomy. Whilst both methods were found to be effective in palliating symptoms of MBO, stent placement was associated with improved QOL related to gastrointestinal function [1]. TPN has also been shown to significantly improve overall QOL, nutritional status and performance level (increased KPS score).

RESULT

MBO is a challenging complication of advanced gynecologic cancers, particularly in ovarian cancer. Clinical decision making involves complex considerations of different approaches available in the articles. Most interventions are based on retrospective studies, usually reported on a specific group of MBO patients and a specific treatment. Apart from confounding variables such as uncontrolled concurrent therapies, each intervention only targeted specific time points of a MBO episode and therefore there is no information on the entire trajectory of MBO, and a prospective study on MBO patients with advanced/recurrent gynecological cancers seems necessary [1]. It should be noted that conducting a clinical trial on MBO patients is very difficult due to the complex nature of the disease and the differences in the definition of primary outcome measure as well as the subacute and recurrent nature of MBO, which are barriers to proper evaluation of treatment effects; therefore, the conduct of prospective clinical trials for MBO is necessary and requires a multidisciplinary team effort to define the complex care approach and improve treatment strategy [1]. Figure 3 shows our proposed algorithm, taking into account all these limitations, and includes the overall lines of examination and treatment of patients with MBO in advanced gynecological cancers. It should be noted that only a small subset of patients with MBO benefits from

surgical interventions. There is ongoing controversy with the use of chemotherapy and TPN, highlighting the need for further investigation.

After early symptom control, patients with MBO can be managed in an out-patient setting (stay at home) by a hospital specialist team including home palliative care services, nursing care at home, and domestic care services. The participation of all treatment teams including gynecologist-oncologist, medical oncologist, oncologist surgeon, nutritionist, interventional radiologist, psychiatrist and discussing with patients and their family about the expectations and possible consequences of each choice for individualized treatment is very effective in the treatment path. It seems that with proper use of this model of care, patients can also enjoy the support of their families that its possible outcome will be increased QOL. This requires continuous and daily monitoring of MBO patients by physicians and nurses who know their symptoms, thus hospital visits are reduced.

Table 1. Differential diagnosis of MBO in peritoneal carcinomatosis [3]

Lesion		Etiology	Associated Conditions/Symptoms
Mechanical			
	Extrinsic	Peritoneal carcinomatosis	GI or ovarian tumors
		Adhesions	Prior surgery, peritonitis
		Hernia incarceration	Congenital or acquired
		Sclerosing mesenteritis	Prior surgery, malignancy (urogenital, GI adenocarcinoma, lymphoma)
		SMA syndrome	Rapid weight loss
		Volvulus	Chronic constipation, congerital aberrant attachments
	Intrinsic or endoluminial	Large/small bowel neoplasms	Colorectal Cancer (CRC)
		Anastomotic stricture	Prior colon resection
		Ischemic stricture	Prior colon resection, Peripheral artery disease (PAD)
		Radiation enteritis/fibrosis	Prior abdominal or pelvic radiation
		Foreign body	Medical device migration (PEG, jejunal tube)
		Intussusception	Small bowel tumor
		Feces	Chronic constipation, impaction
Functional			
	Intramural	Bowel wall infiltration with or without edema	Gastric carcinoma (linitis plastic)
	Drug induced	Anticholinergics, analgesics (opioids), antispasmodics, antihistamines, iron supplements, antiemetics (5-HT3 antagonists)	
	Adynamic (paralytic) ileus	Paraneoplastic syndrome, mesenteric nerve infiltration, postoperative ileus	

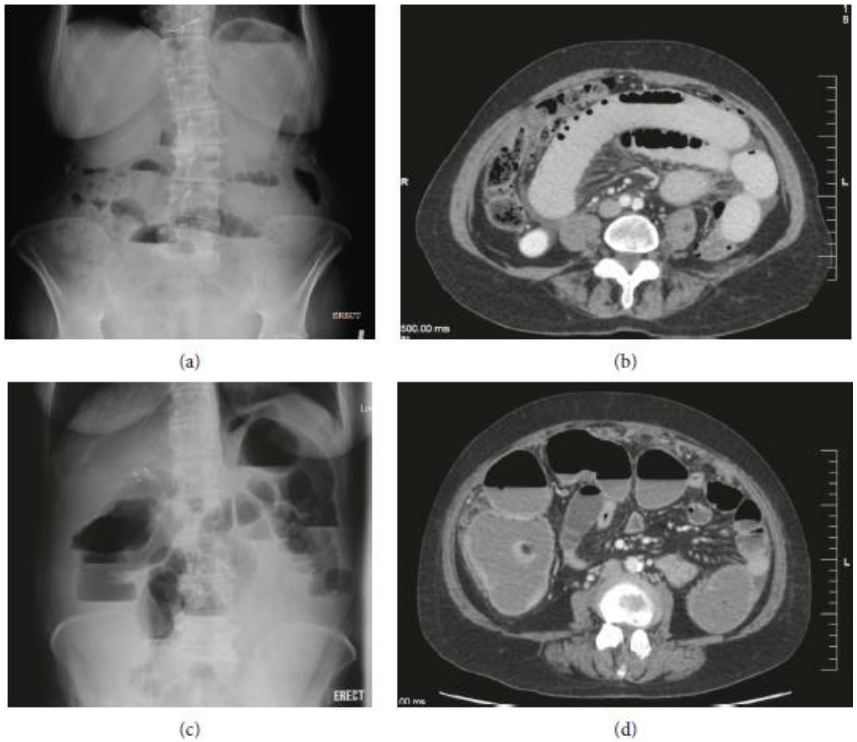

Figure 1. Radiographic images showing MBO. (a) Abdominal radiograph in upright position showing multiple air-fluid levels consistent with small bowel obstruction (SBO). (b) Computed tomography (CT) confirms a high-grade SBO. (c) Abdominal radiographs in upright position showing large bowel obstruction (LBO). (d) CT demonstrates distended and fluid-filled large bowel loops concordant with LBO [1].

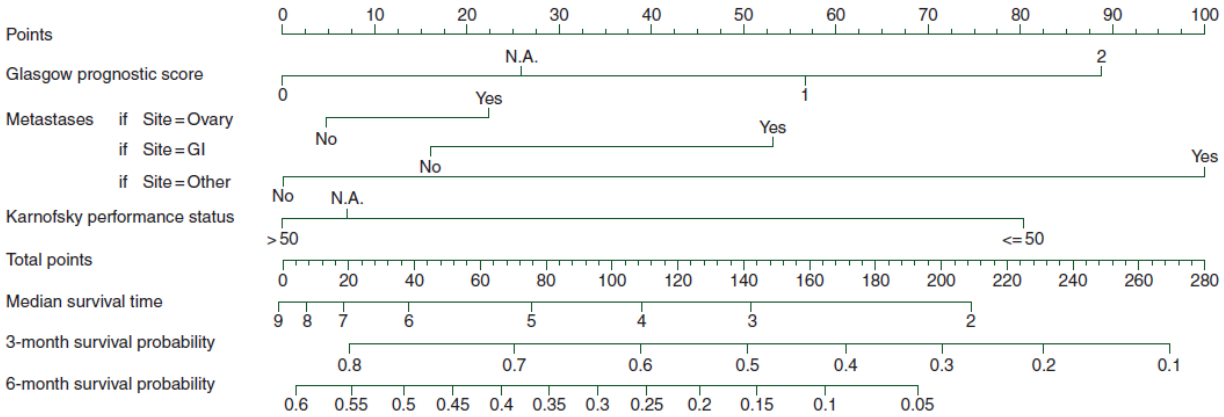

Figure 2. Nomogram estimating the 3- and 6-month survival probability, and median OS of patients with visceral cancer undergoing TPN [13]

Table 2. Modified Glasgow Prognostic Score (mGPS) [10]

Biochemical characteristics	Score
CRP ≤ 10 mg/L + any albumin	0
CRP > 10 mg/L + albumin ≥ 3.5 g/dL	1
CRP > 10 mg/L + albumin < 3.5 g/dL	2

CRP, C-reactive protein

Table 3. Karnofsky performance status (KPS) [11]

Condition	Score	Comments
Able to carry on normal activity and to work. No special care is needed.	100	Normal, no complaints, no evidence of disease.
	90	Able to carry on normal activity, minor signs or symptoms of disease.
	80	Normal activity with effort, some signs or symptoms of disease.
Unable to work. Able to live at home, care for most personal needs. A varying degree of assistance is needed.	70	Cares for self, unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled, requires special care and assistance. [In bed more than 50% of the time].
	30	Severely disabled, hospitalization is indicated although death not imminent. [Almost completely bedfast].
	20	Hospitalization necessary, very sick, active supportive treatment necessary. [Totally bedfast and requiring extensive nursing care by professionals and/or family].
	10	Moribund, fatal processes progressing rapidly. [Comatose or barely arousable].
	0	Dead.

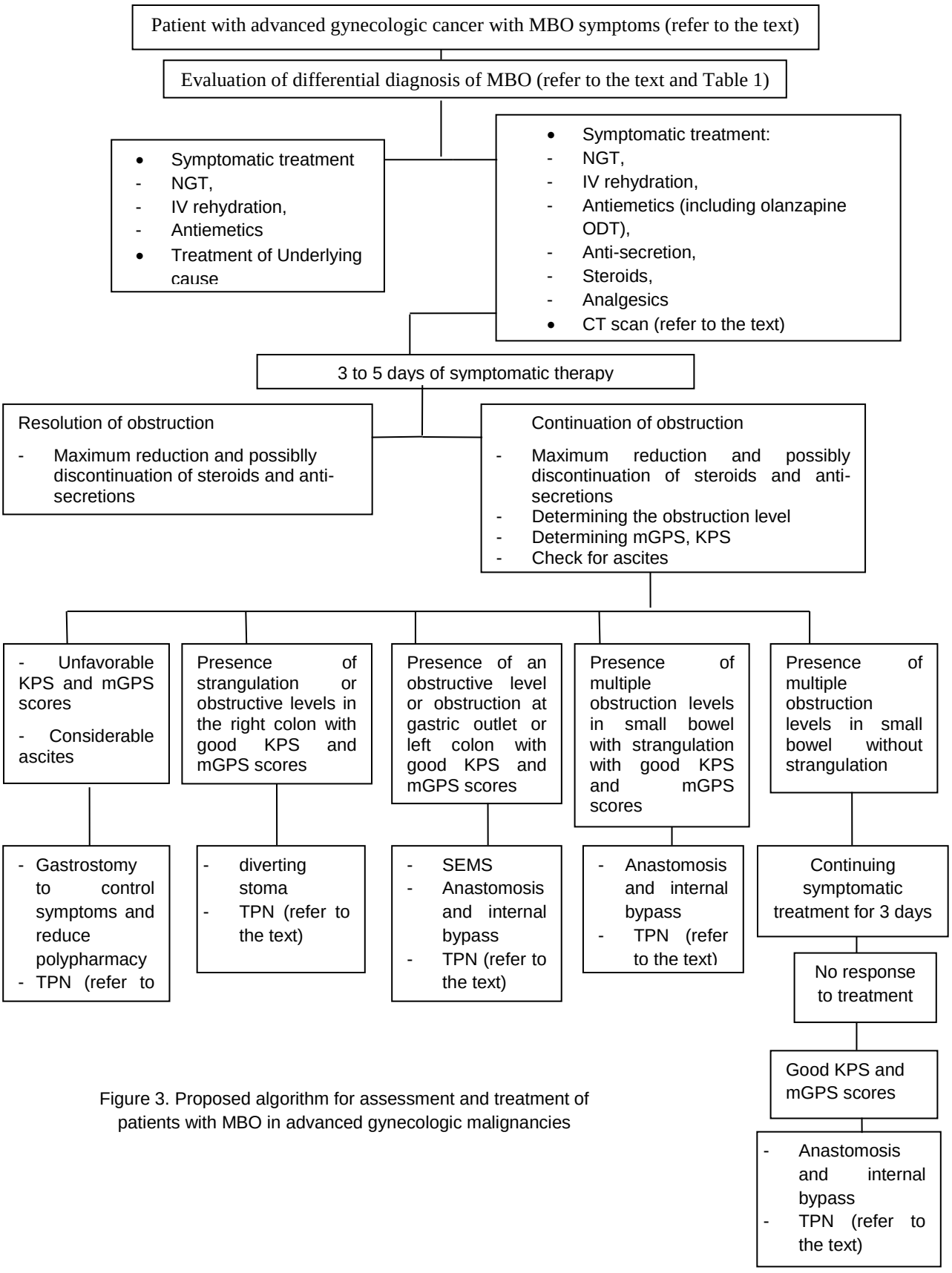

Figure 3. Proposed algorithm for assessment and treatment of patients with MBO in advanced gynecologic malignancies

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