Pathophysiology and Palliation of Inoperable Bowel Obstruction in Patients With Ovarian Cancer

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Abstract Malignant bowel obstruction is the cause of death in the majority of women who die of ovarian cancer. Some patients are considered acceptable surgical candidates for relief of the obstruction. For many patients, however, lack of such surgical options has spawned a broad range of medical interventions, including palliative strategies to target pain and nausea and vomiting. This review discusses the general approach to patients with ovarian cancer and inoperable malignant bowel obstruction, with an emphasis on such palliative strategies.

Every year in the United States, close to 14,000 women die of ovarian cancer [1]. Many suffer from—and ultimately die of—malignant bowel obstruction. In a series of interviews with 10 cancer patients, Gwilliam and Bailey described the emotional ramifications of refractory bowel obstruction [2]. They observed frustration from an inability to eat: "I just miss…some refreshing drinks…and I am desperate—when I look at [food]." One patient said, "You do feel that you're in a little place, just left on your own…like a hostage…as if someone was put in somewhere and told, 'Just have water, shut the door, and get on with it.'"

Once bowel obstruction has occurred, the median life expectancy of patients with ovarian cancer drops to approximately 3 months [3]. Although these patients' time may be short, their suffering remains great. Understanding and treating the signs and symptoms of malignant bowel obstruction in ovarian cancer patients who have no surgical options require urgent attention.

Pathophysiology

How does this emotionally and physically devastating entity arise? Tumor spread is driven by both direct and local extension, as well as by hematogenous and lymphatic dissemination. Although metastases can occur in any location, autopsy series in patients with ovarian cancer illustrate that there is a propensity for peritoneal spread [4–6]. Several patterns of spread converge around the bowel:

- extension of the tumor directly into the bowel wall;
- adjacent, impinging carcinomatosis; and
- adherence of the tumor to the external bowel surface, predisposing patients to kinking and obstruction of the lumen.

As described by Dvoretsky and others [4–6], direct extension of tumor into the bowel wall is a common scenario among patients with ovarian cancer. In fact, wall invasion is strongly associated with obstruction: When present, 71% of these patients also manifested obstruction, whereas obstruction occurred in only 30% of patients with serosal involvement. In this autopsy series, bowel obstruction was multifocal in 76% of the obstructed patients. When the obstruction was multifocal, it involved both the small and large bowels in 79% of cases, the small bowel alone in 13%, and the large bowel exclusively in 8%, although different surgical series describe somewhat different rates of involvement based on site. Of note, Dvoretsky and others did not distinguish and provide prevalence data on complete versus partial obstruction. Despite this limitation, however, the gross descriptions in this series suggest that bowel obstruction tends to occur when malignant ovarian cells invade the bowel muscle, usually at multiple levels within the intestines.

Dvoretsky and others also describe the microscopic appearance of bowel invasion [4–6]. Metastatic spread of ovarian cancer to the intestines

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assumes one of two patterns. The first consists of nests of ovarian cancer cells within the serosa and muscularis propria and is usually associated with lymphatic invasion. The second consists of ovarian cancer cells that efface the architecture of the muscularis propria and the submucosa. Although Dvoretsky describes these patterns of spread as two distinct entities, they may represent a continuum. There also may be considerable overlap in a given patient.

In addition to the gross and microscopic pathology of malignant bowel obstruction, another notable point is that pelvic malignancies—as opposed to abdominal malignancies—appear to predispose patients to bowel obstruction. For example, incidence rates from various series suggest that approximately twice as many patients with ovarian cancer suffer from malignant bowel obstruction than those with colon cancer [7]. The reason for this predisposition is unclear.

Commenting more specifically on benign obstructions, Bass and others offer an anatomic theory [8]: "The bowel is normally tethered more cephalad at the root of the mesentery and is therefore more mobile caudad in the pelvis. Adhesions [or malignancy] forming in the pelvis, where the intestine is normally more mobile, appear to be more likely to produce obstructing torsion." Although torsion is infrequently observed in bowel obstruction from ovarian cancer, few other explanations have been offered to explain this difference in incidence. Whether this lack of tethering provides tumor cells freer access to encircle pelvic bowel, or whether tumor biology might also provide an explanation, is unknown. Nonetheless, clinicians may perhaps need to be more alert for the possibility of bowel obstruction in patients with ovarian cancer than in those with abdominal malignancies.

Consequences of Obstruction

Once it occurs, bowel obstruction leads to proximal distention of the gastrointestinal (GI) tract and pain. GI secretions and futile reattempts at food intake lead to even greater distention and worsening pain. Ironically, the body initially appears to react with more secretions and peristalsis, propagating a vicious cycle. Although data are sparse on the cause of this cycle and symptoms vary depending on the site of the obstruction, it appears that hormonal mediators and specific cells within the proximal section of the obstructed bowel contribute to morbidity.

In one of the few clinical studies to examine the pathophysiology behind the morbidity from malignant bowel obstruction, Prommegger and others evaluated tissue levels of substance P and vasoactive intestinal peptide (VIP) in five women with malignant obstruction of the colon [9]. The site of these patients' primary malignancies was not specified. These two hormones were the focus because substance P is a neurotransmitter that promotes gut motility, and VIP is a neurotransmitter with water-electrolyte secretory effects, as well as restraining effects on gut motility. Both prestenotic and poststenotic bowel extracts were examined for these two neuropeptides by means of radioimmunoassay of tissue homogenates and immunohistochemistry of fixed tissue blocks. Unexpectedly, compared with prestenotic concentrations of substance P and VIP, poststenotic concentrations in tissue extracts were significantly higher. Immunohistochemistry staining of tissue samples revealed denser staining of ganglion cells and fibers for both neuropeptides in the poststenotic bowel. This study did not include a control group of cancer patients with no obstruction to allow for better understanding of which portion of the bowel was more predisposed to abnormal pathophysiology. Despite this study limitation, however, malignant large bowel obstruction might be associated with alterations of neuropeptides across the obstruction at the tissue level, although how these alterations contribute to the morbidity of malignant bowel obstruction has not been elucidated.

To our knowledge, other than the clinical study previously described, few others have examined the mechanisms that account for amplified production of bowel secretions, distention, pain, and the overall morbidity associated with malignant bowel obstruction. Although the obstruction itself occurs as a result of physical effects of the tumor on the bowel, the pathophysiology behind the associated morbidity has been studied only minimally. Animal models might provide some insight, but to our knowledge, no animal model has included and specifically addressed bowel obstruction due to invasive tumor.

Methods used to simulate bowel obstruction have included bowel ligation, a model that is perhaps more indicative of an obstructive benign adhesion or incarcerated hernia than an invasive malignancy. Despite such limitations, these models may provide some insight into the pathophysiology of the morbidity associated with malignant bowel obstruction.

In one study, Basson and others [10] once again implicated VIP by means of a canine model, which manifested an obstruction that progressed from partial to complete over 5 days. Compared with the levels in control animals, VIP concentrations in the portal circulation jumped dramatically, with progression to greater obstruction. These data further implicate this hormone as a potential mediator of aberrant secretions and peristalsis and suggest that VIP contributes to pain and abdominal pressure in these patients.

DISTENTION

In a second study, utilizing a murine model with a similar technique to simulate obstruction, Chang et al [11] examined some of the morphologic changes that accompany bowel obstruction and their functional implications. These investigators examined the cells of Cajal, interstitial cells that affect gut motility and are found throughout the GI tract. They showed that these cells transiently lose their functionality while maintaining their viability in the setting of bowel obstruction. Approximately 2 weeks after the obstruction, the proximal bowel became distended, with a complete loss of electrical slow waves, usually generated by the cells of Cajal. With relief of obstruction, these cells became functional once again, and the slow waves returned. It remains unclear whether this loss of function of the cells of Cajal represents the primary cause of diminished gut motility or an epiphenomenon. Nonetheless, there remains a possibility that this loss of function of the cells contributes to the bowel distention in malignant bowel obstruction, as well as to abdominal distention and discomfort.

RISK OF INFECTION

Finally, several studies have examined the infectious morbidity associated with bowel obstruction. Bacterial translocation can occur with bowel obstruction and refers to the passage of bacteria or endotoxin across the bowel wall, with resulting risk for systemic infection [12, 13]. Although translocation is a real entity in patients with complete obstruction of the large bowel, it remains unclear how frequently it arises in patients with malignant bowel obstruction, especially when the obstruction is partial and when it occurs in an area other than the large bowel. Data from animal models suggest, however, that especially when the obstruction is complete, there is a risk for translocation and subsequent infection in the cancer setting.

Taken together, the foregoing animal studies suggest that hormonal mediators and alterations in bowel function contribute to the morbidity of ovarian cancer patients who suffer from malignant bowel obstruction.

Management

SURGERY

Although surgical options should always be considered, they are usually met with reservations by patients who manifest continued tumor growth with few remaining cancer treatment opportunities. (For patients who are, in fact, considered good candidates for surgery, the reader is referred to another source, where surgical approaches are reviewed in depth [14].) Why is the suggestion of surgery met with ambivalence? The answer to this question remains complicated and controversial. On the one hand, failure to operate on an otherwise previously healthy cancer patient with a non-malignant cause of obstruction or a focal malignant cause is tragic. Although not directly pertinent to ovarian cancer, an experience from one of the Mayo brothers is instructive [15]: "He [Dr. Mayo] had had occasion to perform a postmortem in a case where the certified cause of death was "cancer…," but in which he found the stricture to be benign and that gave him something of a jolt. The man had died of starvation due to a condition that surgery could have cured."

In surgical series, as many as 23% of patients with ovarian cancer are found to have a non-malignant cause of obstruction at the time of surgery (Table 1) [16–30]. Extensive surgical debulking, pelvic or abdominal irradiation, and intraperitoneal chemotherapy are some of the factors that predispose patients to non-cancerous causes of obstruction [31, 32].

On the other hand, two factors often carry weight in reaching the decision not to operate. First, availability of modern radiographic techniques, including computed tomography (CT) and bowel contrast studies [33–35], diminishes the likelihood of missing a readily treatable cause or being misled by "pseudo-obstruction," or Ogilvie's syndrome, a diagnosis that requires a non-surgical approach [36, 37]. Such radiographic techniques can also distinguish preoperatively the patient who has obstruction at one

Peer viewpoints on this article by Drs. William J. Hoskins and J. Cameron Muir appear on pages 334 and 336.

Table 1

Survival and Perioperative Death Rates in Surgical Series of Patients With Ovarian Cancer and Bowel Obstruction

STUDY	N	PATIENTS WITH NON-SURGICAL PALLIATION (%)	SURVIVAL (DAYS)	YEARS INCLUDED	PATIENTS WITH NON-MALIGNANT OBSTRUCTION (%)	PERIOPERATIVE DEATH RATE (%)
Larson, 1989[16]	19	0	102	1980–1987	5	16
Rubin, 1989[17]	54	20	174	1983–1985	0	16
Clarke-Pearson, 1987[18]	49	0	140	1972–1983	14	14
Paganelli, 1990[19]	20	0	780	1979–1987	0	6
Redman, 1988[20]	26	8	81	1976–1986	23	15
Zoetmulder, 1994[21]	30	NA	NA	1984–1991	17	10
Krebs, 1983[22]	98	12	88	1960–1980	NA	12
Piver, 1982[23]	60	18	75	1971–1980	NA	15
Tunca, 1981[24]	90	NA	212	1969–1977	9	14
Lund, 1989[25]	25	NA	68	NA	NA	32
Fernandes, 1988[26]	34	NA	210	1980–1986	NA	NA
Castaldo, 1981[27]	23	NA	NA	1968–1977	NA	13
Solomon, 1983[28]	21	14	243	1978–1982	14	5
Jong, 1995[29]	53	49	> 60	1982–1992	0	NA
Bais, 1995[30]	19	11	109	1981–1982	0	22

NA = not applicable

or two sites in the bowel and thereby identify that patient as a potentially reasonable surgical candidate.

Second, and more important, published surgical series in patients with advanced, refractory ovarian cancer clearly demonstrate that surgery for malignant bowel obstruction appears to detract from survival and quality of life for subgroups of patients (Table 1), even when proposed surgical remedies appear straightforward from a sheer technical standpoint. In these series, perioperative mortality ranges from 5% to 32%, and some patients never leave the hospital. In effect, operating on a patient with ovarian cancer and malignant bowel obstruction who has a projected life expectancy of less than 2 months raises concern for undue suffering toward the end of life [27].

Although survival data with and without surgery (Tables 1 and 2) suggest that surgery does not constitute the first-choice approach for all patients with malignant bowel obstruction from ovarian cancer [16, 20, 21, 25, 26, 38–42], several points should be made in reviewing these compilations of studies:

- First, many patients with malignant bowel obstruction require an initial period of conservative, non-surgical management. Many patients with malignant bowel obstruction from ovarian cancer have a partial bowel obstruction—a diagnosis that typically invokes a less urgent approach than does a complete obstruction. For example, Table 1 shows series of surgical patients, the overwhelming majority of whom were treated conservatively in the hospital for a few days and, in one instance, for close to 3 weeks. Indeed, some of the patients in these series were treated conservatively for a few days, discharged from the hospital, and then operated upon only after rehospitalization several days later.

Because many patients with ovarian cancer suffer from a partial obstruction, the decision is not whether surgery is the first choice or not. Rather, the decision is whether conservative management should eventually, after an unspecified period, culminate in surgery or not in patients who do not recover. Thus, most patients in Table 1 were not only treated surgically but also were treated for a variable period with preoperative, conservative management.

- Second, most of the surgical series cited in Table 1 are more than 10 years old. Advances in imaging and minimally invasive surgery suggest that perhaps surgical mortality has declined since those studies were conducted, whereas advances in palliative drug therapy, as described below, suggest that survival rates from medical therapy may have improved. Thus, conclusions based on these archival series may not be totally germane to ovar-

ian cancer patients who confront malignant bowel obstruction today.

• Finally, the negligible differences in survival between surgically and medically treated patients were not derived from randomized clinical trials but rather from retrospective series, which suffer from selection biases. In view of the clinical complexity of these patients and the dramatic, emotionally charged differences between surgical and medical approaches, it is unlikely that randomized, controlled trials will ever be conducted to determine which approach maximizes survival and quality of life. Sound clinical judgment in a multidisciplinary setting is—and will continue to be—the primary and pivotal thrust in decision-making; the retrospective series in Tables 1 and 2 will provide, at best, only general guidance.

PROGNOSTIC TOOLS

The challenge of deciding when to rely upon surgical, as opposed to medical, palliative options has prompted many investigators to develop prognostic tools to help with decision-making. Most series have defined a poor prognosis as a postoperative survival of less than 2 months, a definition championed by Castaldo and others [27]. Parameters that predict a poor prognosis are shown in Table 3. Krebs and Goplerud [22] went so far as to construct a scoring system with several of these parameters and utilized this scoring system as a predictive instrument.

Not all series, however, have been consistent in defining prognostic parameters and in confirming the validity of such instruments. In fact, most authorities in the surgical literature caution against exclusive reliance on any particular prognostic parameter or instrument, calling instead for evaluating patients on a case-by-case basis and for inviting the patient and family into the decision-making process.

In summary, many aspects of patient selection for surgical versus medical management of malignant bowel obstruction from ovarian cancer remain controversial. Acknowledging this controversy and yet providing guidance based on sound clinical judgment, Rubin offers the following insight in an editorial [43]: "It appears that there are no clear criteria for selecting patients likely to benefit from surgery. Most would agree that patients with extreme tumor burdens, such as bulky carcinomatosis or parenchymal liver metastases, should not be considered for surgery. Some would exclude patients with large amounts of ascites. Probably patients with distant metastases and those with impairment of other vital organs should not have surgery. Patients with multiple sites of intestinal obstruction and those with rapidly progressive disease are not good candidates for surgery. Patients with relatively limited tumor burdens, patients with a single site of intestinal obstruction, and those with a reasonable chance of responding to chemotherapy are better candidates for surgery.... As with most difficult medical decisions where management options are not clearly defined, the best course is usually to present the

Table 2

Strategies and Survival in Patients Receiving Non-Surgical Palliation for Bowel Obstruction due to Ovarian Cancer

STUDY	N	PALLIATIVE STRATEGY	SURVIVAL (DAYS)
Larson, 1989[16]	14	Not reported	92
Redman, 1988[20]	12	Not reported	30
Zoetmulder, 1994[21]	28	Not reported	NA
Hopkins, 1987[38]	6	Venting gastrostomy, intravenous fluids	NA
Tunca, 1981[39]	37	Not reported	64
Isbister, 1990[40]	14	Morphine, metoclopramide	45
Fernandes, 1988[26]	16	Not reported	30
Lund, 1989[25]	28	Not reported	112
Mangili, 1996[41]	13	Octreotide	27
Malone, 1986[42]	10	Gastrostomy for venting, opioids	> 35

NA = not applicable

Table 3

Reported Predictors of Poor Prognosis for Patients With Malignant Bowel Obstruction

Compromised nutritional status, including weight loss
Heavy tumor burden
Ascites
Extensive prior chemotherapy
Previous irradiation
Short interval between cancer diagnosis and obstruction
Abnormal albumin, blood urea nitrogen, or alkaline phosphatase levels
Short interval between chemotherapy and bowel obstruction
A free but prolonged passage through the gastrointestinal tract on contrast studies, which suggests extensive carcinomatosis or a "frozen" pelvis
Palpable abdominal tumor
Obstruction at multiple bowel levels on radiography
Advanced age

reasonable alternatives to the patient and her family as clearly and objectively as possible, and let the patient decide."

A CASE IN POINT

As a case in point, consider a 47-year-old woman who had been diagnosed with stage III epithelial ovarian cancer 4 years earlier. After a debulking procedure and adjuvant chemotherapy, the patient did well until 2 years ago, when she was diagnosed with recurrent disease. Although her cancer initially responded to chemotherapy, it became increasingly refractory to it. After 2 months of intermittent abdominal discomfort, occasional nausea and vomiting, erratic bowel habits, and progressive weight loss, the patient was admitted to the hospital with a worsening of all the foregoing signs and symptoms. A CT scan showed evidence of small bowel obstruction. In addition, this scan showed diffuse peritoneal and pelvic metastatic disease. She was admitted to the medical oncology service and met with her primary surgeon. He advised her that surgical palliative options were not really feasible and that the morbidity of any such procedure would be too high to justify attempting it.

It is in this setting that non-surgical palliative options must be carefully considered.

Antineoplastic Therapy

CHEMOTHERAPY

The patient previously presented would not be a candidate for chemotherapy as a means to treat her bowel obstruction, and few patients are. However, the fact that newly diagnosed ovarian cancer is a relatively chemotherapy-sensitive tumor has prompted several case reports on the use of chemotherapy in this setting. This approach should be considered only with caution because of side effects and possible life-threatening consequences. Publication bias has likely selected for successful reports. Indeed, the chemotherapy option is mentioned here more for purposes of providing a complete review of the literature than for purposes of providing clinical guidance.

In addition, presumably the same principles apply to patients with ovarian cancer and bowel obstruction as to those without bowel obstruction: Heavily pretreated patients and those with a short interval between prior antineoplastic therapy and progressive disease are less likely to respond and are therefore highly unfavorable candidates for such treatment. Finally, adding chemotherapy in this setting—in a group of patients who may be at higher risk for infections from an intra-abdominal source—may result in far greater infectious morbidity than that observed in other patients with ovarian cancer without bowel obstruction.

Nonetheless, at least two small series have reported success. Tunca [39] reported on seven patients with ovarian cancer. All had complete bowel obstruction and were deemed inoperable because of tumor encasement of the intestines. Combining a cisplatin-based chemotherapy regimen with hyperalimentation, Tunca observed that six of these patients responded to chemotherapy, recovered bowel function, and ultimately were discharged from the hospital.

In another series, Drakes [44] reported similar findings. This investigator described three patients with inoperable bowel obstruction that resulted from ovarian cancer. All three patients were treated with chemotherapy and parenteral nutrition, with subsequent resolution of symptoms. This series differed from the series from Tunca in that these three patients were chemotherapy naïve, thus raising the prospect of tumor response to a more favorable level. This point is an important one because most patients with ovarian cancer and inoperable bowel obstruction have already been heavily treated with chemotherapy and are therefore unlikely to respond to more of it, an observation that underscores the limited value of this chemotherapy-driven approach.

IRRADIATION

Ovarian cancer is not only a chemotherapy-sensitive but also a radiosensitive tumor, and irradiation options also have been reported. Again, this approach is mentioned more for purposes of providing a comprehensive assessment of the literature than for purposes of providing clinical guidance. As noted previously, publication bias is likely selecting for success. Because of the inherent challenge of safely radiating a focal symptomatic lesion that is surrounded by vulnerable, unobstructed bowel, this approach is rarely utilized in clinical practice. Nonetheless, a small series of reports, usually retrospective and embedded within larger series of patients who received irradiation for other palliative intentions, encompasses the published literature.

Corn et al [45] briefly allude to a series of pa-

tients with ovarian cancer, 13 of whom received irradiation for "rectal bleeding/bowel obstruction." Although it is unclear how much radiation this subgroup of patients received, the most frequently utilized dose consisted of 3,500 cGy in 14 fractions. Of these patients, 11 went on to attain palliation, and the investigators noted that within their entire cohort, "palliation until death was achievable in 90%."

In a second report, May et al [46] described 11 patients with ovarian cancer and malignant bowel obstruction. Planning and dosing of radiation were highly specialized for each patient, but the investigators reported that 7 patients manifested relief of symptoms lasting 1.5–8 months.

In a third report, Adelson and others [47] described two patients with ovarian cancer and bowel obstruction. These two patients were part of a larger series of patients, most of whom received whole pelvic irradiation of 10 Gy/fraction with administration of at most 3 fractions. Subsequent "coning down" of the field size and individualized dosing and fractions to a symptomatic region were also prescribed. Although these investigators did not specifically comment on the outcome of these two patients, the tumor response rate within the entire group was 54.5%.

Although these small series report relatively favorable outcomes among patients with ovarian cancer and bowel obstruction, they invite a great deal of caution in considering this approach in this setting.

Other Palliative Strategies

In 1985, in a landmark study, Baines and colleagues [3] did what had not been done before: They reported that patients with refractory malignant bowel obstruction could be managed successfully with medical therapy. Recruiting 40 patients from St. Christopher's Hospice in London, these investigators assessed symptom severity at baseline and then serially after initiating drugs and performing minor medical procedures. This cohort consisted of patients with a variety of malignancies, not just ovarian cancer.

Of note, two patients were eventually treated surgically. Otherwise, colic was treated with loperamide, scopolamine (Transderm Scop), atropine, and/or a celiac block procedure. Other abdominal pain was treated with narcotic analgesics. Vomiting was treated with prochlorperazine, haloperidol, and other antiemetics. Diarrhea was

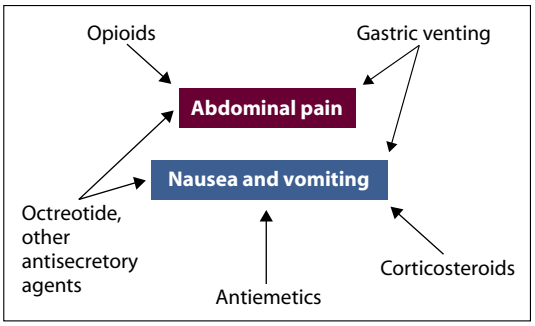

Figure 1 Palliation of Bowel Obstruction

A variety of interventions, including gastric venting, opioids, antisecretory agents, and antiemetics, can palliate the pain, nausea, and vomiting associated with bowel obstruction from ovarian cancer.

treated with loperamide. Constipation was treated with stool softeners. Medications were administered orally, sublingually, and subcutaneously with a syringe driver. The average life expectancy of this cohort, which included 14 patients with ovarian cancer, was 3.7 months. Upon reviewing the outcomes of these medical interventions and the celiac plexus blocks, the investigators concluded that "the distressing symptoms of intestinal obstruction due to far-advanced malignant disease can be controlled by drugs."

Since the publication of this seminal report, medical therapy and minor medical procedures have continued to be utilized in clinical practice and studied in clinical trials among patients who have no other options for malignant bowel obstruction. These approaches have targeted the symptoms previously cited. Ripamonti and colleagues [48] recently have proposed clinical practice recommendations for the medical management of malignant bowel obstruction. These recommendations discuss therapeutic options. The consensus appears to be, however, that decisions on medical therapy, as with surgical therapy, should be individualized for the specific patient.

With this approach in mind, the remaining portion of this review focuses on gastric venting and stent placement, as well as on pharmacologic options, such as narcotic analgesics, octreotide (Sandostatin), corticosteroids, and antiemetics (see Figure 1). Although sporadic anecdotal reports have discussed other approaches, such as local intraluminal lidocaine therapy [49], most of the literature has focused on the procedures, drugs, and drug classes noted above.

GASTRIC VENTING

Gastric venting, or decompression of fluids and gas proximal to the obstruction, plays an important palliative role in patients with ovarian cancer and bowel obstruction. Most patients with bowel obstruction acquire a nasogastric tube early in their hospital course for this purpose. However, the longer the nasogastric tube remains, the higher the risk for morbidity, including nose and throat pain, abscess formation, erosion of nasal cartilage, and social isolation [50, 51]. Therefore, these tubes should not remain for longer than a few days, and some consideration should be given to placement of a gastrostomy tube to take over the task of gastric venting when long-term need is anticipated.

Most studies on gastric venting have been retrospective and therefore have not reported on quality of life. However, despite this limitation, the data appear compelling enough to suggest that gastric venting constitutes a reasonable palliative option. For example, Tsahalina and colleagues [52] retrospectively studied 39 women with inoperable bowel obstruction that occurred as a result of various gynecologic malignancies, as well as from a few miscellaneous non-malignant causes. Seventy-two percent of these women had ovarian cancer. Gastrostomy tubes were surgically inserted in all patients. Thirty-six percent of patients developed immediate relief of nausea and vomiting. Although this percentage is notable, other studies have described that more than 80% of patients derive some control of nausea and vomiting over time.

Moreover, in the study by Tsahalina and colleagues [52], 21 patients died after a median duration of 28 days with the gastrostomy tube still in place, an observation that suggests that the tube continued to palliate to the very end. Five patients had the tube removed because they recovered and did well for several months or years later. This reported and presumed success of gastrostomy tubes underscores the importance of gastric venting as a palliative procedure for patients with ovarian cancer and malignant bowel obstruction.

Radiology-guided gastrostomy tube placement appears to provide the most successful procedural approach. In a meta-analysis, Wollman et al [53] showed that radiologic percutaneous gastrostomy tube placement was superior to surgical or endoscopic placement because of lower rates of morbidity and mortality. Thus, although venting requires an invasive procedure, direct radiologic visualization enhances safety, thereby making it a reasonable palliative option for patients with inoperable bowel obstruction from ovarian cancer. Along these same lines, complications from maintaining gastrostomy tubes over time include tube obstruction that requires replacement, digestion of surrounding skin as a result of leakage of digestive juices from around the tube, abscess formation, and pain when the tube is inadvertently tugged [54].

ASCITES

Although previous authors have expressed concerns about gastrostomy tube placement in patients with malignant ascites, Ryan and colleagues [55] recently reported successful placement of the tube under such circumstances. Acknowledging previous concerns for infection and hemorrhage, these investigators nonetheless reported minimal morbidity from radiology-guided tube placement in 45 consecutive patients with malignant bowel obstruction and ascites. Only 1 of the 45 patients was unable to have a tube placed. These investigators utilized repeat paracenteses prior to and following tube placement. In the absence of ascites, tube placement was accomplished with relative safety. Only three major complications occurred: Two patients developed peritonitis, and one patient developed postprocedural hemorrhage.

Although most clinicians continue to voice concerns about placement of a gastrostomy tube in the setting of malignant ascites, for certain patients, such an approach might be worth attempting after repeated paracenteses.

STENT PLACEMENT

Stent placement across the obstruction constitutes another medical procedure that may help patients with bowel obstruction who have limited surgical options. The majority of studies have been conducted in patients with GI malignancies, but a few case reports have focused on patients with ovarian cancer. The purpose of the stent is to open up a stenosed lumen, with the hope that patency will give rise to functionality. The procedure is usually conducted under endoscopic guidance. For several reasons, this option is available to only a handful of patients [56, 57].

First, some of these patients are in fact surgical candidates, and the stent is considered a short-term palliative option to allow patients extra time to prepare for surgery. Obviously, a large percentage of patients with ovarian cancer and

malignant bowel obstruction are not surgical candidates, and stent placement with such a goal in mind is unrealistic.

Second, multifocal bowel obstruction, a common scenario among patients with ovarian cancer, poses a dilemma: Stents cannot provide bowel patency throughout. One of the few indications for stent placement arises in the patient who has a refractory malignant bowel obstruction, who is not a surgical candidate because of other morbidity, but who has a focal, symptomatic obstruction. This patient might benefit from a stent.

NARCOTIC ANALGESICS

Several recent reviews have outlined the use of narcotic analgesics in cancer pain [58, 59], and these guidelines remain relevant for patients who suffer pain from malignant bowel obstruction. Long-acting medications are preferable, and medications such as a sustained-release fentanyl patch (Duragesic) might offer a greater advantage because of their non-oral method of administration. Because of the constipating effects of narcotics, the importance of administering stool softeners and fiber supplements to patients who maintain some bowel activity should not be underestimated.

To our knowledge, few studies have compared different narcotic analgesics in refractory malignant bowel obstruction. Earlier published reviews suggest the use of long-acting morphine preparations. In addition, a short report by Mercadante and colleagues [60] described two patients with bowel obstruction, one of whom had ovarian cancer. Pain was well managed with oral methadone, another reasonable drug to help with the distention and pain of malignant bowel obstruction.

OCTREOTIDE

Octreotide is a somatostatin analog with multiple indications, including use as an antineoplastic agent for certain tumors and for palliation of patients with severe secretory diarrhea. This hormone analog is thought to work in part by altering the hormonal milieu to the point where certain hormonal mediators of intestinal secretion, such as VIP, are blocked. Several studies suggest that it has efficacy in relieving distention, nausea, vomiting, and pain in patients with malignant bowel obstruction [41, 61–65]. At the same time, promising data have also suggested that the anticholinergic agent hyoscine butylbromide also provides palliation.

These data prompted two randomized trials to compare these two agents [62, 63]. The same group of investigators conducted both trials. A total of 17 patients participated in the first trial, and 18 in the second. Both trials provided compelling evidence that octreotide was the more effective agent in controlling GI symptoms, such as nausea and vomiting and bowel secretory output. In part, the differences in benefit between treatment arms may have arisen as a result of octreotide's rapid onset of action compared with that of hyoscine butylbromide; some octreotide-treated patients appeared to gain an advantage in symptom relief within 24 hours.

In a more recent trial, Mystakidou et al [61] tested octreotide in 68 patients with cancer and refractory, inoperable malignant bowel obstruction. Of note, this cohort consisted of patients with various malignancies, not specifically ovarian cancer. Patients were randomly assigned to one of the following treatment arms in a double-blind manner: octreotide (600–800 μg/day) plus chlorpromazine or hyoscine butylbromide (60–80 mg/day) plus chlorpromazine. Narcotic analgesics were also available to all patients in both arms.

Octreotide-treated patients reported greater improvement in nausea and vomiting, although pain control was comparable in both groups. This trial is notable because it tested combination therapy. The fact that octreotide-treated patients gained better control of nausea and vomiting while also on narcotic analgesics and chlorpromazine speaks to the role of octreotide as a component in combination palliative therapy.

Two final points on octreotide are worth mentioning. First, clinical trials have not yet investigated whether this hormone analog can act as an antidiarrheal agent in patients with malignant bowel obstruction. However, secretory diarrhea can be a distressing symptom for many patients with bowel obstruction, as pointed out by Baines and colleagues [3], despite the presence of obstruction and the use of constipating opioid analgesics. The efficacy of octreotide as an antidiarrheal agent in other settings suggests that it provides similar benefits for patients with malignant bowel obstruction.

Second, a report by Mercadante et al [66] described two patients, neither of whom had ovarian cancer but both of whom had partial bowel obstruction. These investigators suggested that octreotide did more for these patients than control the symp-

toms associated with bowel obstruction. By means of controlling bowel secretions and keeping bowel-wall edema to a minimum, this hormone analog prevented the obstruction from reaching a critical, complete blockage. Such anecdotal reports suggest that octreotide may produce more diverse palliative effects than previously thought.

CORTICOSTEROIDS

Corticosteroids represent another hormone class that is effective in the palliation of patients with refractory, inoperable malignant bowel obstruction. The rationale behind their use is two-fold. First, these agents carry well-described antiemetic effects, a characteristic that offers a major advantage for patients with bowel obstruction who suffer from significant nausea and vomiting. Second, this class of agents also has anti-inflammatory effects. Since some of the symptoms of malignant bowel obstruction center around progressive inflammation of the bowel wall in proximity to the obstruction, such anti-inflammatory properties might also provide a major therapeutic advantage for patients with malignant bowel obstruction.

Philip et al conducted one of the first trials of corticosteroids in patients with malignant bowel obstruction [67]. Their cohort of 13 patients, 11 of whom had ovarian cancer, received dexamethasone (8 mg daily either intravenously or subcutaneously). Nine patients reported improvement in pain, nausea, and vomiting, and such effects were sustained for more than 1 month.

These promising data led to placebo-controlled trials, which yielded less definitive results. Feuer et al [68] conducted a meta-analysis that included all published and unpublished trials. A total of 10 trials were included, although some of them also included retrospective data. These authors observed nothing more than a trend toward improvement in the symptoms of bowel obstruction with corticosteroids. In view of the finding that the side-effect profile of these agents was acceptable, an argument can be made for reserving corticosteroids for bowel obstruction patients who suffer recalcitrant nausea and vomiting, although the overall role of corticosteroid therapy in bowel obstruction remains controversial.

ANTIEMETICS

To our knowledge, no clinical trials have compared different antiemetics in the medical management of malignant bowel obstruction. Anecdotal reports have suggested that a variety of agents, all of which are familiar to the practicing oncologist, are available and likely to help. They include phenothiazines, 5-hydroxytryptamine$_3$-receptor antagonists, and, as noted previously, corticosteroids. Loprinzi and others [69] reviewed the use of these antiemetics in general oncology practice, and their remarks likely pertain to patients with malignant bowel obstruction as well.

Two points deserve special attention. First, several investigators have commented on the most appropriate use of metoclopramide, noting that it has favorable antiemetic properties but should be reserved only for patients with partial obstruction. Because this agent promotes gut motility, its use in patients with complete obstruction would likely exacerbate pain. Although no data substantiate this claim, it should likely be accepted at face value.

Second, the frequent use of morphine or morphine derivatives is often blamed for nausea. However, prior studies have shown that the nausea associated with morphine is dose-dependent and diminishes at higher doses [70]. Thus, when nausea and pain coincide, decreasing morphine doses may not be the best option. Upward titration of drug doses may be preferable.

TOTAL PARENTERAL NUTRITION

The medical literature contains a number of case reports and small series, each of which suggests some clinical benefit with the use of total parenteral nutrition in the setting of small bowel obstruction [71, 72]. In reviewing such reports, it is important to acknowledge that this success is in large part attributable to selection bias. Presumably, only a subset of viable patients with indolent tumors is receiving total parenteral nutrition. It is likely this selection bias—not exclusively the initiation of total parenteral nutrition—that accounts for the success described in these reports.

Several prior reviews and consensus recommendations have instructed against the routine use of total parenteral nutrition in the setting of malignant bowel obstruction [48, 73]. Increased morbidity, the propagation of a false sense of hope among patients and family members, and unjustified expense have all served as strong reasons against its routine initiation.

Conclusion

Malignant bowel obstruction represents an emotionally and pathophysiologically complex, end-of-life event for many patients with ovarian cancer. Surgical palliation remains the treatment of choice when this option is technically feasible and when the patient's life expectancy exceeds 2 months. Many patients do not meet these criteria, however. For these patients, other palliative strategies, including the administration of narcotic analgesics, antiemetics, antisecretory agents, and procedures to allow gastric venting, should be pursued.

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PEER VIEWPOINT

Commentary by William J. Hoskins, MD

The management of intestinal obstruction in the patient with advanced ovarian cancer is one of the most difficult clinical problems faced by the gynecologic oncologist. The patient has often lived with her disease for some time and may well have responded to a variety of chemotherapeutic regimens. She is often not otherwise seriously ill and may have been functioning quite well at home before the gradual onset of intestinal obstruction.

The authors have described the problem of intestinal obstruction in ovarian cancer and have provided an admirable review of the pathophysiology of the condition. They have clearly stated the clinical problem and the difficulty of its management. They have provided an excellent bibliography for the scholar of ovarian cancer and the management of this all too frequent complication.

In this commentary, I would like to make several points to clarify the discussion and to offer some personal perspectives drawn from a long career in the management of this disease. I hope these comments will add to the excellent review provided by Jatoi et al.

The first major decision to make in the management of intestinal obstruction in patients with ovarian cancer is to determine where in the disease process the obstruction has occurred. If the patient is newly diagnosed and is presenting with intestinal obstruction at the onset of the disease, the questions to ask are whether the patient can undergo primary surgery immediately and whether her physical condition is so compromised that a primary surgical approach is too dangerous. If the patient is in good condition, primary cytoreduction, with resection of bowel as necessary to relieve the obstruction, is the treatment of choice and has a high success rate. If the patient is too compromised for

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primary surgery, neoadjuvant chemotherapy followed by surgery after three or four courses of chemotherapy is the best option. If the patient's nutritional status is compromised, interval hyperalimentation is indicated. Abu-Rustum et al [1] found that hyperalimentation was efficacious in patients who presented with intestinal obstruction but had not received chemotherapy. If this course of action is chosen, the patient may benefit from a temporary percutaneous endoscopic gastrostomy (PEG).

The second major decision to make is whether a patient who has received prior therapy is refractory to chemotherapy. This decision is based on the number of prior therapies and the duration of the disease-free interval prior to presentation with intestinal obstruction. The fewer the chemotherapeutic regimens and the longer the disease-free interval, the more likely the patient will be responsive to salvage therapies. The major decision here will be whether to go immediately to surgery to relieve the obstruction and perform secondary cytoreduction or to support the patient while salvage chemotherapy is administered. The longer the disease-free interval, the more likely a primary surgical approach is indicated. In their review, the authors point out that 23% of patients had a non-malignant cause of their obstruction. It is in this setting of late recurrence where such a finding might be suspected, and if there is any doubt as to the cause of the obstruction, surgical exploration is indicated.

Finally, the third decision point occurs in the patient who has had multiple therapies and has persistent disease that is refractory to additional chemotherapy. In this situation, the questions are whether the patient will benefit from a surgical approach and should the patient be managed with a PEG and supportive care, as so well outlined by the authors in their discussion of palliative medications. There are several good articles on this topic in the literature, and they have been reviewed by Feuer et al [2]. The numbers are sobering. If the goal of the surgery is to enable the patient to go home with enough oral intake to sustain her, the operation has a success rate of about 60%. Unfortunately, the operative mortality (death before leaving the hospital) is in the neighborhood of 15%, and the serious morbidity is about 30%. Even in those 60% of patients who are considered to have had a successful operation, the life expectancy is about 4 months, and the cause of death is usually recurrent intestinal obstruction. Also, 30%–40% of those patients who can be discharged home will require some type of intestinal stoma.

I concur with the authors of this article that the best insight into the difficult decision process in this condition was stated by Steve Rubin [3] when he wrote, "As with most difficult medical decisions where management options are not clearly defined, the best course is usually to present the reasonable alternatives to the patient and her family as clearly and objectively as possible and let the patient decide."

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PEER VIEWPOINT

Commentary by J. Cameron Muir, MD

The article by Jatoi et al provides a broad overview of the many issues critical to the palliation of patients with malignant bowel obstruction (MBO). This review discusses the range of therapeutic considerations for patients with MBO, from surgical evaluation when the obstruction is operable to interventional techniques when the obstruction is inoperable, including venting gastrostomy and expandable metallic stents. Jatoi et al also cover the potential medical therapies, such as chemotherapy, radiation, total parenteral nutrition, opioids, antiemetics, antispasmodics, and anti-inflammatories.

There are a number of goals in the course of cancer therapy, from cure to a slowed progression of the disease ("disease-modifying therapy") to true palliation. True "palliation" can be defined as a therapy with the primary aim of symptom relief. It is important to evaluate the patient with advanced, inoperable MBO due to ovarian cancer from a truly palliative perspective. In this setting, three primary outcomes must be evaluated to help determine goals of care and treatment options. First, symptom control must be obtained from the therapy. Second, quality of life must be improved. Finally, each treatment option's likely benefits and side effects must be weighed, given a limited prognosis (as fraught with ambiguity as prognosis can be) [1].

TREATMENT CONSIDERATIONS IN MBO

In the past 10–15 years there has been a laudable effort by a few groups to evaluate the optimal management of patients with MBO.

- *Surgical:* Baines [2] has clearly stated that "surgical treatment, aimed at restoring the continuity of the bowel lumen, should be considered for every patient with cancer who develops intestinal obstruction." However, there are a surgical mortality risk and significant morbidity associated with major abdominal surgery in the setting of advanced ovarian cancer–each of which can have a profound negative impact on the palliative endpoint of quality of life. In fact, in an aggregation of nearly 10 studies on this subject, with over 650 patients in total, the operative mortality was 18.6%, and significant morbidity resulted from various complications, including infection/sepsis, wound dehiscence, enterocutaneous fistulae, abscess, anastomosis dehiscence, intestinal bleeding, and venous thrombosis/pulmonary embolism. Furthermore, in those patients who survived surgery, the median survival time was 5.3 months.
- *Interventional:* There has been a great deal of interest in the management of MBO with expandable metallic stents. These stents have been found to be highly effective in palliating MBO symptoms (> 90%) when there is a single site of intestinal obstruction that is readily approachable endoscopically (ie, in either the proximal small bowel or distal colon). The patient with ovarian cancer is less likely to benefit from this intervention, as she usually has multiple sites of obstruction from peritoneal and intestinal carcinomatosis across much of the intestine, which is not amenable to stent placement [3]. The median prognosis after stent placement for MBO has been shown to be 4–6 months—similar to the operative prognosis but with lower up-front risk [4].
- *Medical:* Medical management of MBO has been shown to be highly effective at palliation [5, 6]. As we have learned from the literature on pain, a "mechanistic approach" to MBO management is helpful in guiding therapy. Most patients with MBO have constant pain and nausea due to intestinal distention; thus, antiemetics and analgesics are indicated. For constant pain, morphine is the "gold standard" opioid analgesic. However, caution must be used in the setting of dehydration and/or renal insufficiency that may accompany MBO due to potential accumulation of toxic neuroexcitatory morphine metabolites. Hydromorphone (Dilaudid) is a semi-synthetic opioid agonist lacking toxic metabolites. In addition to the standard routes of administration, hydromorphone can be administered subcutaneously, making it ideal (and for some the drug of choice) for MBO [7].

For antiemesis, haloperidol, a potent dopamine antagonist (with fewer side effects than those of other dopamine antagonists, such as prochlorperazine and promethazine), is considered by many in palliative medicine as the proper antiemetic for MBO [8]. In the setting of partial obstruction, prokinetic agents such as metoclopramide may be beneficial; however, if there is total obstruction, these prokinetic agents should be discontinued.

Colicky pain represents a different pain mechanism, which must be treated differently from continuous pain to achieve adequate analgesia

without side effects. The colicky pain in MBO is thought to be due to luminal spasm in conjunction with peristalsis converging on the site of obstruction. Agents with anticholinergic activity decrease smooth muscle tone and reduce peristalsis. Additionally, activation of muscarinic receptors results in a beneficial decrease in intestinal fluid secretions [9]. Hyoscine and scopolamine are both available in the United States for this purpose. Opioids can help to palliate the symptom of colicky pain, but they do not address the underlying mechanism of the pain. Ventafridda et al [5] demonstrated good palliation (decreased pain, total control of vomiting in all but high proximal obstruction) from a combination of morphine, scopolamine, and haloperidol.

For inflammation, corticosteroids provide benefits by decreasing the inflammatory response and resultant edema, as well as relieving nausea through both central and peripheral antiemetic effects. In one study of patients with MBO, in the subset of patients who did not have a nasogastric tube, 68% had symptom relief from methylprednisolone [10].

Octreotide (Sandostatin) has been shown not only to palliate the symptoms of intestinal obstruction but also to directly slow and even reverse the associated downward spiral. In the setting of MBO, the clinical effects of octreotide are evident through inhibition of multiple secretagogues (thus reducing intestinal fluid secretion), as well as decreasing peristalsis. Riley and Fallon [11] reported a series of 24 patients with MBO in whom 14 patients had a 100% response (defined as no vomiting) to octreotide infusion and 4 patients had some improvement. Mercadante found that distress from symptoms of MBO was significantly reduced from the combination of morphine, haloperidol, and octreotide [12], and Mystakidou et al [13] found octreotide to be superior to hyoscine (when each was given with chlorpromazine) in relieving nausea and vomiting associated with MBO. In addition, the majority of patients with MBO who received medical management in these clinical trials survived 3–4 months.

Thus, both the literature and clinical palliative care practice demonstrate that we can achieve true palliation of MBO and similar survival with aggressive medical management, compared with surgical and interventional approaches. Randomized trials to compare these approaches, as well as comparative studies to optimize our therapy for aggressive medical management, are still needed. Yet much of the research into palliative medicine is hindered by the focus on curative and disease-modifying interventions. Furthermore, education about the optimal aggressive palliative management of MBO is needed so that clinicians may feel better equipped to manage this very challenging clinical scenario.

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Bowel obstruction caused by cancer is referred to as malignant bowel obstruction [1]. In everyday practice, however, it is often difficult to differentiate malignant from benign bowel obstruction, as cancer patients, especially those who have a history of abdominal surgery, can develop bowel obstruction from benign etiologies (eg, adhesions).Â Malignant bowel obstruction is common in patients with abdominal or pelvic cancers.Â Ripamonti C, Mercadante S. Pathophysiology and management of malignant bowel obstruction. In: Oxford Textbook of Palliative Medicine, 4th ed, Hanks GW et al. (Ed), Oxford University Press, Oxford 2010. p.850.