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REVIEW

Palliative care in ovarian carcinoma patients—a personalized approach of a team work: a review

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Abstract Most ovarian cancer patients are diagnosed in an advanced stage; and after the initial treatment experience disease recurrence, which eventually becomes palliative. Many questions arise in this setting including how to address patients in the palliative setting, how to discuss end-of-life issues, and how to manage symptoms. In this review, we discuss the timing and setting of end-of-life discussion in the context of end-stage ovarian cancer. We review the approach to relieving disease burden by improving and decreasing symptoms. These symptoms include recurrent ascites, bowel obstruction, pain, pulmonary effusion, and deep vein thrombosis.

Keywords Ovarian cancer · Palliative · Pain · Bowel obstruction · Ascites

Introduction

In 2016, estimated 21,580 women will be diagnosed with epithelial ovarian, fallopian tube, or primary peritoneal cancer in the United States; and approximately 14,300 of them will die from the disease [1]. The vast majority of patients with these cancers present with advanced malignancy, stage III or IV disease, with widespread tumor dissemination within the abdominal cavity, with or without tumor spread to the liver, lungs, or distant organs [1]. This is the deadliest of all gynecologic cancers. Though it accounts for only 3% of all cancer cases in women, ovarian cancer is the fifth leading cause of cancer-related death [2]. Although more than 70% of women with advanced disease respond to the initial chemotherapy, most become subject to recurrent disease within the peritoneal cavity and eventually become resistant to chemotherapy [3]. Once the disease recurs, it usually becomes incurable despite further chemotherapy and surgery, and patients eventually die of their disease.

Symptom management of patients with ovarian cancer is performed along a continuum: beginning at diagnosis, continuing through curative treatment and for some will continue when disease recurs.

For patients with end-stage ovarian cancer, palliative services, including actively setting achievable patient-centered goals for medical care and aggressive symptom management, should be routinely offered, alongside curative and disease-modifying treatments.

At the recurrence setting, ovarian cancer patients may have a variety of symptoms, including emotional and psychological issues, as well as physical symptoms including pain, bowel symptoms (chronic constipation, obstructions, and diarrhea), abdominal bloating due to recurrent ascites, dyspnea due to pleural effusion or pulmonic congestion, and deterioration in quality of life. In this review, we address issues related to end-stage ovarian cancer patients and review the options for treatment aimed to improve pain control and quality of life.

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Ovarian cancer end-stage disease

The primary intervention for patients with ovarian cancer is complete/optimal surgical cytoreduction. In the case of advanced disease, either debulking surgery followed by chemotherapy using paclitaxel plus carboplatin, with or without biologic agents, or neoadjuvant chemotherapy with interval debulking is performed [2]. In cases of recurrence, most women eventually become resistant to the first-line therapies and require treatment with second-, third-, and possibly fourth-line chemotherapy regimens. Advanced ovarian cancer runs a chronic course. By the end of the second to the fourth line of chemotherapy, a time comes when patients are left without any available cancer-specific treatment options despite the presence of a progressive disease. At this point, only palliative and supportive care can be offered.

The goal in end-of-life care is to provide maximum palliation of symptoms and maximal psychological support. End-of-life care should emphasize the shift from curing the disease to major efforts for palliation and control of symptoms that are caused by the disease. Achieving this dramatic change in attitude entails the incorporation of palliative care teams for patients and their caregiving network, family, and friends.

With the extension of survival for ovarian cancer, and the multiplicity of options for ongoing chemotherapy, the decision to stop chemotherapy or other interventions may emerge from any of the multiple conversations over time, which are aimed at balancing the potential side effects of new chemotherapies or other treatments against the expected benefit and impact on quality of life for the patient. In this setting of continuing conversation between the health care team and the patient, with or without her significant support individuals, a point is often recognized at which the ongoing therapy, aimed at disease control or cure, appears to incur more harm than benefit on quality of life. At this point, the transition to comfort based end-of-life care becomes more clear, although palliative care may well have been initiated for some symptoms prior to this point.

Patient perspectives of the meaning of high-quality end-of-life care emphasize the importance of interactions that most caregivers would identify as communication, accessibility, and emotional support. Surprisingly, compared to other terminal patients, oncology patients have been found to hold on more strongly to the desire to maintain hope [4]. Keeping this door open, while realistically knowing the true prognosis, and at the same time, pursing palliative care, is a real challenge. On one hand, ovarian cancer, which in the past caused a more rapid death, now follows a more chronic course. Alongside the progressive administration of palliative care treatments, this affords patients and families a longer time to pass through the phases of dying, and the opportunity to bring to closure key goals for the individual. Still, the exact time for the end-of-life discussion and for addressing wishes of patients regarding the end-of-life is a key matter during such period. A higher level of comfort in discussing end-of-life care topics such as do-not-resuscitate orders with family members of gynecological cancer patients was found to be significantly associated with decreased death anxiety [5].

In a retrospective study of women who died of ovarian cancer, Lopez-Acevedo et al. described the prevalence, timing, and setting of documented end-of-life discussions in patients with advanced ovarian cancer; 80% of the patients had documented end-of-life discussions. The median interval from the end-of-life discussion until death was 29 days. Forty-four percent of the patients had the discussions as outpatients and 56% as inpatients. An end-of-life discussion at least 30 days before death was associated with lesser: chemotherapy in the last 14 days of life, hospitalization time in the last 30 days ($p < 0.001$), ICU admission in the last 30 days ($p = 0.005$), and chance of dying in an acute care setting ($p = 0.01$) or being admitted to a hospice for $\leq$3 days ($p = 0.02$). They concluded that end-of-life care discussions occur too late in the disease process. Adherence to end-of-life quality measures can be achieved with earlier end-of-life care discussions [6]. Brown et al. surveyed 110 gynecological oncological patients regarding their knowledge of advance directives and their completion of advance directives. The majority of patients had heard about advance directives (75%). Only 49% had completed a living will or medical power of attorney. Young age, lower level of education, disease-related interference with daily activities, and a higher level of death anxiety were associated with decreased rates of completion of advance directives [7]. A few structured programs on decision-making and advanced care planning have recently been proposed for advanced cancer patients. Such structured programs have been reported to help patients realize the importance of prospective decision-making in guiding their treatment pathways prior to the end-of-life and to understand and discuss future healthcare decision-making [8].

Major problems for end-of-life of patients with ovarian cancer

Pain management

The spectrum of symptoms in advanced ovarian cancer results from various complications and the involvement of different systems, due to the natural spread of the disease. One of the aspects of pain control at the end-of-life is understanding the origin of the pain experienced by the patient (somatic visceral or neuropathic), the level of the pain, and its location. Multiple assessments are needed, because the type of pain and its level tend to shift with

disease progression. The strategy is to focus not only on the type and level of pain, but also on the level of consciousness, level of activity, and the level of control desired by the patient [9]. Most would recommend applying the World Health Organization (WHO) guidelines for relief of cancer pain. The analgesic ladder simplifies pain management strategies and promotes consensus about the progressive increase in analgesics according to cancer pain severity and analgesic response. The WHO analgesic ladder specifically emphasizes individualized assessment of pain, continuous analgesia associated with an adequate design of rescue doses, the oral route as preferable for analgesic administration, progressive increases in dose, and regular review of analgesia. The use of a 1–10 pain scale fixes patients' assessment of their pain on the tier and provides the basis for a management strategy [10]. More specifically, this three-tier pain ladder starts from low to increasing levels of pain and increasing strategies, from acetaminophen and nonsteroidal anti-inflammatory drugs to opioid analgesics for more severe pain. However, the guidelines are not adequately employed. Carlson et al. reviewed studies that evaluated the effectiveness of the WHO guidelines. They found that 20–100% of patients with cancer pain receive pain relief according to the use of the WHO guidelines—while considering their status of treatment or end-of-life care. Part of the explanation for the lack of adoption of the WHO guidelines is that they may be considered outdated by many, because they are not specific to the pharmacological and interventional options used in contemporary pain management practices [11].

Some ovarian cancer patients experience severe nociceptive pain which usually require narcotic medications. The goal is adequate base pain coverage with every 8–12 h dosing, and adequate breakthrough pain coverage with immediate-release agents [12]. Short-acting opioids, with morphine as the most common, are widely used for the treatment of severe pain in patients with cancer because of their safety, multiple routes of administration, ease of titration, reliability, and effectiveness for all types of pain [13]. There is no evidence to support superior efficacy or tolerability of any agent over another [14]. A recent Cochrane review confirmed the long standing efficacy of oral morphine in cancer pain [15]. The combination with acetaminophen is commonly selected. For moderate pain (step 2 in the WHO analgesic ladder), a mixed mechanism drug such as Tramadol or Tapentadol can be used.

Following selection of a starting opioid dose, adjustment is almost always required. Continuous or frequently recurrent pain is most effectively managed with a fixed schedule, "around-the-clock", opioid regimen. The absolute dose of the opioid is inconsequential, as long as the balance between analgesia and side effects remains acceptable for the patient. However, the need to titrate to relatively high doses should be accompanied by careful reassessment of the pain and drug effects. For patients with severe pain, rapid titration of the opioid dose may be achieved using intravenous dosing at short intervals. If a patient is given a short-acting opioid and needs several doses per day, a switch to a long-acting modified-release formulation can improve convenience and adherence. A fentanyl patch is used to avoid intravenous administration, for patients who require continues baseline coverage, yet unreliable for taking doses of pain medication. Data from clinical trials about the potential for a relatively reduced risk of constipation from transdermal fentanyl are conflicting [16–18]. Nonetheless, three meta-analyses have found a significant advantage for transdermal fentanyl over sustained release oral morphine in terms of this side effect [19–21]. Fentanyl may be preferred over morphine in patients with renal insufficiency due to lack of active metabolites. The downside of the patch is the long time it takes to reach peak levels [22]. Methadone, which has been utilized as a second-line option, can be particularly helpful when morphine is not adequate, such as for patients with neuropathic resistant pain [23]. Breakthrough pain is a transitory severe acute pain that occurs on a background of chronic pain that is adequately controlled by an opioid regimen. Given its high prevalence in patients with cancer pain, and its negative clinical consequences, a treatment approach known as "rescue" dosing has become widely accepted. Typically, a short-acting supplemental opioid is offered on an as needed basis for breakthrough pain in conjunction with a fixed scheduled long-acting drug. Depending on the dose required and other factors, the rescue drug may be a single entity oral formulation, such as immediate-release morphine, oxycodone, hydromorphone, or oxymorphone [24]. A typical dose chosen for rescue is 5–15% of the basal daily requirement of opioid. Breakthrough pain may also be targeted with one of the newer rapid onset, transmucosal fentanyl formulations, which are specifically indicated for cancer-related breakthrough pain [25].

A pump with a patient-controlled analgesia (PCA) option can be used to administer continuous infusion by either the intravenous (IV) or subcutaneous (SC) route, and thereby facilitate the option of "rescue doses". PCA devices are programmed for the size of the dose, the minimum time between doses (lockout interval), and the cumulative dose allowed in one or 4 h. The use of IV forms of opioids with PCA pumps can be accomplished in the home setting if needed [26]. SC infusion of opioids can also be used, with near equivalent efficacy in the home setting, as well [27].

Many ovarian cancer patients are in the severe category of pain at the end of life; this might necessitate combining two opioids especially during escalation, to control pain [9]. When doing so, the anticipated side effects might shorten the time to death, which are well-recognized consequences of ensuring maximal palliative care. A common approach to the management of poorly responsive pain is

known as "opioid rotation", which is defined as a switch from one opioid to another in an effort to provide better outcomes. The rationale for this strategy is based on pharmacologic and clinical observations that suggest that a change in drug is more likely than not to improve the balance between pain relief and side effects [28].

Other kinds of ovarian cancer-related pain, such as neuropathies, may be treated with anticonvulsants, most commonly used is gabapentin. Tricyclic anti-depressants may be helpful, as they also treat underlying depression [29]. Corticosteroids can provide additional pain relief, mainly for pain related to inflammatory nerve ends. In extreme cases, regional nerve blocking or epidural analgesia is needed. The last few hours of life can be marked by either increased or decreased pain, and an appropriate strategy should be established as part of a pain control program. Rolnick et al. reviewed the analgesic drug therapies received in the last 6 months of life by 421 women who died of ovarian cancer [30]. The use of medications typically prescribed for moderate-to-severe pain ("high intensity" drugs) increased as women approached death. At 5–6 months before death, 55% of women were either on no pain medication or on medication generally used for mild pain; only 9% were using the highest intensity regimen. The percentage on the highest intensity regimen (drugs generally used for severe pain) increased to 22% at 3–4 months before death and 54% at 1–2 months. Older women (70 or older) were less likely to be prescribed the highest intensity medication than those under age 70 (44% vs. 70%, $p < 0.001$). This finding that only 54% of women with pain were given high intensity medication near death indicates room for improvement in the care of ovarian cancer patients at the end of life [30].

Recurrent ascites

Malignant ascites is a manifestation of end-stage events in a variety of cancers; they are most common in ovarian cancer and are associated with a poor prognosis.

In a study of 209 patients with malignant ascites, Ayantunde et al. found ovarian cancer to be the most common cancer to cause ascites. More than one-third of the women with ovarian cancer developed ascites during the course of their disease; no association was found with any specific histological subtype [31]. Overall, 58% of cancer patients had symptoms related to the ascites; 54% presented with ascites at the initial diagnosis of their cancer. Paracentesis was given to 112, diuretics to 70, and chemotherapy to 103 patients. The median survival following diagnosis of recurrent disease with ascites was 5.7 months. Ovarian cancer favored longer survival compared to other cancers, while low serum albumin, low serum protein, and liver metastases adversely affected survival [31]. Ascites at presentation was found to be an independent prognostic factor for time to relapse [31]. Peritoneal dissemination is associated with a rapid production of ascites, which, in turn, leads to severe abdominal distention, pressure on lymphatics, and obstructed efflux [32]. This causes abdominal pain, nausea, fatigue, constipation, dyspnea, umbilical hernia, and edema in the lower extremities. Once disease becomes chemoresistant, intractable ascites can be a major problem and the majority of patients are subjected to frequent paracentesis to temporarily alleviate symptoms.

The management of ascites is summarized in Table 1. In an evaluation of the use of palliative services in gynecologic oncology patients during the last 6 months of life, the most common procedure performed was paracentesis, accounting for 22.6% of procedures [33]. Large volumes of fluid

Table 1 Management of ovarian cancer-related ascites

Treatment		Advantages/benefits	Risks
Invasive procedures	Paracentesis	Easy to do Large volumes of fluid are drained—most cases lead to improvement in symptoms	Continuous leakage Bowel perforation Hospital stay Formation of loculations
	Peritoneovenous shunts	Palliating symptoms in 70% of patients	Major complication rate of 6% including pulmonary edema, pulmonary embolus, shunt blockage, and infection
	Catheter drainage	Easy to self-drain No need for repeated paracentesis	Infection rate of 11%
Pharmacological	Diuretics	30% of patients will have reduction of ascites	Dehydration Electrolyte disturbances Effect is quiet limited
Targeted therapies	VEGF	May prolong time to the next paracentesis	None has been effective in prolonging treatment
	Catumaxomab	Proven to be effective in reducing ascetic flow	Limited effect
	Aflibercept	Diminished clinical symptoms	None has been shown to increase survival
	TNF alpha		

can be removed. However, this must be balanced with colloid infusions and risks subsequent to further decreases of intravascular albumin and protein concentrations, which may worsen ascites and associated symptoms. Other complications of paracentesis include infection, continuous leakage from the drainage site, loculation formation, and, occasionally, bowel perforation. Paracentesis often requires hospital stay and may have to be frequently repeated. To reduce the need for multiple procedures, and with it admissions, peritoneovenous shunts may be used to direct ascitic fluid through a one-way valve into the vena cava. This may palliate symptoms in up to 70% of patients [34, 35]. However, major complications occur in 6% of patients including pulmonary edema, pulmonary embolus, shunts blockage, and infection.

Catheter drainage is an alternative form of management. Catheters, made from flexible silicone with a polyester cuff, are tunneled subcutaneously towards the peritoneal cavity, and are easy to self-drain, thus enhancing patient autonomy while negating the need for repeated paracentesis. A systematic literature review assessed indwelling intraperitoneal catheters as a safe and effective palliative strategy for the management of refractory malignant ascites, despite an 11% infection rate [36]. Moreover, a reported 100% technical success rate for the insertion of a drain, and an associated low complication rate, supports their use as a first-line approach in patients with refractory malignant ascites [37]. However, a Cochrane review aimed to assess the management of catheter drainage for malignant ascites in gynecological cancer found no relevant studies on the topic, and was unable to make recommendations regarding the management of drains for malignant ascites in women with gynecological cancer [38].

Diuretics may reduce ascites in more than 30% of patients during some weeks. Administration of the adjusted dose of a combination of potassium sparing diuretics (spironolactone) and loop diuretics is recommended. Since some patients treated with diuretics may present with dehydration or electrolyte disturbances, the use of such drugs in the management of ascites is limited [39].

Targeted therapies have also been proposed as novel therapeutic options for ovarian cancer-related ascites. A few agents have demonstrated effectiveness in reducing the volume of ascites, yet none has been effective for prolonged and meaningful treatment.

The tri-functional anti-epithelial cell adhesion molecule and anti-cluster of differentiation three monoclonal antibody catumaxomab have been assessed in the therapy of malignant ascites, and been shown to significantly reduce the ascitic flow rate when applied into the peritoneal cavity [40]. The anti-angiogenic targeted agent bevacizumab has also demonstrated benefit in the symptomatic treatment of malignant ascites, significantly prolonging the time until the next paracentesis [41]. Vascular endothelial growth factor (VEGF) Trap, or aflibercept, is a fusion protein that inhibits VEGF-receptor binding. Aflibercept has proven to be effective in the reduction of ascites, diminishing clinical symptoms of ascites and prolonging the time to the next paracentesis [42]. Intraperitoneal human recombinant tumor necrosis factor (TNF) alpha was used for the therapy of malignant ascites. In a study performed by Hirte et al., the efficacy of paracentesis plus TNF alpha, versus paracentesis alone, was not found to be effective in preventing the recurrence of ascites in patients with recurrent ovarian cancer [43]. Other agents were evaluated including interferons and metalloprotease inhibitors; all had limited efficacy in reducing the volume of ascites in cancer patients [44–46].

Bowel obstruction

Bowel obstruction is a common feature of advanced or recurrent ovarian cancer. Unlike primary colorectal cancers, in which the cause of obstruction is mostly due to intraluminal compression of the large bowel [47], ovarian cancers more commonly cause small bowel rather than large bowel obstruction by extrinsic compression of tumor mass and enlarged lymph nodes. Other causes of obstruction include tumor infiltration of the mesentery, bowel muscle, or nerves. Edema of the bowel wall, fecal impaction, and constipating drugs such as opioids can contribute to the development and severity of bowel obstruction. Women with obstructions are usually suitable for surgical management. More than 20% of ovarian cancer patients experience an episode of bowel obstruction along the course of the disease [48]. In an assessment of gynecological women towards the end of life, the most common cause for admissions was gastrointestinal issues, and the most common surgical major procedure performed during the last 6 months of life was intestinal surgery for obstruction [33].

Bowel obstruction may cause severe symptoms, including pain, nausea, vomiting, and, of course, constipation. Since the majority of women are already at risk for constipation due to medications (opioids, as well as serotonin antagonist antiemetics), and low motility of the bowel, initiation of a bowel program is a component of palliative care. Diet should include low fiber and increased amounts of fluids. Both peristaltic stimulants and fecal softeners may be required for an adequate bowel program with rectal laxatives added as needed [49]. Usually, the use of propulsive agents such as anthranoid laxatives or polyphenolic compounds rather than stool softeners provides better management of constipation related to drugs such as opiates [50]. A randomized trial comparing octreotide (which inhibits growth hormone, glucagon, and insulin) and scopolamine butylbromide in symptom control of 97 patients with inoperable bowel obstruction due to advanced ovarian cancer found octreotide

to be more effective than scopolamine butylbromide in controlling gastrointestinal symptoms of bowel obstruction [51]. In addition, there are pharmacological options to consider, with haloperidol being an additional choice for antiemetics in the setting of bowel obstruction [52]. Steroids have also been used to relieve bowel obstruction, yet their effect has been controversial. They may reduce the level of obstruction indirectly by reducing tumor edema [53]. However, a Cochrane systematic review of the use of corticosteroids in bowel obstruction related to gynecological or gastrointestinal malignancies showed no evidence that corticosteroids were effective in treating bowel obstruction [54].

Palliative surgery is the only alternative to restore the continuity of the bowel lumen. Four surgical options should be considered: placement of colorectal stents, stoma formation, bypassing the obstruction and resection of the bowel. Many women with advanced stage disease are not eligible for surgery because of technical difficulties that preclude restoring intestinal transit or due to poor general status. Poor general health or nutritional status, diffuse peritoneal carcinomatosis, palpable masses, advanced age, ascites, prior radiation, and multiple obstructed sites carry higher morbidity and mortality rates. Thus, careful selection of patients increases survival and extends the symptom relief period [55]. Furnes et al. conducted a retrospective study to identify and improve the outcome of bowel obstruction in women with a history of a gynecologic cancer. They found that ovarian cancer, residual tumor during initial surgery, and chemotherapy were all associated with malignant bowel obstruction. Surgery solved 84% of malignant bowel obstructions, but median survival was brief (2.5 months) when compared to benign bowel obstruction. They concluded that women with malignant bowel obstruction should be carefully identified and treated to improve quality of life rather than subjected to emergency surgical procedures [56]. Another recent retrospective evaluation of patients with recurrent ovarian cancer reported shorter hospitalization, more effective pain reduction, a higher number of chemotherapy lines, and less frequent re-obstruction among those who received surgical rather than medical treatment. However, no differences in post-palliation episodes of vomiting, and in the type of diet were recorded. Median survival after palliation was longer among those who received surgery [57]. In an analysis of 8607 women with stages IC-IV ovarian cancer, above 65 years of age, from the surveillance, epidemiology, and end results (SEER)-medicare database, surgical management of obstruction was associated with lower 30-day mortality (13.4% in women managed surgically vs. 20.2% in women managed nonsurgically), but equivalent survival after 30 days [58]. Others confirmed that although ovarian cancer is incurable, palliative surgery may extend survival and improve the quality of life of women with disease complications, following improvement in the nutritional state after treatment for intestinal obstruction (enable oral nutrition) [59]. A Cochrane review failed to identify subgroups of women who are likely to benefit from one treatment or the other due to the scarcity and low quality of data. However, weak evidence supported surgical management to prolong survival [60].

Table 2 Management of ovarian cancer-related bowel obstruction

Treatment		Advantages/benefits/r isks
Early management	Low fiber and increased fluid amounts	
Initial pharmacological treatment	Peristaltic stimulants: Anthranoid laxatives or Polyphenolic compounds	Provides better management of constipation related to drugs
	Fecal softeners	
	Rectal laxatives	
Advanced pharmacological options	Haloperidol	Diminished clinical symptoms
	Steroids	May reduce obstruction related to tumor edema
Surgical management	Placement of colorectal stents	Careful patients selection is important with exclusion of patients with the following: Poor general health or nutritional status Diffuse peritoneal carcinomatosis Palpable masses Advanced age Ascites Prior radiation Multiple obstructed sites
	Stoma formation	
	Bypassing the obstruction	
	Resection of obstructed loop	
Options for symptoms management	Nasogastric tube	Provides quick relief, however, uncomfortable, and may be ineffective for longer period
	Gastrotomy	Relieves gas pressure Risks: needs surgical intervention, complications (leakage, peristomal infection, obstruction, PEG tube migration, catheter malfunction, hemorrhage, and peritonitis)

Careful pre-operation evaluation should include imaging studies (CT, gastrografin enemas) that identify multiple sites of obstruction. Failure to identify such sites increases the risk for failure of surgery and increased pain, morbidity, and mortality.

Symptom management is usually needed during the treatment of bowel obstruction. Nasogastric tubes provide quick relief, but are uncomfortable, and may be ineffective in longer term management of symptoms. Gastrostomy relieves gas pressure that is produced in the presence of intestinal obstruction, by placing a tube in the intestinal tract, usually via the nasal passages and the stomach (nasogastric route), and provides nutrition when the obstruction is resolved [61]. This may be an alternative for nasogastric tubes, without the disadvantages of the latter; however, it requires surgical intervention and sedation. Gastrostomy relieves symptoms within days in more than 90% of patients, and might enable oral nutrition in some. The complications rate is 20% and includes leakage, peristomal infection, obstruction, PEG tube migration, catheter malfunction, hemorrhage, and peritonitis [61]. Others reported limited advantages and high complication rates [62]. Distal rectal obstruction can sometimes be relieved through the use of stent placement [47]. The management of ovarian cancer-related bowel obstruction is summerized in Table 2.

Pulmonary symptoms

Dyspnea is a common symptom in patients with end-stage ovarian cancer, and may result from pleural effusion, severe ascites, pulmonary metastasis, or pulmonary embolus. When cause related treatment is not possible, the palliative management of dyspnea is based on opioids, steroids, oxygen, and measures to promote relaxation.

Opioid treatment for dyspnea serves to reduce the sensation of breathlessness, reduce anxiety, reduce oxygen consumption, and increase tolerance to effort. Few studies have confirmed their efficacy in reducing dyspnea and the sensation of breathlessness in cancer patients [63].

Pleural effusion is a very common complication of advanced ovarian cancer, and was reported in 12% of women with ovarian cancer, and treated in less than half of them [64]. Steroids and diuretics may improve dyspnea associated with pleural effusion for short periods of time. Thoracentesis gives immediate relief; however, re-accumulation is common. A repeated procedure might be an option; however, the risk for pneumothorax (4%) and the expected discomfort should be taken into account. When life expectancy is more than a few weeks, and pleural effusion is the main reason for symptoms, other options need to be considered. A tunneled closed system, pleural catheter, can provide considerable relief without requiring major surgery and is successful in 80% of cases [65]. Another option for these patients is chemical pleurodesis, with chemical agents, including talc (most commonly used) or bleomycin, tetracycline, or doxorubicin, directly applied with video-assisted thoracoscopic surgery (VAST) [66]. In the setting of palliative care, the procedure is safe and effective in reducing symptoms of dyspnea, with an estimated 70–90% of cases reaching dyspnea control [67]. Success is more limited in the setting of repeated prior thoracentesis; scaring makes the procedure less effective. Some patients present with a fever and moderate-to-severe pain around the time of installation. Other complications include arrhythmias, pneumonitis, and empyema. The procedure is done in the hospital and, as mentioned above, is not free of complications. Therefore, benefits and risks should be carefully weighted towards the end of life. Pleurodesis should be offered only to those for whom it might alleviate symptoms of dyspnea. In a retrospective study of patients with gynecologic malignancies who underwent planned video-assisted thoracoscopic surgery (VATS)/pleurodesis, 69% had ovarian cancer. In 17%, the procedure was performed in the palliative setting. The majority (88%) of patients underwent talc pleurodesis. Seven patients (17%) were readmitted within 30 days; 6 were for complications unrelated to their VATS. Median time to death after VATS was 104 days [68].

Management of pulmonary metastases in the end-of-life setting, even if solitary, should be focused on symptom relief.

Thrombosis prophylaxis

The incidence of venous thromboembolism (VTE) is higher in ovarian than other cancers. A retrospective review reported an almost 10% incidence of VTE among ovarian cancer patients; of them, half had pulmonary embolus. One-third of the patients developed VTE during chemotherapy treatment [69]. In the recurrent setting, the risk for VTE increases and women appear to have the highest risk for developing VTE when ascites exists and during the first 2 months following chemotherapy initiation. In contrast to primary ovarian cancer, VTE does not seem to affect overall survival in relapsed malignant ovarian disease [70]. Risk factors of palliative care cancer patients to develop VTE include immobilizations, recent surgery, and previous VTE [71]. In the end of life for cancer patients, when curative therapy is no longer the intent of treatment, continued anticoagulation for VTE for palliative purposes continues to remain a controversial topic; no large randomized trials have been conducted to guide clinicians in this setting. Soto-Cárdenas et al. reported that in a population of palliative care cancer patients with VTE, all the patients received anticoagulation treatment after diagnosis. The complications observed were VTE recurrences (8.5%), VTE-related deaths (15.5%),

and bleeding events (11.3%) [71]. Even in the event of confirmed diagnosis of VTE, physicians of various disciplines disagree regarding the appropriateness and ethical justification of anticoagulation treatment for patients who were symptomatic for VTE but at the end of life existed on a shifting continuum. A lack of immediate benefit coupled with the discomfort of a daily injection influenced some not to prescribe anticoagulation therapy. The point at which anticoagulation injections should be stopped in patients at the end of life is also inconclusive [72]. In a review on anticoagulation treatment in patients with advanced cancer, Noble et al. found that low-molecular-weight heparin (LMWH) is more effective than warfarin in the secondary prophylaxis of VTE. The duration of treatment is controversial, and since the prothrombotic tendency is to be stay, indefinite treatment is generally recommended. For women with contraindications to anticoagulation, inferior vena cava filters can be considered, but their use should be determined on an individual basis, including decisions to initiate, continue, and stop anticoagulation [73].

Conclusions/summary

Most ovarian cancer patients eventually die of their disease. Most encounter pain, recurrent ascites, pleural effusion, dyspnea, and sometimes bowel obstruction and VTE. In the passage from curative to palliative care, the primary tenets of palliative care at the end of life should be upheld: symptom management, establishing goals of care in line with patients' values and preferences, and consistent and sustained communication between the patient and all those involved in her care. In the palliative setting, we should state patient-centered achievable goals for medical care and aggressive symptom management. The healthcare team should be familiar with the options for treatment and for alleviation of symptoms. A multidimensional evaluation and multidisciplinary intervention is frequently needed to assist patients with advanced stage ovarian cancer.

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Compliance with ethical standards

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