END OF LIFE CARE AND ASSISTED DYING

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In women presenting tumor relapse or with metastatic disease at diagnosis, definitive remission is no longer achievable, despite improvement in diagnosis, surgery and medical treatment.

Therefore, the early integration of palliative care in managing women with recurrent disease is highly recommended because of the early appearance of symptoms, involvement of abdominal/ pelvic organs and tissues, and decreased quality of life.

Healthcare professionals should be able to recognise the different stages of the clinical course of the disease and discuss with patients, families and caregivers essential issues concerning the late stage disease (Figure 1).

Shared decision-making on the discontinuation of active treatment has primary importance. It should be done considering clinical and tumor features, previous patient history, and the patient's knowledge of the diagnosis and wishes. Clinicians should not administer chemotherapy in the last weeks of life. One study in patients with gynae-cological cancers showed that the use of palliative chemotherapy had increased in recent years, with an increase in hospital admissions and invasive procedures in the last three months of life, with at least one palliative chemotherapy session administered within the last 30 days of life. The author concluded that a greater awareness of the value of chemotherapy discontinuation at the end of life is highly desirable (1).

The role of palliative care goes beyond symptom management. Identifying patients for whom home care is an option and addressing patients' and families' needs (social issues, psychological support, advance directives discussions, spiritual beliefs, practices around death) represent some of the particular issues typically carried out by the multidisciplinary palliative care team.

End of Life Care

End-of-life care is the sum of medical, social, psychological and spiritual support to patients facing the last stage of

their lives. In the ESMO Clinical Practice Guideline: care of the adult cancer patients at the end of life(Eol), Eol starts when patients reach a point of rapid physical decline, typically the last few weeks or months before inevitable death (2).

Patients suffering from advanced gynaecological malignancies frequently experience tumour-related symptoms and complications; their recognition and management are essential to improve their quality of life (QoL).

Tumour-related complications result from local or distant progression manifesting with gastrointestinal symptoms (bowel obstruction, anorexia, nausea, vomiting), pain (localised or radiating neuropathic pain, bone pain), and respiratory symptoms (Table 1). Patients experience psychological frailty with fear, anxiety and existential distress. The multidisciplinary palliative care team has the task to early recognise, evaluate, manage and monitor these symptoms to achieve the best QoL This Eol patient care can be carried out either in the hospital or at home, depending on the patient's and family's choice and the availability of human and structural resources.

Management of Some of the Most Common Symptoms

Malignant Bowel Obstruction

Above all, malignant bowel obstruction (MBO) is a distressing outcome in patients with abdominal and pelvic cancer in the advanced and terminal stages of the disease (2).

MBO may be

- 1. the first clinical manifestation of intra-abdominal or pelvic cancer
- a consequence of disease progression in end-stage cancer patients
- 3. partial or complete
- 4. at single or multiple sites.

Gastrointestinal	Genitourinary	Neurological	Psychological	Other	Systemic
bowel obstruction malignant ascites vomiting fistulas constipation	tumor ulceration fistulas vaginal bleeding vaginal discarge acute kidney injury hematuria dysuria	pelvic nerve infiltration refractory neuropathic pain delirium symptomatic brain metastasis	depression anxiety fear spiritual distress	sovrainfection pleural effusion dyspnea leg-lymphedema	anorexia weight loss fatigue cachexia

Table 1. Main local or distant complications of advanced gynaecological tumors.

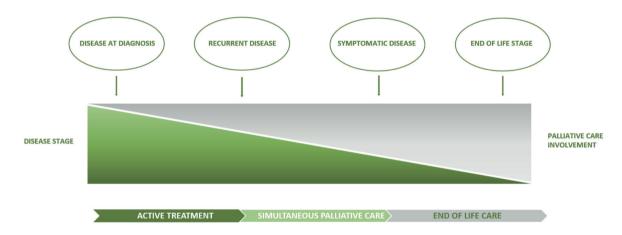


Figure 1. The transition from active potentially curative antitumor treatment to palliative care to end-of-life care.

The small bowel is more commonly involved than the large bowel (61% vs 33%), in >20% of patients both are involved. Retrospective and autoptic studies show that the frequency of MBO ranges from 5 to 51% of patients with gynaecological cancers, mostly ovarian cancer, and is a major cause of death.

Pathophysiological Mechanisms of MBO

Mechanical obstruction: in ovarian cancer small bowel is involved with extrinsic compression by tumor masses and enlargement of lymph nodes. Functional obstruction (or adynamic ileus): in ovarian cancer, it is caused by tumor infiltration of the mesentery or bowel muscle or nerves (carcinomatosis), or by malignant involvement of the coeliac plexus Other causes such as inflammatory oedema, faecal impaction, dehydration, constipating drugs (such as opioids, anticholinergics, etc.) may contribute to the development of MBO or the worsening of the clinical picture.

The main symptoms of MBO are nausea, vomiting, colicky and/or continuous abdominal pain, dry mouth, constipation, and overflow diarrhoea, depending on the type and level of obstruction (Figure 2).

ASSESSMENT: clinical: intensity of nausea, pain, dry mouth; **quantity:** type of vomiting and **radiological:** xRay, CT, endoscopy.

Patient-reported outcome (PRO) and Health-Related Quality should be integrated into the decision-making. The evaluation of treatment efficacy in all patients with recurrent tumors, and follow-up of QoL and symptoms should be integrated into routine practice. PRO measurements can help evaluate the benefit a patient has and could expect from the treatment and monitor the side effects of the treatments to help the physician modify the therapy (3).

MANAGEMENT of MBO (4, 5) MBO should be managed on an individual basis.

SURGERY: it is the first treatment to be considered.
However, the role of surgery in MBO needs to be carefully evaluated using validated outcome measures of symptom control and QoL scores. Surgery should not routinely be undertaken in patients with poor prognostic criteria such as intra-abdominal carcinomatosis, poor performance status, massive ascites, low albumin level, rapidly progressive disease with no further availability of effective antitumor therapies

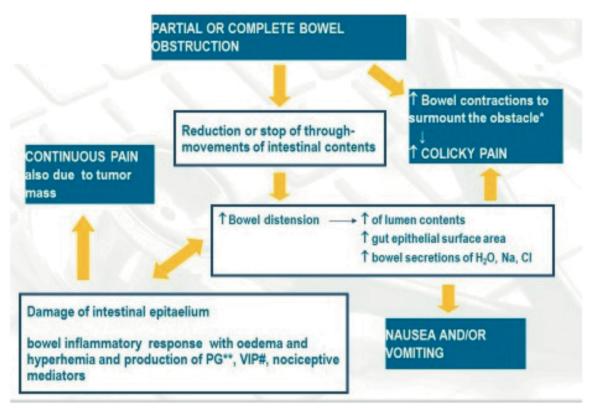


Figure 2. Mechanism and symptoms of malignant bowel obstruction.

- MEDICAL MEASURES: such as analgesics, antisecretory drugs, and antiemetics, administered alone or in combination, should be used to relieve symptoms and to avoid the use of a Nasogastric Tube (NGT) when possible (Figure 3).
- 3. ENDOSCOPIC MANAGEMENT with stents should always be considered.
- NGT should be used only as a temporary measure and a venting Percutaneous Endoscopic Gastrostomy (PEG) should be considered if drugs fail to reduce vomiting to an acceptable level.
- TOTAL PARENTERAL NUTRITION (TPN) should be considered only in patients who may die from starvation rather than tumor spread.
- 6. PARENTERAL HYDRATION is sometimes indicated to correct nausea, and regular mouth care is the treatment of choice for dry mouth.
- A COLLABORATIVE APPROACH by surgeons and palliative care physicians can offer patients an individualised and appropriate symptom management plan.
- 8. PSYCHOSOCIAL SUPPORT: The early detection of psychosocial distress, sexual dysfunction and psychiatric comorbidity, and the identification of psychosocial

care needs, are of major importance. A stepped-care model of interventions, including counselling, psychoeducation and psychotherapy, is the best approach in all areas of psychosocial care for patients with gynaecological cancers. Patients should receive a personalised survivorship care plan to cope with the physical and psychosocial long-term side effects of disease and therapy and to preserve QoL.

Urinary Tract Obstruction

Malignant obstructive uropathy (MOU) may occur due to ureteral obstruction by a relapsing tumor or as a complication of surgery or radiotherapy. Clinical effects may depend on the time course of obstruction (6). Progressive hydronephrosis may ensue, leading to pain, a sense of abdominal tension and acute kidney injury (AKI). Hematuria, often due to tumor invasion of the bladder, may appear as external signs and may further worsen MOU. The development of pyelonephritis can also precipitate the clinical course and the development of AKI. MOU is a urologic emergency that prompts hospital admission, usually in the intensive care unit (ICU), to manage complex life-threatening symptoms. In case of confirmation of hydronephrosis by radiological imaging, done without contrast medium, a percutaneous nephrostomy is also performed in advanced cancer patients to relieve the obstruction and reverse the

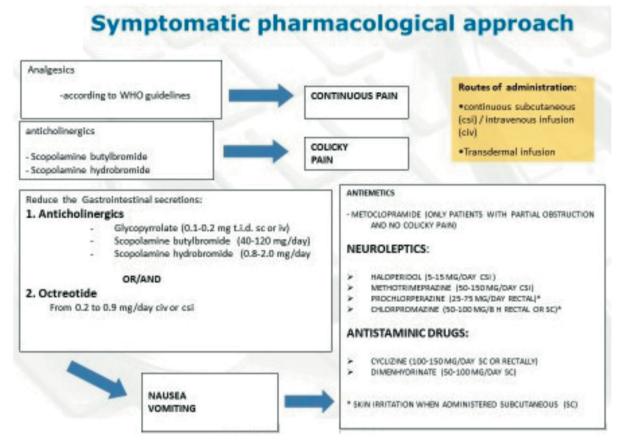


Figure 3. Pharmacological management of malignant bowel obstruction.

uremia with a relatively low-risk procedure, also in very ill patients. Retrograde stenting of the ureter allows bypassing obstruction by a metal stent. This procedure, however, is more cumbersome, poses a risk of further bleeding and requires anaesthesia. Therefore, this procedure is rarely offered as palliative treatment in recurrent gynaecological cancers unless there is an extended life expectancy. The surgical manipulation of an obstructed urinary tract is very often associated with sepsis that should be promptly treated according to guidelines; the treatment with the proper antibiotic therapy, selected according to bacteria cultures in blood and urine, should be started as soon as possible In case of a septic shock, the decision to be made is whether the patients should be transferred to ICU for a short trial of intensive antibiotic treatment and proper supportive care Indeed, despite patients being at the end of their life, it would not be acceptable to let them die due to the acute complication of a procedure and not of cancer itself. This possibility must be considered when discussing with patients the potential implications of nephrostomies or stenting.

Moreover, while in patients with newly diagnosed/advanced tumors uremia should be actively treated and re-

lieved, in patients with recurrent disease relieving uremia might allow the tumor to grow further and produce more cumbersome symptoms instead of letting the patient die from uremia. These aspects should be discussed in advance with the palliative care team, the patients, their families and caregivers.

Terminal Uremia

If nothing is attempted, uremia will ensue because of hydronephrosis. In this case, great attention must be paid to emotional symptoms due to the awareness of the progression of the disease and worsening of the general conditions, in particular when the patient understands that she is not passing urine anymore or when there are other frightening symptoms like bleeding In this case, if acute measures are excluded, a shift towards end-of-life care is recommended because the survival of patients with progressive renal failure is in the order of days. Increasing analgesia and sedation are appropriate measures to let patients die comfortably.

Bleeding

External bleeding may be seen in the late stages of several cancer, up to 12% of genitourinary tract or gynaecological

cancers. Bleeding can be due to local factors (e.g., tumor infiltration of genitourinary tissues or blood vessels) or systemic factors (i.e., coagulopathy) that can be related to cancer itself or systemic or local therapies (e.g., anticoagulants or radiotherapy) (7). Often, a combination of factors exists and can precipitate acute bleeding, either internal or external. In ovarian cancer, the bleeding can be occult, even though massive. Notwithstanding the cause and the site, severe bleeding may lead to acute hypovolemic shock, with acute hypotension, tachycardia, oliguria, pale skin and mucosae, and confusion. This can induce massive suffering even in terminally ill patients who are well prepared for dying. Sometimes the bleeding can be so severe and rapid to induce a sudden death. Such an event must be discussed in advance with the patient and the family to plan which care would be best provided. In this scenario, it is important that the palliative care team respects the patient's autonomy and fosters the expression of personal values that may lead to choosing one therapeutic option over another. Hypovolemic shock is a fatal complication and must prompt emergency medical advice if not expected as a terminal event. A bedside ultrasound evaluation may show fluid collection, which can be difficult to distinguish from ascites. A contrast CT scan is necessary to require a direct explorative laparoscopy or radiology interventions unless the clinical picture is not so severe. Immediate supportive measures include restoration of circulating blood volume with intravenous fluids and blood products such as packed red cells and coagulation factors. Vasoactive agents like noradrenaline are indicated. The controlling measures may include surgical hemostasis, arterial embolisation, or abdominal packing. The involvement of the palliative care team will be important in case of complicated or prolonged ICU stays in patients with advanced cancer due to their poor life expectancy and the already low-performance status before the event.

Aggressive therapy is not indicated if the patient has entered an end-of-life phase. General comfort measures should be implemented instead, including appropriate treatment of pain and anxiety. If this approach has been discussed in advance, an advanced plan of care has been already defined and can be implemented, including deep, continuous, palliative sedation. Education and re-education of caregivers are very important in this last accelerated phase. The constant presence of the palliative care team is useful to relieve the sense of suffering that such an event will pose to the patient and the family.

Bleeding can also manifest as continuous or semicontinuous external blood loss Vaginal bleeding commonly occurs in advanced cervical and endometrial cancers; vaginal packing can control moderate bleeding. For more severe bleeding, vaginal packing can be undertaken in a surgical setting, with anesthesiology assistance for sedation or support. Hemostatic agents can be used in adjunct to vaginal packing, both locally and intravenously, e.g., tranexamic acid. Bed rest and urinary catheterization are important comfort measures. Depending on the clinical scenario, intravenous fluids and blood products may be useful. Hemostatic radiation is usually not indicated unless there is infiltration of the lower pelvic structures. This option should be discussed with a specialist and, in case, proposed to patients with clear, palliative intent.

In case the external bleeding is not controllable with those measures, the indications for more invasive procedures, such as arterial embolisation or surgery, must consider the patient's wishes and risk/benefit ratio. There are cases in which terminal bleeding is expected and where it would be more appropriate to put in place simple measures and implement analgesia and sedation than undertaking invasive therapies in an acute setting, with no significant benefit in survival but certainly with an increase of the personal experience of suffering.

Assisted Dying

When cancer progresses, some patients will start considering having more control over their end-of-life. Palliative and hospice care can help, but some patients will ask to end their suffering through assisted dying (8). Different terminologies are used to describe hastening death practices. Modern literature uses neutral terms to distinguish these practices from classical suicide or other end-of-life medical decisions, such as withholding or withdrawing treatments. The term assisted dying includes the practices also called assisted suicide, physician-assisted suicide, medical aid in dying, assisted dying, physician-assisted dying, voluntary euthanasia, direct euthanasia, and death with dignity (9). All assisted dying legislation has some commonalities in terms of indication, legal aspects, and safeguards; they establish which health conditions can be considered, that mental capacity should always be evaluated, how the request should be formally expressed, for how long patients should wait until the procedure is granted, which clinical evaluations patients should undergo (10). Laws also require the physician to report the practice to designated national bodies. In most jurisdictions, around 80% of persons who ask for assisted dying receive hospice or palliative care services, and euthanasia is far more frequently requested than assisted suicide (8). The most commonly used drugs for euthanasia are benzodiazepines, barbiturates, and muscle relaxants in different dosages, sequences and combinations. The drug usually prescribed to patients opting for assisted suicide is barbiturate.

From a practical point of view, it is not easy to find the protocols applied for carrying out euthanasia once it has been legally requested and approved. Generally, it can be carried out in a patient's home or a dedicated facility. Family members may attend or not, as per the patient's choice. The team that carries it out may consist of medical staff, nurses, and others, such as psychologists or social workers. The drugs can be administered as a drink or an intravenous (IV) infusion. The theoretical advantage of oral administration is to make the process less medicalised. An anxiolytic drug and antiemetics may precede the administration of the lethal mixture. Drinks may contain elevated doses of barbiturates, other cardiotoxic drugs, or respiratory blockers, such as opiates. Disadvantages could be nausea, vomiting and inhalation, particularly in patients with swallowing deficits. This may trigger undignified or distressing situations where the patient is not dying, or the process is slow with additional suffering. IV administration is more effective and quicker, although it may be perceived as less natural, particularly when euthanasia is practised at home or in a family setting. IV administration requires a stable route of administration to avoid the extravasation of drugs that can make the procedure less effective and painful. An anaesthetic and a muscle relaxant are normally administered (10).

The word "euthanasia" derives from ancient Greek, meaning "good death", i.e., death without suffering. Euthanasia is opposed to a painful or undignified death that can occur with the progression of the disease and increasing the burden of symptoms. The World Medical Association, in 2015, defined euthanasia as an act of "knowingly and intentionally performing an act that is intended to end another person's life". A homogeneous definition of euthanasia is lacking due to its medical, cultural, and legal implications. Euthanasia is typically distinguished from withholding or withdrawing life-sustaining treatments. Some experts still define this last as "passive euthanasia" (i.e., letting the patient die of their disease). "Indirect euthanasia" may refer to all medical practices not primarily intended to cause the patient's death but contributing to death (i.e., highdose opiates to relieve untreatable pain at the end-of-life) (11). However, in countries where a palliative care movement and practice exist, euthanasia is well distinguished from the withholding/withdrawal of life-sustaining treatment and deep palliative sedation. Even though palliative care and euthanasia are usually considered alternatives, some experts argue that both practices share the issue of promoting and valuing patients' autonomy and aiming to relieve suffering (10). On the other hand, assisted suicide is defined as a person intentionally helping another person to terminate their life at that person's voluntary and competent request. The characteristic of assisted suicide is that the patient should be capable of self-administer the lethal drug. At the same time, euthanasia implies that a physician (or other professional) administers the drug to a competent patient who requested the act.

Assisted dying, where its practices are legal, should meet different criteria depending on the laws of the country (9):

- The patient is a competent, informed person, voluntarily asking for it.
- The patient is suffering from a serious, incurable illness and is afflicted by an unbearable suffering.
- The act of euthanasia is performed knowingly and compassionately for the patient.
- The act must respect the dignity and be non-violent.
- The actual provider of euthanasia should not have any direct interest in it.

Different forms of assisted dying are legal in several countries, and their number is growing steadily. In 2023 The Netherlands, Belgium, Spain, Luxembourg, Switzerland and Italy and, outside Europe, New Zealand, Australia, Canada, Colombia and some states in the US (California, Colorado, District of Columbia, Hawaii, Montana, Maine, New Jersey, New Mexico, Oregon, Vermont and Washington) have legalised euthanasia, assisted suicide or both practices (9).

The Netherlands was the first country to legalise euthanasia; it allows euthanasia for terminally ill children of >12 years, while the Groningen Protocol authorises euthanasia for newborns with "unbearable suffering". In the Netherlands, euthanasia is also allowed for patients who fail to die quickly after performing assisted suicide. All those countries require at least one written statement to request an assisted death. Most countries ask for an independent medical consultation on the case. Conscientious objection to performing assisted dying is allowed in all countries. In contrast, most doctors refuse to participate in assisted dying not only for conscientious objection reasons but also for anticipated personal or professional reasons such as stress and fear of stigma.

Data on patients who accomplish assisted dying are not easy to obtain due to privacy policies or lack of public registries in all jurisdictions, even though a "posthoc" report to deputed committees is required in all countries but Canada. Advanced cancer is the most common cause of the request. In some reports, cancer patients were diagnosed at least one year before. Up to 30-40% are still under active treatments with or without simultaneous palliative care, with a prognosis of up to one year. Amongst non-on-cological diseases, neurological progressive conditions like amyotrophic lateral sclerosis are the most common cause of requests. In some countries, the law allows foreseeing

euthanasia in advanced directives in case of future loss of neurocognitive competency.

The origin of the wish for assisted dying is multifaceted. In general, the reported suffering that triggers the request for assisted dying is typically multidimensional and "unbearable suffering" is requested by most countries where assisted dying is legal (12).

Physical pain and symptoms are not prominent motivations for patients to opt for assisted dying. Fears of medicalised death, growing dependence on others, and uncertainty can all contribute to patients' choices. Social isolation and other non-medical factors can sometimes affect the patient's choice (12).

More often, patients report unbearable suffering caused by fears or impending loss of independence in daily activities and autonomy with the perception of a loss of dignity and of meaning to stay alive. In many cases, the choice of assisted dying belongs to the patient's existential sphere, resulting from cultural and philosophical views of life. The prospect of dying by assisted dying may date decades before the illness. The decision-making can be characterised by steps triggered by specific experiences during the illness and its treatments (12).

Assisted dying has been reported to be a possible way for patients to control their dying process (11). Good quality palliative care, which promotes patients' values and choices, provides good control of symptoms, and considers all the aspects of suffering, is usually deemed necessary as an alternative to assisted dying. However, in the "real world" experience, some patients will prefer to be fully relieved by the suffering altogether with their life than coping with an unbearable, even though palliated, burden. This is a matter of personal choice, where values such as dignity, quality of life, and religious and cultural factors compose a personal view.

Assisted dying is a complex and challenging experience for those involved and can represent one of the most difficult decisions patients and their families ever make (12). Deciding on assisted dying can be characterised by intense negotiations to reach an agreement between families, professionals, and other stakeholders involved in the procedure. Accepting assisted dying in jurisdictions that permit these practices may vary among the family and healthcare professionals involved, usually depending on personal values (12). Patients may encounter stigmatisation and obstacles in their decision-making; for example, it is known that although family members may often support the patient's choice, family opposition is a common predictor of patients not achieving assisted suicide. Professionals must be aware of their values and principles and use conscious

objection to avoid moral dilemmas. The voluntary role of healthcare professionals in assisted dying practices should always be assured.

The overall goal of care agreed upon with patients requesting assisted dying should be to maximise informed autonomy and offer the best bio-psychosocial and existential comfort options. To deal with assisted dying requests, knowing national and regional laws and institutional policies and openly explaining them to patients is important. In terms of clinical evaluation, the multidimensional origins of the unbearable suffering should be explored and addressed, and all options for multidisciplinary care should be discussed with the patient. Sources of hope, meaning and healing should also be explored. A biographical approach (such as life history) will encourage a person-centred practice and elicit patients' and families' values and life goals. Clinicians should also discuss with patients the roles of family members in assisted dying and explore if and to what extent families have been involved in decisionmaking (12).

The complexities of assisted dying in countries where it is legal are several and include an objective assessment to define suffering as "unbearable", the best way to define a prognosis and how long life would be expected to naturally last without assisted dying, non-compliance with the policy of reports and the risk of overzealous use of assisted dying or its underestimation. Additional controversial issues are whether assisted dying should be granted in cases of existential suffering without underlying medical conditions and the support that should be offered to teams performing assisted dying.

In conclusion responding to assisted dying requests remains a complex task that requires experience and specific competencies. Clinicians should respect patients' autonomy while operating in team, follow law requirements and ensure appropriate support and counselling across the continuum of care. It is crucial to preserve mutual respect, open communication and institutions should provide means of debriefing opportunities for the teams during decision making and after patient's death.

Conclusion

Managing patients with gynaecological cancers at the end of their life requires a multidisciplinary approach because of the variety of physical and psychological symptoms, their intensity, and the suffering of patients, families and caregivers. A concerted approach among the palliative care team, gynaecologists, and medical oncologists, respect, good communication and training are essential to assure an acceptable quality of life and a dignified death.

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