



ESMO management and treatment adapted recommendations in the COVID-19 era: gynaecological malignancies



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ABSTRACT

The rapid spread of severe acute respiratory syndrome coronavirus 2 infection and its related disease (COVID-19) has required an immediate and coordinate healthcare response to face the worldwide emergency and define strategies to maintain the continuum of care for the non-COVID-19 diseases while protecting patients and healthcare providers. The dimension of the COVID-19 pandemic poses an unprecedented risk especially for the more vulnerable populations. To manage patients with cancer adequately, maintaining the highest quality of care, a definition of value-based priorities is necessary to define which interventions can be safely postponed without affecting patients' outcome. The European Society for Medical Oncology (ESMO) has endorsed a tiered approach across three different levels of priority (high, medium, low) incorporating information on the value-based prioritisation and clinical cogency of the interventions that can be applied for different disease sites. Patients with gynaecological cancer are at particular risk of COVID-19 complications because of their age and prevalence of comorbidities. The definition of priority level should be based on tumour stage and histology, cancer-related symptoms or complications, aim (curative vs palliative) and magnitude of benefit of the oncological intervention, patients' general condition and preferences. The decision-making process always needs to consider the disease-specific national and international guidelines and the local healthcare system and social resources, and a changing situation in relation to COVID-19 infection. These recommendations aim to provide guidance for the definition of deferrable and undeferrable interventions during the COVID-19 pandemic for ovarian, endometrial and cervical cancers within the context of the ESMO Clinical Practice Guidelines.

INTRODUCTION

The rapid evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to pandemic level has posed an unprecedented challenge to the health services at different levels requiring a global response to adapt rapidly to a fast-changing situation.¹ The spread of the COVID-19

requires mitigation policies at political and social levels to contain the diffusion of the virus. While healthcare facilities (outpatient and inpatient based) have responded quickly to guarantee the adequate acute care of patients with COVID-19 related complications, management of non-COVID-19 diseases needs to be redefined to guarantee continuum of care according to the highest gold standards, evidenced-based knowledge and value-based priorities.²⁻³ Vulnerable populations with chronic diseases are at significant risk of acquiring COVID-19 infection, with the frequent development of complications causing a disruption in their care plan.⁴ Patients with cancer are at higher risk of severe complications due to their immunosuppressive status and the high prevalence of comorbidities.⁵⁻⁶ Thus, the oncology community has had to reshape the organisation of daily standard activities and care facilities to protect patients and healthcare providers from the spread of the infection while maintaining access to oncological care through a framework-defined prioritisation of resources. Strategies to minimise risks have been broadly endorsed: establishment of checkpoints to triage patients for COVID-19 symptoms, frequent handwashing and use of protective masks, a reduction of the outpatient visits or replacement by telemedicine, engagement of primary healthcare sectors, patient education, reorganisation of outpatient clinics to guarantee social distancing and more frequent remote support especially when visits and assessments are cancelled or postponed.³⁻⁷⁻¹⁰

National and international guidelines are followed to prioritise oncological interventions, focusing on a continuous risk/benefit ratio assessment to select the best treatment option available. While some strategies and

definition of priorities might be similar across tumour types (eg, treatment with curative intent, management of symptoms, acute complications of surgery or medical or radiation interventions), specific considerations are needed for each disease entity to define which treatment can be delayed, and for how long. Gynaecological malignancies are commonly associated with risk factors and cancer-related complications (eg, median age at diagnosis >60 years, comorbidities, thromboembolic events) that overlap with those observed during COVID-19 infection.^{11 12} The management of gynaecological cancers is based on a multidisciplinary approach in which surgery plays a primary role. For patients with a new diagnosis of an apparent early stage cancer, a delay in surgery could be considered as there is no immediate risk to life. However, when surgical intent is curative, any delay must be balanced against the effect this might have on patients' overall survival (OS). In advanced stage cancer, where the intent of surgery may not be curative, any delay in surgery needs to take account of the consequence this might have on disease-related complications and improvements in progression-free and OS and quality of life (QoL). The high complexity of some surgical interventions for gynaecological cancers requires the availability of intensive care units facilities which can be overwhelmed during the infective emergency. Moreover, a nasopharyngeal swab for COVID-19 diagnosis should be carried out in all patients undergoing surgery. A careful identification of the requirements to support patients in the postsurgical recovery is also relevant, given the higher susceptibility to infections and complications during this time. When it is not possible to guarantee adequate surgical or medical care access, referral to a COVID-19 free comprehensive cancer centre (Oncological Hub) highly specialised for the treatment of gynaecological malignancies should be discussed. Chemotherapy is a key component of the multidisciplinary treatment of gynaecological malignancies. During this extraordinary pandemic, it is important to evaluate the potential risks of immunosuppression or adverse events, which might require hospital admission or more frequent outpatient visits. Adjustments to the dose of drugs or schedule of administration should be considered to mitigate this risk. Thus, different aspects have to be sought and a careful discussion with patients and their families on the expected benefits and potential additional risks in this particular situation is necessary. In addition, testing of patients for SARS-CoV-2 before starting chemotherapy may be considered according to local practice and institutional directives, taking into account that infected patients are more contagious during the first days when no symptoms have occurred in the greater majority of cases.

Clinical research is a key element in the care of patients, many of whom are receiving treatment within a clinical trial. Regulatory agencies (eg, European Medicines Agency; Food and Drug Administration) have provided guidance on extraordinary measures to adjust clinical trials in order to protect patients safety and trial

conduct.^{13 14} Investigators and sponsors need to also consider specific ongoing national recommendations that might differ from a country to another. Patients in a clinical trial should continue to receive treatment if it does not pose safety concerns. Accrual of new patients to a clinical trial depends on local resources, the patients' social conditions and geographical considerations; it should only occur if compliance to the protocol can be guaranteed and when data collection, particularly safety reporting can be assured. Priority should be given to clinical trials where there is a high likelihood of benefit of the trial treatment. The impact of protocol deviations on the subsequent clinical data and trial primary endpoints should also be considered.

In the coordinated effort to deliver high-level oncological care while facing COVID-19 pandemics, the European Society of Medical Oncology (ESMO) defined a tiered approach across three levels of priorities, namely: tier 1 (high priority intervention), 2 (medium priority) and 3 (low priority)—defined with the criteria of the Ontario Health Cancer Care Ontario, Huntsman Cancer Institute and Magnitude of Clinical Benefit Scale (MCBS), incorporating the information on the value-based prioritisation and clinical cogency of the interventions.^{15 16}

- ▶ *Tier 1 (high priority)*: patient's condition is immediately life threatening, clinically unstable and/or the magnitude of benefit qualifies the intervention as high priority (eg, significant OS gain and/or substantial improvement of the QoL).
- ▶ *Tier 2 (medium priority)*: patient situation is non-critical but delay beyond 6–8 weeks could potentially impact overall outcome and/or the magnitude of benefit qualifies for intermediate priority.
- ▶ *Tier 3 (low priority)*: patient condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude of benefit (eg, no survival gain with no change to or reduced QoL). Reassessment of deferrable interventions is advisable to confirm the level of priority remains unchanged overtime.

The peculiarities of gynaecological malignancies previously described have been considered along with the national and international guidelines to define COVID-19 adapted recommendations.^{3 15 17–19} These recommendations provide a guide for physicians managing ovarian, endometrial and cervical cancer while facing the COVID-19 pandemic, without replacing the current ESMO Clinical Practice Guidelines^{20–22} and have adapted them in the context of value-based priorities similarly to what has been implemented in the ESMO MCBS.¹⁶ These recommendations do not substitute the adoption of broader national health and social strategies to protect patients and communities, but they can be integrated to mitigate the negative impact of COVID-19 and guarantee a coordinated global response.

The present manuscript has been developed according the ESMO guidelines for patients' management during

the COVID-19 pandemic, available at <https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/>.

In addition, the pandemic is evolving and these recommendations could be reassessed and adapted to the current status of the SARS-CoV-2 infection and the local and national resources availability.

MANAGEMENT OF EPITHELIAL OVARIAN CANCER

Ovarian cancer (OC) represents the leading cause of death from gynaecological cancer in developed countries. The disease spread at the diagnosis and the residual tumour at the end of the surgery are the most important prognostic factors for OS. According to the 2018 ESMO-ESGO consensus conference recommendations, the standard surgical staging of apparently early stage epithelial OC (International Federation of Gynaecology and Obstetrics 'FIGO' stages I and II tumours) includes total hysterectomy, bilateral salpingo-oophorectomy (BSO), peritoneal and lymph node sampling and omentectomy.²⁰ In advanced stages, primary cytoreductive surgery followed by platinum-based combination chemotherapy is the standard treatment. However, a patient's clinical condition and frailty score should be carefully considered since extensive surgery has a non-negligible incidence of surgically-related complications. This underscores the importance of managing patients with OC in highly specialised gynaecological oncology centres by a multidisciplinary team (MDT). Besides patients' status, surgical resection may not always be possible due to tumour extension; neoadjuvant chemotherapy (NACT) followed by interval debulking surgery may be an alternative option.²⁰

Maintenance therapies, such as bevacizumab and poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi), significantly improve the progression-free survival following platinum-based chemotherapy and are part of the standard of care. Particularly, PARPi are completely changing the therapeutic algorithm of primary and recurrent disease.

Outpatient visits

During the COVID-19 pandemic, reorganisation of outpatient activities is necessary to reduce hospital visits and maintain the recommended preventive measures in the outpatient setting. Priority should be given to treating conditions for which a delay could compromise outcome and QoL (eg, symptomatic ascites or pleural effusion in newly diagnosed OC, acute abdominal pain or intestinal obstruction or postsurgical complications). Hospital visits may be postponed up to 6 weeks for newly diagnosed patients who do not exhibit critical symptoms and those with planned postoperative follow-up. These situations should be considered as medium priority but should nevertheless be managed in a reasonable timeframe.

To reduce the number and the duration of the visits, alternative approaches (eg, telemedicine or phone

consultations) should be put in place to assess patients on treatment the day before an infusion, and to address new problems or symptoms resulting from treatment.⁴ The safety monitoring of patients receiving oral treatments (eg, hormonal therapy, PARPi maintenance) should be organised through a system of telemedicine, with scheduled blood tests and imaging done close to home, and the postal delivery of oral medications. A regular remote contact with patients is recommended to identify changes promptly as the clinical situation might modify the level of priority.

Follow-up visits could be postponed up to a maximum of 6 months and eventually managed through telemedicine. Imaging should be guided based on clinical symptoms and/or Ca125 value (table 1).

Imaging

Imaging continues to have an important diagnostic role for symptomatic patients with advanced OC to identify intestinal obstruction or abdominal perforation, as these are considered a high priority for intervention. It remains an important investigation for patients with symptoms typically associated with a diagnosis of advanced OC (eg, ascites, bowel obstruction, abdominal swelling). Accurate preoperative imaging can guide the surgical approach and select patients who could benefit from primary debulking surgery. However, some sites will not be able to prioritise the CT scans during the COVID-19 crisis and may base their evaluation on clinical or ultrasound examination or ask the patients to perform the CT scan in another facility closer to their home.

The radiological assessment of the response to treatment, usually carried out by CT scan and evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) tool²³ is a critical component of the primary endpoint for the majority of clinical trials as well as a fundamental instrument used in clinical practice. For imaging within clinical trials, it is strongly recommended to perform the CT scan according to the schedule of the study if possible (table 1).

Surgical oncology

During an infectious disease pandemic, patients with cancer may face difficulties, such as access to hospital and deferred surgery. Different patients' characteristic and tumour prognostic factors should be taken into consideration when deciding how long surgery could be delayed. Life-threatening clinical conditions related to tumour spread, such as intestinal obstruction, bowel perforation, peritonitis, postsurgical complications, torsion of a pelvic mass or urinary obstruction should be considered as high priorities for surgery. Residual disease is the most important prognostic determinant following surgery, so primary cytoreduction should not be deferred beyond 6 weeks during the COVID-19 outbreak. NACT may be considered in frail patients or in those for whom complete cytoreduction is not achievable. Interval debulking surgery should ideally be performed after 3–4 cycles. However, in cases

Table 1 Ovarian cancer: priorities in outpatient visits and staging

High priority	Medium priority	Low priority
Outpatient visits		
<ul style="list-style-type: none"> ▶ Potentially unstable (acute abdominal pain, intestinal obstruction, complications during postsurgery recovery). ▶ Symptomatic new patient (symptomatic ascites or pleural effusion, intestinal obstruction). 	<ul style="list-style-type: none"> ▶ Newly diagnosed asymptomatic patients, no prior surgery. ▶ Postoperative patients with no complications. ▶ Patients continuing on ChT (telemedicine where possible). ▶ Established patients with new problems or symptoms from treatment (convert as many visits as possible to telemedicine appointments). 	<ul style="list-style-type: none"> ▶ Follow-up visit on PARPi maintenance; most can be managed through telemedicine with blood tests and imaging done close to home. Explore postal drug delivery. ▶ Maintenance bevacizumab: if facilities exist to continue, supervision can be performed by telemedicine, ensuring BP and urinalysis are monitored. ▶ Survivorship visits off study.
Imaging		
Symptomatic patient (intestinal obstruction, abdominal perforation).	Diagnostic imaging for clinical suspicion of ovarian cancer (clinical, US).	<ul style="list-style-type: none"> ▶ Follow-up visit out of study.* ▶ Follow-up visit on PARPi maintenance.

*For patients on clinical trials, seek information about changes in management for individual studies from the coordinating trials unit for treatment frequency, blood investigations and imaging.

BP, blood pressure; ChT, chemotherapy; PARPi, poly-ADP ribose polymerase inhibitors; US, ultrasound.

where there is a suboptimal response to chemotherapy and/or persisting poor general condition of the patient or when is not considered safe to perform a major surgical procedure due to the pandemic situation, surgery could be deferred and chemotherapy continued. For all these reasons, consideration should be given to identify highly specialised COVID-19-free centres that could undertake these complex treatments, while minimising infection risk (table 2).

Medical oncology

It is important to underline that the potential benefits of chemotherapy are unchanged, but the risk of harm is increased during COVID-19 to a level that is difficult to quantify. Health prioritisation during this time should take into consideration the most effective treatment approaches.

Postoperative chemotherapy for early stage OC should be considered as a high priority for patients with high-grade serous or endometrioid histological subtypes, since an improvement in OS has been demonstrated.²⁰ Adjuvant chemotherapy in low-grade serous or endometrioid early-stage OC is low priority because of limited benefit and hormonal therapy alone could be considered in selected cases.

In advanced stages, first-line postoperative chemotherapy in high-grade serous and endometrioid subtypes is high priority, while chemotherapy for clear cell or mucinous tumours can be postponed because of lower benefit (medium priority). Also in advanced low-grade serous or endometrioid cases, postoperative chemotherapy is low priority.

When chemotherapy is indicated, standard combination with carboplatin and paclitaxel should be administered, if deemed safe. Granulocyte growth factors in selected cases or other strategies, such as adopting a

4-weekly schedule of treatment, could be considered to reduce hospital visits and the risk of myelotoxicity. Ongoing treatments should be completed, particularly in the context of clinical studies, as any compromise in dose intensity may adversely impact prognosis.

Bevacizumab should be used with caution because of the increased risk of arterial hypertension and thromboembolic events that may worsen COVID-19 outcome.^{11 12}

The benefit of maintenance PARPi, particularly for patients with breast cancer gene (BRCA)-mutated OC in the recurrent and front-line setting, has been clearly demonstrated.^{24 25} Moreover, significant benefit of PARPi maintenance has been proven in BRCA wild-type platinum-sensitive recurrent OC.²⁶ Shortening the duration of chemotherapy to 4–5 cycles in responding patients before starting the maintenance treatment could be considered, especially in the setting of recurrent disease.

Chemotherapy for platinum-sensitive relapse should be delivered within a maximum of 6 weeks, and earlier in symptomatic patients, given the chance to obtain a long-lasting clinical benefit.

After failure of platinum-based treatment, patients' outcome is commonly poor and chemotherapy provides limited benefit. However, some patients may derive an improvement in QoL and disease-related symptoms: a careful evaluation is therefore warranted, taking into consideration patients' performance status, expectations and the likelihood of response. A thorough discussion with patients and families should influence the decision to start a non-platinum regimen or to adopt alternative palliative strategies to manage symptoms (table 2).

MANAGEMENT OF ENDOMETRIAL CANCER

The management of patients with endometrial cancer during the COVID-19 pandemic is particularly

Table 2 Ovarian cancer: priorities in surgical, medical and radiation oncology care

High priority	Medium priority	Low priority
Surgical oncology		
<ul style="list-style-type: none"> ▶ Radiologically confirmed intestinal obstruction in newly diagnosed patient. ▶ Bowel perforation, peritonitis. ▶ Postsurgery complications (perforation, anastomotic leak). ▶ Pelvic mass with torsion or causing urinary or intestinal obstruction. 	<ul style="list-style-type: none"> ▶ Establishment of cancer diagnosis when high suspicion exists (eg, diagnostic laparoscopy). ▶ Primary cytoreductive surgery. ▶ Possible interval debulking surgery following review by multidisciplinary team. Continuation of first-line therapy with postponement of surgery should be considered as an option. ▶ Symptomatic patients with inoperable primary or recurrent cancer requiring palliative cancer procedures (eg, diverting colostomy, venting PEG tubes). 	<ul style="list-style-type: none"> ▶ Risk-reducing surgery for genetic predisposition to gynaecological cancer. ▶ Benign-appearing ovarian cysts/masses. ▶ Recurrent cancer requiring palliative resection. ▶ Oligometastatic first relapse where complete resection is feasible.
Medical oncology in advanced disease		
<ul style="list-style-type: none"> ▶ NACT in symptomatic patients. ▶ Postoperative ChT or continuation of postoperative ChT for high-grade serous/endometrioid tumours. Importance of BRCA testing continues as these patients are eligible for PARPi and should be considered for shortened ChT cycles. ▶ Continuation of treatment in the context of a clinical trial.* 	<ul style="list-style-type: none"> ▶ First-line postoperative ChT in advanced-stage clear cell or mucinous tumours. ▶ ChT for high-grade serous/endometrioid symptomatic platinum-eligible recurrent patients. 	<ul style="list-style-type: none"> ▶ ChT for high-grade serous/endometrioid platinum non-eligible symptomatic recurrent patients. ▶ Symptomatic slowly growing recurrent disease. ▶ ChT for recurrent low-grade serous tumours.
Medical oncology in early disease		
<ul style="list-style-type: none"> ▶ Adjuvant ChT for stages I-IIA high-grade serous/endometrioid. ▶ Continuation of treatment in the context of a clinical trial.* 	<ul style="list-style-type: none"> ▶ Adjuvant ChT for stages IC-IIA infiltrative mucinous. 	<ul style="list-style-type: none"> ▶ ChT for IC IIA low-grade serous/endometrioid/clear cell/expansile invasion mucinous. ▶ IC low-grade serous endometrioid/expansile/invasion mucinous, ChT possible option, considered less essential and to be discussed with the patient, taking into account the risk/benefit ratio.

*For patients on clinical trials, seek information about changes in management for individual studies from the coordinating trials unit for treatment frequency, blood investigations and imaging.
BRCA, breast cancer gene; ChT, chemotherapy; NACT, neoadjuvant chemotherapy; PARPi, poly-ADP ribose polymerase inhibitors; PEG, percutaneous endoscopic gastrostomy.

challenging due to the vulnerability of this patient population. Age at diagnosis >60 years, obesity, uncontrolled diabetes, high prevalence of cardiovascular and respiratory comorbidities are common features of women diagnosed with endometrial cancer and lead to a significant increased risk for severe complications and fatal outcome following SAR-CoV-2 infection.¹¹ The prioritisation of the interventions for the investigation and treatment of this disease should take account of these factors and be discussed within an MDT. Radical and curative treatment delay could be reasonably foreseen for low-grade cases apparently confined to the uterus, while those with high-grade or advanced uterine cancer, commonly associated with cancer-related symptoms, require rapid access to medical care. The identification of conditions in which

a delay might compromise patients' outcome is of utmost relevance.

Outpatient visits

In the outpatient setting, acute or severe tumour-related symptoms such as persistent severe vaginal bleeding, acute abdominal pain, anuria, symptoms of deep vein thrombosis or pulmonary embolism and symptoms possibly related to a recent surgery or ongoing radiotherapy require immediate assessment and proper interventions. The assessment of patients with non-critical clinical conditions (eg, mild postmenopausal bleeding) and oncological consultations to discuss and plan an adjuvant treatment has to occur in a reasonable timeframe especially when a curative treatment is possible and a delay of more

Table 3 Endometrial cancer: priorities in outpatient visits and staging

High priority	Medium	Low
Outpatient visits		
<ul style="list-style-type: none"> ▶ Potentially unstable (acute abdominal pain, complications in the postsurgery recovery or during/after pelvic RT). ▶ Systematic persistent severe bleeding from primary/recurrent tumour. ▶ Anuria, symptoms of DVT/PE in patients with confirmed diagnosis of endometrial cancer. 	<ul style="list-style-type: none"> ▶ Investigations for postmenopausal bleeding (US, hysteroscopy). ▶ Postoperative patients with no complications requiring adjuvant treatment. ▶ Established patients with new problems or symptoms from treatment (convert to telemedicine visits as many visits as possible). ▶ Follow-up visits in the context of a clinical trial.* 	<ul style="list-style-type: none"> ▶ Fertility-preserving therapy in premalignant disease (AH or (EIN)). ▶ Follow-up in high-risk patients after primary treatment (postpone up to a maximum of 6 months if no symptoms). ▶ Follow-up in intermediate-low-risk patients (convert to telemedicine). ▶ Slowly growing asymptomatic vaginal/central recurrence.
Imaging		
<ul style="list-style-type: none"> ▶ Bowel perforation, peritonitis. ▶ Postsurgery complications (perforation, anastomotic leak, PE, abscess, haemorrhage). ▶ Ureteral compression or dislocation with hydronephrosis. ▶ Completion of staging workup (eg, CT scan). 	<ul style="list-style-type: none"> ▶ Tumour evaluation if clinical suspicion of tumour recurrence after radical treatment. ▶ Follow-up visit (clinical and pelvic examination) after palliative treatment for advanced/recurrent disease (postpone up to 2 months). ▶ Follow-up visits in the context of a clinical trial* ▶ Follow-up visits in the context of fertility-sparing treatment of low-risk endometrial cancer. 	<ul style="list-style-type: none"> ▶ Follow-up visits out of study (blood tests and imaging close to home, convert to telemedicine if possible).

*For patients on clinical trials, seek information about changes in management for individual studies from the coordinating trials unit for treatment frequency, blood investigations and imaging.

AH, atypical hyperplasia; DVT, deep vein thrombosis; EIN, endometrial intraepithelial neoplasia; PE, pulmonary embolism; RT, radiotherapy; US, ultrasound.

than 6–8 weeks will have a negative impact on patients' outcome. Low priority hospital visits should be minimised and alternative approaches (eg, telemedicine or phone consultations) considered if this will not compromise the safety of the patients. Fertility-preserving therapy in premalignant disease (atypical hyperplasia (AH) or endometrial intraepithelial neoplasia (EIN)) and clinical assessment of patients with slow-growing asymptomatic vaginal or pelvic recurrence can be delayed unless potential unstable conditions will occur. Follow-up visits with clinical and pelvic examination could be postponed up to a maximum of 6 months in curatively treated asymptomatic high-risk patients and converted to telemedicine for intermediate–low-risk patients (table 3).

Imaging

Despite the difficulties to categorise the different possible clinical scenarios, the priority of the diagnostic workup should be adapted to the possible impact on patient's outcome and QoL. Differential diagnosis of life-threatening conditions related to the underlying malignancy or to postsurgical complications (eg, bowel perforation, peritonitis, anastomotic leak, pulmonary embolism or hydronephrosis) requires immediate imaging. In patients with newly diagnosed endometrial cancer, staging CT scan is crucial to define the best treatment strategy and needs to be planned with high priority especially when curative treatments are possible.

When a tumour recurrence after radical treatment for early disease is suspected, radiological images should be performed in an adequate timeframe within a maximum of 2 months. In the palliative setting, imaging may be delayed in clinically stable patients (medium priority). Outside of a clinical trial, follow-up imaging as well as blood tests can be safely performed closer to patients' home and follow-up visits converted in telemedicine, if feasible (table 3).

Surgical oncology

Surgery (hysterectomy±BSO and sentinel node biopsy (SLN) or lymphadenectomy) is the cornerstone for the management of newly diagnosed endometrial cancer in the cases apparently confined to the uterus and needs to occur as soon as possible.²² Laparoscopy is also a justifiable approach when performed by an expert gynaecology oncologist surgeon because of the reduced postsurgical recovery, complications and costs. The priority-based framework for surgical management of endometrial cancer must take into account tumour biology (histological subtype and grade), clinical stage, patients' general conditions and comorbidities and the possible risks from COVID-19 infection to estimate for how long a radical surgery could be safely delayed without compromising the chance of a curative approach. Potential unstable medical conditions like uterine haemorrhage, radiologically confirmed peritonitis, postsurgical (perforation,

Table 4 Endometrial cancer: priorities in surgical, medical and radiation oncology care

High priority	Medium	Low
Surgical oncology		
<ul style="list-style-type: none"> ▶ Uterine/pelvic haemorrhage. ▶ Radiologically confirmed peritonitis. ▶ Complication during/after RT for primary tumour/pelvic recurrence (fistulisation/bowel perforation). ▶ Acute postsurgery complications (perforation or ureteral dissection, bleeding). 	<ul style="list-style-type: none"> ▶ Hysterectomy (±BSO)+SLN sampling/lymphadenectomy in newly diagnosed endometrial cancer apparently confined to the uterus. 	<ul style="list-style-type: none"> ▶ Risk-reducing surgery for genetic predisposition to endometrial cancer. ▶ AH/EIN not controlled with HT. ▶ Reparation of asymptomatic fistula. ▶ Resection of slowly growing central recurrence.
Medical oncology		
<ul style="list-style-type: none"> ▶ ChT in previously untreated symptomatic metastatic or recurrent disease not sensitive to HT. ▶ Continuation of medical treatment in the context of a clinical trial.* ▶ ChT±RT post surgery in high-risk patients 	<ul style="list-style-type: none"> ▶ Metastatic/recurrent disease slowly growing potentially hormone-sensitive (G1–2, hormone receptors-positive, consider HT). 	<ul style="list-style-type: none"> ▶ Second-line ChT in patients not suitable for HT.
Radiation oncology		
<ul style="list-style-type: none"> ▶ EBRT±ChT post surgery in high-risk patients. ▶ RT for symptomatic unresectable primary tumour not suitable for surgery. 	<ul style="list-style-type: none"> ▶ Brachytherapy in intermediate–high risk. ▶ RT with curative intent for isolated vaginal relapse after surgery. 	<ul style="list-style-type: none"> ▶ RT for asymptomatic vaginal/pelvic recurrence.

*For patients on clinical trials, seek information about changes in management for individual studies from the coordinating trials unit for treatment frequency, blood investigations and imaging.

AH, atypical hyperplasia; BSO, bilateral salpingo-oophorectomy; ChT, chemotherapy; EBRT, external beam radiotherapy; EIN, endometrial intraepithelial neoplasia; G, grade; HT, hormonal therapy; RT, radiotherapy; SLN, sentinel lymph node.

ureteral dissection, bleeding) or radiotherapy complications (fistulisation, bowel perforation) require a prompt access to surgical theatre. Risk-reducing surgery for cancer predisposition and AH/EIN not responding to hormonal treatment is low priority (table 4).

Medical oncology

Ongoing medical treatment should continue adjusting doses and schedules, when appropriate. First-line chemotherapy for symptomatic metastatic or recurrent endometrial cancer not sensitive to hormonal treatment and adjuvant chemotherapy (with/without radiation treatment) in high-risk patients have the highest priority. In grade 1–2 metastatic/recurrent endometrial cancer, hormonal treatment could be considered as first-line option. Patients receiving hormonal treatment should be carefully monitored due to the known thromboembolic risk associated both to the viral infection and the hormonal agent. After failure of platinum-based treatment, patients' outcome is commonly poor and second-line chemotherapy options are limited with minimal benefits expected. In this situation, best supportive care is recommended (table 4).

Radiation oncology

Radiation therapy has a fundamental role in the multidisciplinary management of endometrial cancer and is commonly used with curative intent. Daily access to radiation oncology departments, risks of cross contamination

from equipment and the need to maintain dose intensity can be a real challenge to the management of patients. Immediate treatment should be offered to the patients with symptomatic primary tumour not suitable for surgery. Adjuvant external beam radiation treatment in high-risk endometrial cancer (with/without chemotherapy) is also of high priority given the curative role of this approach. Adjuvant brachytherapy and radiation treatment for vaginal cuff relapse can be planned as medium priority when a curative intent is foreseen, while treatment of asymptomatic vaginal or pelvic relapse can be safely delayed according to type and grade of symptoms (table 4). Similarly to other pelvic malignancies, hypofractionated radiotherapy could be considered, even though supportive data are not yet available in gynaecological cancer.

MANAGEMENT OF CERVICAL CANCER

In the treatment of patients with cervical cancer, the priority should be given to diagnosis, staging workup and treatment of potentially or already unstable life-threatening conditions and localised disease suitable for curative treatment. The combined chemoradiotherapy (CRT) approach is high priority in locally advanced stages. The MDT discussion is necessary to define the best treatment and the availability of resources for the management of patients with cervical cancer.

Table 5 Cervical cancer: priorities in outpatient visits and staging

High priority	Medium	Low
Outpatient visits		
<ul style="list-style-type: none"> ▶ Potentially unstable (acute abdominal symptoms, complications in the postsurgery recovery, complications during/after pelvic radiotherapy, renal obstruction). ▶ Symptomatic persistent severe bleeding from pelvic/vaginal ulcerated tumour. ▶ Anuria, symptoms of DVT in patients with confirmed diagnosis of cervical cancer. ▶ New histologically confirmed patient, no prior surgery, for staging workup (blood tests and imaging close to home if possible). 	<ul style="list-style-type: none"> ▶ Postoperative patients with no complications. ▶ Established patients with new problems or symptoms from treatment—convert as many visits as possible to telemedicine appointments. ▶ Follow-up visit (clinical and pelvic examination) after palliative treatment for advanced/recurrent disease (postpone up to 2 months). 	<ul style="list-style-type: none"> ▶ Follow-up visit (clinical and pelvic examination) after radical treatment for early disease (postpone up to 6 months). ▶ Survivorship visits off study.
Imaging		
<ul style="list-style-type: none"> ▶ Bowel perforation, peritonitis. ▶ Postsurgery complications (perforation, anastomotic leak). ▶ Ureteral compression or hydronephrosis. ▶ Neurological symptoms suggesting nerve root/spinal involvement. ▶ Staging workup (if not done). 	<ul style="list-style-type: none"> ▶ Tumour evaluation if clinical suspicion of tumour recurrence after radical treatment for early disease. ▶ Follow-up visit (with also clinical and pelvic examination) after palliative treatment for advanced/recurrent disease (postpone up to 2 months). ▶ Follow-up visits within a clinical study.* 	<ul style="list-style-type: none"> ▶ Follow-up visits out of study (blood tests and imaging close to home, convert to telemedicine if possible).

*For patients on clinical trials, seek information about changes in management for individual studies from the coordinating trials unit for treatment frequency, blood investigations and imaging.

DVT, deep vein thrombosis

Outpatient visits

The aim of high priority outpatient visits is to prevent and identify possible tumour or treatment-related complications and to define the best optimal treatment for newly diagnosed patients. In the latter case, patients should be scheduled for staging workup (CT scan and blood tests) close to home, if possible, followed by MDT discussion. Unstable patients with life-threatening conditions as acute abdominal symptoms, bleeding or anuria must be seen as soon as possible. Patients with symptoms possibly related to previous surgery or ongoing radiotherapy should be seen as high priority. For postoperative patients without complications, a visit delay up to 6–8 weeks is acceptable, if no adjuvant treatment is planned. Assessments of patients after palliative treatment for advanced/recurrent disease can be postponed up to 2 months, if patient remains clinically stable. Follow-up visits after radical treatment for early disease or survivorship visits after the end of a study can be postponed up to a maximum of 6 months in asymptomatic patients (table 5).

Imaging

Imaging in patients with acute abdominal symptoms and life-threatening conditions, or complications from surgical or radiotherapy interventions (eg, bowel perforation, peritonitis, anastomotic leak, ureteral compression or hydronephrosis) is high priority. Patients with acute rapidly worsening of peripheral neurological symptoms as in case of nerve root compression or spinal involvement must perform CT scan as soon as possible.

The imaging performed for staging workup is also high priority in patients with a new suspicious or histologically confirmed diagnosis of cervical cancer because of the negative impact of a delay in the selection of the best treatment and on the outcome. Imaging for suspicion of tumour recurrence after radical treatment for early stages could be delayed up to a maximum of 2 months because of the prognostic value of an early detection suitable for a localised curative approach.²¹

Follow-up imaging within clinical trials or after palliative treatment for advance or recurrent disease has a medium priority. For patients enrolled in clinical trials, schedule of assessments should be maintained as close as possible to the study requirements balancing the need of a safety control and patients' risk of hospital visits (table 5).

Surgical oncology

The management of a radiologically confirmed bowel perforation, peritonitis or surgery/radiotherapy complications (perforation, ureteral dissection or fistulisation) cannot be delayed. Surgical curative therapy in cervical cancer depends on the stage. Microinvasive cervical cancer (stage IA1) has a very slow progression time, and trachelectomy±SLN sampling could be postponed up to 2 months. For patients with FIGO stages IA2, IB and IIA, the radical curative surgery can be planned within a maximum of 6–8 weeks.

Treatment for asymptomatic fistula, slowly growing central recurrence or premalignant disease can be

Table 6 Cervical cancer: priorities in priorities in surgical, medical and radiation oncology care

High priority	Medium	Low
Surgical oncology		
<ul style="list-style-type: none"> ▶ Radiologically confirmed bowel perforation, peritonitis. ▶ Complications during/after radiotherapy for pelvic recurrence (fistulisation/bowel perforation). ▶ Acute postsurgery complications (perforation, ureteral dissection). 	<ul style="list-style-type: none"> ▶ Radical hysterectomy±BSO and lymphadenectomy stages IA2, IB1–IIA. ▶ Trachelectomy (hysterectomy)±SLN sampling stage IA (postpone up to 2 months). 	<ul style="list-style-type: none"> ▶ Repair of asymptomatic fistula. ▶ CIN3 conisation (if appropriate). ▶ Resection of slowly growing central recurrence. ▶ Consider postponing total pelvic exenteration after the COVID-19 pandemic.
Medical oncology		
<ul style="list-style-type: none"> ▶ Continuation of medical treatment in the context of a clinical trial.* ▶ Stage IB3†, IIB–IVA ChT in association with radiotherapy (CRT). ▶ Stage IVB first line, first local recurrence after >12 months from primary CRT: cisplatin/paclitaxel+bevacizumab (if not contraindicated). When cisplatin is contraindicated, consider carboplatin/paclitaxel or topotecan/paclitaxel with bevacizumab. 	<ul style="list-style-type: none"> ▶ Continuation of standard ChT in case of confirmed significant benefit. 	<ul style="list-style-type: none"> ▶ Second-line ChT according to clinical need, patient wishes and resource availability.
Radiation oncology		
<ul style="list-style-type: none"> ▶ Pelvic EBRT in association with ChT (CRT) stage IB3, IIB–IVA. ▶ Spinal cord compression, brain metastases, other critical metastatic lesions. 	<ul style="list-style-type: none"> ▶ Salvage radiotherapy for symptomatic localised recurrence (central, retroperitoneal lymph nodes). 	<ul style="list-style-type: none"> ▶ Palliative radiotherapy for asymptomatic recurrence not amenable to surgery.

*For patients on clinical trials, seek information about changes in management for individual studies from the coordinating trials unit for treatment frequency, blood investigations and imaging.

†2018 International Federation of Gynaecology and Obstetrics classification.

BSO, bilateral salpingo oophorectomy; ChT, chemotherapy; CIN, cervical intraepithelial neoplasia; CRT, chemoradiotherapy; EBRT, external beam radiation treatment; SLN, sentinel lymph node.

postponed after the peak of the COVID-19 pandemic. Pelvic exenteration is an invasive extensive surgical procedure with very restricted indications and requires a prolonged and demanding postsurgical management, and thus, it can be postponed when possible (table 6).

Medical oncology

All the patients with a new diagnosis of cervical cancer stages IB3–IVB or with a symptomatic metastatic recurrence need a systemic treatment.²¹ Concomitant CRT for locally advanced cervical cancer or first-line chemotherapy with/without bevacizumab in the metastatic setting is high priority. Also in patients with pelvic/abdominal recurrence after 12 months from primary CRT, cisplatin and paclitaxel combination with/without bevacizumab is a high priority intervention because of the known improvement in OS reported with the combination. When cisplatin is contraindicated, combination of carboplatin or topotecan with paclitaxel can be considered. The use of bevacizumab carries the hypertension and thromboembolic side effects which are additional risk factors for a negative outcome of the COVID-19 infection. Bevacizumab, however, is the only agent for which an improvement in OS has been reported in this difficult setting and its use should be

discussed with patients taking into account the structural resources available and the local and national guidelines.²⁷ The continuation of treatments started before the COVID-19 period is medium priority and should be continued if a clinical benefit has been reported, possibly adjusting doses and schedules after a case-by-case discussion. For patients progressing after first-line chemotherapy, there are not effective second-line options and their use should be discussed with patients according to clinical needs, patient's wishes and conditions and available resources²¹ (table 6). The decision on the administration of immune checkpoint inhibitors, where approved, needs to be balanced against the risk of immune-related adverse events, particularly pneumonitis, whose signs and symptoms might overlap with the ones of interstitial pneumonitis commonly observed in patients with COVID-19 infection.

Radiation oncology

Curative treatment for locally advanced cervical cancer (stages IB3, IIA–IIB) is of high benefit in terms of overall and disease-free survival and should be offered taking into account the risks associated with daily accesses to hospital. Palliative radiotherapy for symptomatic spinal cord compression, brain metastasis or other critical



lesions cannot be postponed and should be prioritised over symptomatic localised central or retroperitoneal lymphonodes recurrence. Treatment of asymptomatic pelvic recurrence not amenable to surgery has low priority and can be delayed (table 6).

CONCLUSIONS

COVID-19 pandemic is forcing the healthcare providers to rethink the management of patients with cancer to align with global response plans to contain SARS-CoV-2 spread and, as a consequence, the burden on the healthcare systems. Despite differences might exist between countries and regions, a coordinated response is essential to define strategic plans to protect vulnerable subjects.

In the oncology setting, a value-based framework to define level of priorities has been developed to provide guidance to surgical, medical and radiation oncology communities within the framework of a multidisciplinary approach. The tiered approach in three different levels of priority (high, medium and low) endorsed by ESMO has leveraged the specific recommendations according to tumour types and ESMO clinical guidelines.

For the management of patients with gynaecological malignancies during the COVID-19 emergency, special consideration has to be given to the frailty of this population, often of older age, with significant comorbidities and high symptomatic tumours. However, high quality standard of care delivered by an MDT is able to favourable impact patients outcome in the majority of cases and this has been considered while defining level of priorities.

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