


# Covid-19: What is the best approach in gynecological oncology patient management during the coronavirus pandemic?

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## Abstract

Coronavirus (COVID-19) infection is a new major concern and a global emergency in almost all countries worldwide; due to the higher sensibility of cancer patients, they are more susceptible to severe and fatal infections, being nearly 10 times more likely than in healthy individuals infected with this virus. Although the aggressive nature of a cancer is a matter of concern, our exact role as oncologists in this time of restricted resources is not fully clarified. Regarding some consensus recommendation for postponing surgery, there is still an essential need for a single approved protocol regarding each type of malignancy. Iran, as one of the first involved countries in this crisis in Asia, which also has a high prevalence of gynecological malignancies, will certainly require an individualized decision-making schedule based on the most accepted global consensus opinion. Considering our restricted health system resources, herein we tried to introduce a logical gynecologic cancer management protocol based on the stage and survival expectancy of each tumor, along with reviewing all recent recommendations. The limited statistics published in this short period of time have obliged us to mainly focus on expert opinions, and the individualized clinical judgments should be agreed upon by multidisciplinary tumor board consensus. In conclusion, the COVID-19 pandemic overshadows all aspects of medicine, and decision making in gynecological oncology patients requires precise and appropriate judgment based on the available local resources.

## KEYWORDS

coronaviruses, COVID-19, gynecology, oncology, pandemic, surgery

## 1 | INTRODUCTION

The COVID-19 infection crisis was first announced on February 6, 2020, by the WHO; subsequently, the unknown prognosis of the disease turned it into a global emergency which does not seem to be limited to the present or even the near future.<sup>1</sup> Accordingly, a worse prognosis is predicted for patients with comorbidities such as immunocompromised cancer patients. The statistical data initially reported by

China revealed the mortality rate of COVID-19 to be about 0.9% in healthy individuals, reaching up to 6–10.5% in cases with a positive medical history, for example cancer patients. These patients are more susceptible to severe infection with an almost 3.4 times higher rate of intensive care unit bed requirement and an approximate mortality rate of 49%.<sup>2–6</sup>

What makes the situation more challenging is the low accuracy of COVID-19 screening tests, even as low as 36% in some centers.

This could lead to the unwanted exposure of cancer patients and asymptomatic healthcare providers; however, the routine testing of malignant patients with a prophylactic goal also does not make sense.<sup>7</sup>

Taking into account the aggressive nature of neoplasms and the current restricted healthcare resources, there is an absolute need for a practical management guideline in cancer patients. Considering our role as a gynecological oncologists has made us try to provide a reasonable protocol for such patients. For this purpose and due to the limited statistics published so far, a review of all the recent oncological recommendations in COVID-19 crisis based on expert opinions have been done, focusing mainly on gynecological oncology patients.<sup>8-14</sup>

There is no need to note that all decision-making should be based on an informed consent from the patient after explaining the exact costs and benefits.<sup>15,16</sup>

### 1.1 | Review of the cancer patients' management guidelines in the COVID-19 pandemic

As explained before, cancer patients seem to be at higher risk of COVID-19 infection due to their underlying comorbidities including chronic respiratory and cardiac diseases, age over 65 years, diabetes mellitus, the ECOG performance status of  $\geq 2$ , current chemotherapy and the complicated level of surgery.<sup>17,18</sup> On the other hand, there is no approved recommendation on the effectiveness of prophylactic antiviral drugs in immunocompromised patients and this issue is currently under investigation.<sup>19</sup>

The British Gynecological Cancer Society has recommended limiting surgery to patients with an expected survival of over 12 months whom have not responded to other alternative therapies. Radiotherapy and neoadjuvant chemotherapy could be considered as an alternative approach when there are not adequate acceptable surgical resources.<sup>15</sup> Other consensus recommendations include 2–4 weeks delay in performing surgery, with strict follow-up and documentation of the reason for any variation in surgery.<sup>6,20</sup> Informed consent for each individual decision-making should be followed.<sup>15</sup> A full review on the other oncology consensus suggested approaches in each gynecological malignancy is summarized in Tables 1–3. Considering all these valuable opinions we recommend a practical guideline focusing on instructions for low risk contacts and a specially-designed gynecological-oncology decision-making protocol for middle and low income countries like our society, with the aim of limiting the spread of COVID-19 infection; Tables 4 and 5.

### 1.2 | The optimal advice for limiting the risk of COVID-19 infection in gynecological oncology cases<sup>5,13,17,20-23</sup>

1. Appointment management should be done by phone contact initially, asking about infection symptoms and assessing the need for in person visit.

2. Checking the body temperature of the cancer patient and their companions when attending the office.
3. CDC and WHO have recommended proper face mask, preferably N95 usage or face shields for caregivers in medical offices.
4. Limiting contact with other family members; they should not be allowed to even enter the waiting room except for disabled patients with one companion.
5. Prioritized visiting for new cases of cancer, molar pregnancy and symptomatic patients in whom cancer progression or recurrence is suspected.
6. Providing the possibility of distant counselling by designing a specific cyberspace for providing psychological support of such patients instead of face to face visits.
7. Using strategies to reduce the number of healthcare providers in contact with each patients (physicians, nurses and other employees) as far as possible.
8. Taking notice of proper social distancing as the most important preventative measure while patients are in the waiting room and the office.
9. According to CDC recommendations patient surveillance should be postponed to the furthest acceptable time according to each cancer guideline; for example for cancers with a surveillance period of every 3–6 months, arrange appointments for 6 m later, except for symptomatic patients or those showing signs of disease progression.
10. Screening procedures such as mammography and pap smears should be delayed.
11. All decision-making should be based on local multidisciplinary tumor board (MDT) recommendations and most of these sessions should be held via video-conferences.

### 1.3 | Gynecological-oncologist planning suggestions during COVID-19 infection crisis<sup>6,13,15,20</sup>

To best manage gynecological cancer cases, in addition to considering the disease stage and other risk factors, decision-making by the MDT board is indispensable. For example, in patients with an ovarian mass, evaluations include multiple factors such as age, family history of breast or ovarian cancer, physical examination, imaging and tumor markers.

During the present pandemic seeking the best local solution for reducing the number of elective surgeries is an essential requirement. Considering these factors, some reasonable suggestions for gynecological oncology patients' management, based on symptoms, stage of disease and life expectancy have been provided in Tables 4 and 5.

In addition to choosing the optimal approach in gynecological cancer cases, there are some other recommendations for reducing the effect of treatment adverse events on patient survival. As mentioned before, cancer patients are at a higher risk of severe COVID-19 infection mainly due to their immunocompromised situation and the high possibility of unwanted exposure. Several practical suggestions to minimize the adverse effects of treatment are as follows:

**TABLE 1** Endometrial cancer and COVID-19 crisis: review of literature recommendations for gynecological malignancies management in the present pandemic

The special character of cancer:	Ramirez et al G <sup>13</sup>	MEDSCAPE G <sup>12</sup>	British G <sup>15</sup>	Radiotherapy G <sup>29</sup>	European G <sup>30</sup>	American G <sup>31</sup>
Surgery is feasible						
Early stage, low grade	HT (systemic or levonorgesterol IUD)	D4-6 <sup>W</sup>	HT during D10-12 <sup>W</sup>	HT	D8 <sup>W</sup>	D8 <sup>W</sup>
Early stage, high-grade (grade 2, 3) or high-risk histology	Simple H+ BSO ± (SLNB or adjuvant therapy if indicated)	D 4-6 <sup>W</sup>	D4 <sup>W</sup>		D8 <sup>W</sup>	D18 <sup>W</sup>
Unfit patient for surgery, (±comorbidity)			Levonorgesterol IUD (consider)	HT or BRT (EBRT could be postponed)		
More advanced cancer with documented pathology	Systemic therapy			systemic therapy or RT (Locally advanced)		
Adjuvant chemotherapy						
Low-risk cancer			Omit or delay			
High grade or advanced			If ChT is not available, it could be D3 <sup>M</sup>			
Stage 4			Choice is single agent ChT but HT is an alternative.			
Recurrence:			Based on symptoms, Postponing treatment or HT is possible			
Radiotherapy						
Moderate-risk factor			Omit BRT			
High risk			Level 5 for RT			
Very high risk positive margin, tumoral residue, positive LN			Level 3 for RT			
Candidate for Def. RT			Level 3 for RT			

BRT, brachytherapy; BSO: bilateral salpingo-oophorectomy; ChT, chemotherapy; CON, conization; CIN3, cervical intraepithelial neoplasm grade 3; Def, definitive; D, delay up to; EBRT, external beam radiotherapy; G, guideline; H, hysterectomy; HT, hormonal therapy; IUD, intrauterine device; LN, lymph node; mi, microscopic; M, month; N, neoadjuvant; RS, radical surgery; RT, radiotherapy; SLNB, sentinel lymph node biopsy; S, surgery; W, week. Level 1: high chance of cure; Level 2: intermediate chance of cure, Level 3: low chance of cure, high chance of increasing life extension; Level 4: low chance of cure, intermediate chance of increasing life extension; Level 5: noncurative treatment with 50% chance of palliation; Level 6: noncurative treatment, the line effect is on life extension.

#### 1.4 | Operative precautions in gynecological oncology cases during the COVID-19 crisis<sup>23-27</sup>

- Whenever possible consider testing for coronavirus infection in every surgical candidate.
- Inform patients about the probability of infection with the contagious COVID-19 virus and its possible complications.
- Avoid operation on a confirmed or suspected case of COVID-19 infection whenever possible, unless it presents as an emergent or urgent situation.
- If possible, use separate surgical facilities for suspected/proven COVID-19 cases and cases without COVID-19.
- Reduce the number of assistants as far as possible so that only the primary healthcare workers are involved during surgery, except for emergencies; staff replacement should not be allowed during the operation.
- Special personal protective equipment is necessary for the staff involved in surgery and they should be well trained for their proper usage according to CDC and WHO guidelines.
- Electro-surgery tools should be used with minimal power and their application should be limited as much as possible as they can cause particle aerosolization.
- Negative pressure is the optimal condition for the operation room, especially during anesthesia intubation and extubation. At least a

**TABLE 2** Cervical cancer and COVID-19 crisis: Review of valuable literature recommendations for gynecologic malignancies management in the present pandemic

The special character of cancer	Ramirez et al G <sup>13</sup>	MEDSCAPE G <sup>12</sup>	British G <sup>15</sup>	Radiotherapy G <sup>29</sup>	ASCCP G <sup>32</sup>	ACSG <sup>33</sup>	American I G <sup>31</sup>	Canadian G <sup>34</sup>
<b>Surgery</b>								
Suspicious for invasion in screening tests	CON or simple trachelectomy for mi. cancer	CON	CON					
Early stage	Approved centers: S and in low risk cases: simple trachelectomy± SLNB Other centers: D6-8 <sup>w</sup> if staging is completed	D4-6 <sup>w</sup>	Consider Def. RT or ChT D4 <sup>w</sup> for S or BRT is optimal	Def. RT instead of RS	D4 <sup>w</sup> and for CIN3 D3 <sup>M</sup>	D several <sup>w</sup> and for CIN3: D8-16 <sup>w</sup>	D8 <sup>w</sup>	D4 <sup>w</sup> or even more
Gross tumor	N. ChT							
Locally advanced:	RT					No delay		No delay
<b>Chemotherapy</b>								
Locally advanced			Level 1 for ChT-RT (no delay)					
Stage 4			The first line ChT (palliative ChT is Level 4)					
Recurrences			The first line ChT (palliative ChT is Level 4)					
<b>Radiotherapy</b>								
Moderate risk factor				No need for adjuvant RT				
High risk factor				D12 <sup>M</sup>				
Very high risk (tumoral residue, positive margin, positive LN or aggressive histology)			Adjuvant RT (with Level 3)	Adjuvant RT				
Def. RT Or intrauterine BRT			No delay (Level 1)	.				

BRT, brachytherapy; ChT, chemotherapy; ChT-RT, chemo-radiotherapy; CON, conization; CIN3, cervical intraepithelial neoplasm grade 3; Def, definitive; D, delay up to; EBRT, external beam radiotherapy; G, guideline; mi, microscopic; LN, lymph node; M, month; N, neoadjuvant; RS, radical surgery; RT, radiotherapy; SLNB, sentinel lymph node biopsy; S, surgery; W, week. Level 1: high chance of cure; Level 2: intermediate chance of cure; Level 3: low chance of cure, high chance of increasing life extension; Level 4: low chance of cure, intermediate chance of increasing life extension; Level 5: noncurative treatment with 50% chance of palliation; Level 6: noncurative treatment, lonely increase chance of increasing life extension for 1 year.

**TABLE 3** Vulvar cancer and COVID-19 crisis: review of valuable literature recommendations for gynecologic malignancies management in the present pandemic

Guideline	British G <sup>15</sup>	Radiotherapy G <sup>29</sup>	ACS G <sup>33</sup>
Surgery			
VIN3			D several <sup>W</sup>
Vulvar cancer	Greater utilization of Def. RT or N. ChT is suggested. In surgical candidates, D4 <sup>W</sup> and SLNB is recommended.		No delay
Nonoperable		Radical RT and concurrent ChT.	
Chemotherapy			
Stage 4 or First recurrences	The first-line ChT (palliative treatment is Level 4)		
Radiotherapy			
High-risk patient (tumoral residue, positive margin, positive LN)	Adjuvant RT (Level 3)	Adjuvant RT is recommended.	

BRT, brachytherapy; ChT, chemotherapy; CON, conization; CIN3, cervical intraepithelial neoplasm grade 3; Def, definitive; D, delay up to; EBRT, external beam radiotherapy; G, guideline; IUD: intrauterine device; mi, microscopic; LN, lymph-node; M, month; N, neoadjuvant; RS, radical surgery; RT, radiotherapy; SLNB, sentinel lymph node biopsy; S, surgery; W, week.

- separate room with appropriate ventilation should be considered for patients suspected for COVID-19 infection.
- The emergency operation room should be separated from the elective one.
  - Separate cleaning and sterilization of surgical instruments in touch with suspected patients for COVID-19 should be mandatory.
  - Due to limited data on the best procedure for restricting the probability of viral transmission (minimally invasive or open surgery), if the laparoscopic approach is preferred, it should be performed with utmost caution.

### 1.5 | Chemotherapy during COVID-19 crisis in gynecological oncology cases<sup>15,17,20,28</sup>

- With regard to the United Kingdom National Health Service (NHS) recommendations, it would be better to categorize patients according to the risk-benefit ratio for chemotherapy, and substitute it with alternative therapies and less resource-intensive regimens.
- For patient protection during the 5- to 10-day neutropenia period between the chemotherapy cycles, routine GCSF administration is recommended in patients receiving combination therapy. Although Society of Gynecologic Oncology (SGO) recommends GCSF to be administered for older patients with comorbidities.
- After phone-counseling to reduce the face-to-face contact and hospitalization rate, chemotherapy is recommended in patients with normal blood indices (ANC  $\geq 1.5$  and no lymphopenia) and no accompanying morbidities.
- Blood transfusion should not be performed in asymptomatic patients solely based on laboratory tests; prophylactic erythropoietin or iron transfusion may be considered in anemic cases.

- Patients with high-grade serous and endometrioid ovarian cancer are expected to respond well to first-line platinum-based chemotherapy (unlike mucinous tumors) and should be considered for chemotherapy prescription.
- The preferred approach for systemic chemotherapy with a curative intent in germ cell tumors is:
  - Do not prescribe adjuvant chemotherapy in stage 1, unless MDT individualized planning.
  - First- and second-line treatment for metastatic diseases should not be stopped without MDT justification.
  - Conventional dose instead of a high dose regimen is the treatment of choice.

### 1.6 | Radiotherapy during COVID-19 crisis in gynecological oncology cases<sup>4,5,13,15,21,29</sup>

- Proper time planning is essential for each patient for reducing the waiting time.
- Only one companion with a proper face mask could accompany the patient in the medical center, after being checked for fever and infection symptoms.
- "Hypo-fractional RT" is recommended for reducing the frequency of patient and healthcare provider exposure; this means increasing the dose to reduce the prescribed number of fractions.
- One other useful advice is reducing the number of intrauterine device insertions.
- Postponing palliative RT, but not therapeutic RT with a curative intent for rapid progressive cancers is advisable.
- There is still no indication for delaying or interrupting brachytherapy sessions (indeed in noninfected COVID-19 cases) even in the present pandemic.

**TABLE 4** Priority of surgery based on the chance of cure and life expectancy in gynecologic oncology patients

Priority	Cancer	Ovarian cancer	Endometrial cancer	Cervical cancer	Vulvar cancer	GTD-GTN
1A Emergent surgery	Surgery within 24 hours, Life-threatening situation.	Or-Torsion Of Rupture Suspected malignant pelvic masses <ul style="list-style-type: none"> <li>Peritonitis</li> <li>Anastigmatic bowel leakage</li> <li>Bowel perforation</li> </ul>	Life-threatening bleeding without response to conservative management	Life-threatening bleeding without response to conservative management and RT		<ul style="list-style-type: none"> <li>Massive bleeding from molar pregnancy requiring evacuation or hysterectomy</li> </ul>
1b Urgent	Surgery within 72 hours.	<ul style="list-style-type: none"> <li>Acute mechanical bowel obstruction</li> <li>Impending intestinal perforation</li> </ul>	Life-threatening bleeding without response to conservative management	Life-threatening bleeding without response to conservative management and RT		<ul style="list-style-type: none"> <li>Molar pregnancy</li> </ul>
2 Nonurgent surgery	D4 <sup>W</sup> might be possible if it does not lead to progression.	<ul style="list-style-type: none"> <li>Stage 1,2 ovarian cancer</li> <li>Cytoreductive surgery after 6 courses of N, ChT</li> </ul>	<ul style="list-style-type: none"> <li>High grade/high risk uterine cancer, all stages (e.g., endometrial and sarcoma histotypes)</li> <li>Grade 1 endometrial cancer when HT is contra-indicated or impossible</li> <li>diagnostic D&amp;C hysteroscopy</li> </ul>	Early stage (Stage1b1)	Resection of vulvar cancer	
3 Elective surgery	D10-12 <sup>W</sup> has no adverse effect on patient survival.	<ul style="list-style-type: none"> <li>Benign ovarian mass or cyst</li> </ul>	<ul style="list-style-type: none"> <li>Early stage, low grade uterine cancer</li> <li>Hysterectomy for benign disease</li> <li>complex atypical hyperplasia/endometrial intra-epithelial neoplasia</li> </ul>	<ul style="list-style-type: none"> <li>Early Stage (Stage 1a1,,1a2) CIN 2-3</li> <li>Cervical AISInadequate colposcopy and concern for invasive cancer -mi. cervical cancer completely excised with CON or LEEP</li> </ul>	VAIN/VIN 2-3-	

CIN, cervical intraepithelial neoplasia; ChT, chemotherapy; CON, conization; D&C, dilation and curettage; D, delay up to; GTD-GTN, gestational trophoblastic disease and neoplasia; HT, hormonal therapy; LEEP, loop electrosurgical excision procedure, mi, microscopic; N, neoadjuvant; RT, radiotherapy; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; W, week.

**TABLE 5** Gynecologic cancer management guideline during the COVID-19 pandemic

Gynecologic malignancy		Preferred approach
Ovarian mass		
Suspected pelvic mass	RMI $\geq$ 200	Candidate for surgery (evaluate the possibility of surgery by MRI)
	RMI < 200	D3-6 <sup>M</sup>
New case, assess surgery possibility:	Possible	Surgery D2 <sup>W</sup>
	Impossible	Tissue biopsy or cytology then ChT (carboplatin $\pm$ paclitaxel + filgastrim)
Patients scheduled for IDS		Review the surgical possibility after 6 cycles of ChT, it is best performed 3-4 weeks after the end of ChT.
Patient scheduled for adjuvant ChT		Stop treatment earlier than planned, There is no evidence that 6 cycles of adjuvant ChT are superior to 5 cycles.
Recurrent ovarian cancer	Platinum sensitive	1. ChT for symptomatic patient 2. In asymptomatic patient delayed treatment or HT
	Platinum resistance	Alternative strategies to manage symptoms like endocrine therapy
Endometrial cancer		
Early stage, low grade (Grade 1)		D 10-12 <sup>W</sup> and conservative therapy with systemic HT or IUD.
Early stage with; comorbidity, obesity or unfit for operation		Conservative therapy with systemic HT or IUD or Intrauterine BRT (external RT could be delayed more)
Early stage with high-risk factor (grade 2, 3 or high-risk histology)		Surgery D 4 <sup>W</sup>
Advanced		Systemic therapy
Recurrences		Postponing treatment or HT is possible.
Cervical cancer		
CIN3		Diagnostic procedures (CON) d12 <sup>W</sup>
Microscopic invasion which completely resected via conization		Surgery D10-12 <sup>W</sup>
Early stage		When access to surgery is limited, consider radical RT or N. ChT (Def. RT is preferred to radical surgery)
1. Candidate for Def. RT or intrauterine BRT		No delay
2. Candidate for surgery like young patients who need to preserve ovarian function		Confirm localized disease with imaging <sup>a</sup> , D6-8 <sup>W</sup> is possible Consider SLNB if possible
Locally advanced		No delay for ChT-RT
Stage 4 or recurrences		Palliative ChT
Vulvar cancer		
VIN3		Surgery D several <sup>W</sup>
Early stage, Surgical candidate		Surgery D 4 <sup>W</sup> and SLNB if possible Consider radical RT or N. ChT as an alternative option
Stage 4 or the first recurrence		Palliative ChT (the first line)

BRT, brachytherapy; ChT, chemotherapy; ChT-RT, chemo-radiotherapy; CIN3, cervical intraepithelial neoplasm grade3; CON, conization; D, delay up to; HT, hormonal therapy; IUD, intra uterine device with levonorgesterol; IDS, interval debulking surgery; N, neoadjuvant; M, month; RMI: risk of malignancy index; calculated (based on CA125, menopausal status and ultrasound finding); RT, radiotherapy; SLNB, sentinel lymph node biopsy; VIN3, vulvar intraepithelial neoplasm grade 3; W, week.

<sup>a</sup>Imaging studies here conclude CT scan or PET/CT scan if accessible.<sup>13</sup>

- The suggestion in COVID-19 -infected patients is to postpone RT for 1-2 weeks.
- When there are limited anesthesia and imaging resources, the other choice in non-referable patients is the administration of two to three fractions per insertion with a minimum gap of 6 hours between each fraction and the use of a smaller applicator like "Smit sleeve" which eliminates the need for anesthesia.
- Postponing surgery in cervical cancer cases and planning for radiotherapy seems to be the best decision, which would be administered with a boost dose of 16-20G for 8-11 fraction); the alternative approach in patient with confirmed-nonbulky tumor, especially in reproductive age is surgery, obviously with permitted delay. In the aim of selecting patient that could be candidate for surgery, imaging could be helpful. The preferred modality in such

a situation is PET/CT scan, if feasible and the alternative method is CT scan.

10. As immunocompromised patients are at a higher risk of severe COVID-19 infection, in those with cervical or vulvar cancer who are candidates for definitive chemoradiotherapy, the suggested chemotherapeutic agent should be altered. It means that for patients under 70 years of age carboplatin should be replaced by cisplatin, as a lower immunosuppressive effect has been reported for cisplatin. On the other hand, those older than 70 years are solely a candidate for RT with no concurrent chemotherapy.
11. The suggested dose for reducing the number of sessions is 45G in 25 fractions and 50.4G in 28 fractions. Similarly, for patients older than 70 years radiation dose reduction is recommended.
12. In centers with no access to IMRT, the conformal radiotherapy method is acceptable, whereas in case of tumoral lymph nodes, an integrated boost technique should be used.

## 1.7 | What is on the way?

Our proposed guideline is based on the current limited known data on the coronavirus outbreak and our country's available resources. As cancer surgery is not an example of elective surgery, proper and individualized decision making regarding the operation schedule is necessary. Therefore, the present guideline providing recommendations for our society which has limited resources for confrontation with COVID-19 infected patients may not be completely applicable in other nations. While data on the nature of this virus and the management details are limited, the present guideline has provided some useful decision making and clinical judgment suggestions, but it should be kept in mind that updated data regarding this issue might be released in the near future.

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