



Short Communication

Management Options for Gynecological Cancers in Low- to Middle-Income Countries amidst COVID-19 Pandemic

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Abstract

Objective: Due to Covid-19 pandemic, the oncologists and cancer patients are in a dilemma, whether they should continue with the planned treatment or wait till the pandemic is over. This review is intended to explore the management options for gynaecological cancers during the pandemic. **Data sources:** We searched for literature from Pubmed database and oncological societies pertaining to the management of gynaecological cancers and Covid-19 pandemic. **Study Selection:** For such once in a century pandemic, there is a paucity of evidence based literature. Therefore, to address this issue all the available relevant studies were reviewed. **Results:** Definitely, a deviation from a standard care for a longer period i.e. beyond 4-6 weeks may lead to a significant impact on over all outcomes. As this current scenario is one of the first after the advent of modern medicine, there are no clear-cut evidence based suggestions to adopt for clinicians. Various organizations like NCCN, ACS, SGO, ESMO have suggested few recommendations for present situation. Here again, a role of multidisciplinary team is of pivotal importance and every case merits discussion by multi-disciplinary team (MDT) before finalizing a strategy. We share our perspective on the issue, which is based on currently available evidences as well as the practices we intend to follow at our centre. We agree that the quality of evidence remains of low grade and are mostly based on expert recommendations with an aim to tide over this period of around 4-12 weeks. **Conclusion:** Precise triage of patients will play a pivotal role in preserving resources and protecting health care workers and patients. The expertise at the respective oncology centres, prevalence/incidence of COVID-19 cases in that area, the support system of the hospital and the patient profile should direct the changes in practices. We also recommend that the standard therapy should be resumed as soon as the situation improves.

Keywords: COVID-19, gynecological cancers, pandemic

INTRODUCTION

The COVID-19 pandemic has made the world stand still. Almost every country is fighting to stop the spread of

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COVID-19 in the best possible manner. The biggest challenge is being faced by the medical fraternity, particularly oncology services. Cancer patients and oncologists are in a dilemma that whether they should continue the treatment or wait till the pandemic is over.

Health-care system of a country is usually the reflection of the economic strata of a country. The health-care system in low- to middle-income countries is not at par with the economic world and has limited human resources, medical supply, and infrastructure.

In this crisis situation, we should try to maintain an optimal quality of oncology services and at the same time, we need to ensure the safety not only of our patients, but also of their caretakers and our health-care workers. Therefore, it has become essentially indispensable to explore options that could reduce the frequency of surgical/medical interventions that may be associated with complexity, prolonged procedure or operative time, risk of major blood loss, necessitating blood products, risk of infection to the medical personnel, or admission to high-dependency unit or intensive care units (ICUs).

NEED FOR THE REVISED MANAGEMENT OPTIONS DURING THE COVID-19 PANDEMIC

The American College of Surgeons (ACS) and the Centers for Medicare and Medicaid Services have categorized most gynecologic cancer cases as semi-urgent (i.e., nonelective) surgeries, second only to trauma cases and surgical emergencies in their importance. The ACS further opines that if treatment of cancer cases is significantly delayed, this could result in a significant patient harm.^[1] Addressing this concern, Turaga and Girotra concluded in their comprehensive study involving >4 million cancer patients that most cancer surgeries can be safely delayed for around 4 weeks without having a significant impact on patient survival or cancer progression measured by completeness of resection.^[2]

Chemotherapy and other anticancer modalities may result in significant immune compromise in patients, rendering them more susceptible to viral and other infectious illnesses. The recent Wuhan experience of 1524 patients noted that the infection rate in cancer patients was double than that of the general population (odds ratio, 2.31; 95% confidence interval, 1.89–3.02).^[3] In addition, over 41% of COVID-19 infections were contracted in the hospital.^[4] Cancer patients admitted due to COVID-19 were at significantly higher risk of severe events (composite end point: percentage of patients admitted to ICU, ventilated, or death) compared with patients without cancer (seven [39%] of 18 patients vs. 124 [8%] of 1572 patients; $P = 0.0003$). Similarly, patients who underwent chemotherapy or surgery within the previous month had a numerically higher risk of severe events.^[5]

An important part of management of cancer during this period is to discuss in detail every aspect of modified strategies

to be adopted, with the patient. They have to be explained about the risks involved with multiple hospital visits and increased complications associated with chemotherapy and surgeries. They should also be explained about the likely harms caused by the delay in standard cancer therapy. If required, a documented consent taken by the clinician may also be appropriate.

The most contentious issue during the management of cancer is the time period for which the cancer therapy has to remain disrupted during this crisis. Definitely, a deviation from a standard care for a longer period, i.e., beyond 4–6 weeks, may significantly impact over all outcomes. As this current scenario is one of the first after the advent of modern medicine, there are no clear-cut evidence-based suggestions to adopt for clinicians. Various organizations such as National Comprehensive Cancer Network/European Society for Medical Oncology have suggested few recommendations for the present situation. Here again, a role of multidisciplinary team (MDT) is of pivotal importance, and every case needs discussion by the MDT before finalizing a strategy.

We are sharing our perspective on the issue, which is based on the currently available evidences as well as the practices we intend to follow at our center. We agree that the quality of evidence remains of low grade and are mostly based on expert recommendations with an aim to tide over this pandemic period. The changes in practices should be directed by the expertise at the respective oncology centers, prevalence/incidence of COVID-19 cases in that area, and the support system of the hospital and patient profile. The period of 4–12 weeks can be used as buffer for planning and prioritizing disease and stage specific treatment for patients on active treatment and for those who are on waiting list.

Organ-wise management options

A. Ovarian cancer

1. Ovarian cancer – early stage:
 - a. Symptomatic management
 - b. Wait and watch strategy.
2. Advanced ovarian cancer
 - a. Choice of neoadjuvant regimen (NACT)
3–4 weekly paclitaxel and carboplatin (TP) may be appropriate. Addition of growth factors during the course may be preferable^[6,7]
 - b. Intraperitoneal chemotherapy and other invasive procedures should be avoided
 - c. Patients should be started on poly ADP ribose polymerase inhibitors (PARPi), if eligible and affordable, after a good response to initial few cycles of chemotherapy
 - d. Oral hormonal monotherapy can be considered in patients with low-grade serous ovarian cancers^[6-9]
 - e. Post upfront cytoreduction, attempt should be made to start adjuvant chemotherapy (TP, 3–4 weekly) as early as possible.

3. Patients due for interval cytoreduction
 - a. Patients waiting for interval cytoreduction may go for few more cycles of chemotherapy with growth factor support
 - b. Patients with post 6 cycles of NACT may wait for 4–6 weeks for surgery
 - c. Emergency surgery indications – Obstruction, bowel perforation, peritonitis, torsion, and rupture of suspected malignant pelvic masses.
 4. Maintenance therapy
 - a. Oral PARPi can be considered in a patient with high benefit-to-risk ratio (i.e., BRCA mutation) and tumors with homologous recombination deficiency. Although PARPi is an expensive treatment, it should be offered to patients if they can afford it with the help of civil societies, nongovernmental organizations, or government aid
 - b. Olaparib demonstrated high efficacy as a maintenance treatment in first and subsequent lines of therapies for platinum-sensitive BRCA1/2-mutated ovarian cancer patients^[10,11]
 - c. BRCA testing should be done before starting first-line PARPi. Whereas patients with a positive family history who had already been tested for BRCA can be shifted on olaparib easily
 - d. Niraparib and rucaparib proved to be effective in maintenance setting for platinum-sensitive recurrent ovarian cancer regardless of BRCA status^[12,13]
 - e. For patients already on bevacizumab maintenance, therapy may be continued provided that drug-related complications such as hypertension are controlled.
 5. Recurrent disease
 - a. In platinum-sensitive recurrent disease, platinum-based chemotherapy should be offered
 - b. In patients with complete response or partial response to platinum-based chemotherapy, maintenance therapy with PARPi is recommended. Similarly, in those patients who cannot tolerate further platinum-based chemotherapy, PARPi may be offered as monotherapy in select cases^[14]
 - c. Platinum refractory cases should be managed symptomatically or with single-agent paclitaxel.
- B. Carcinoma cervix**
1. Carcinoma *in situ*/preinvasive disease: The American Society for Colposcopy and Cervical Pathology recommends that women presenting with low-grade cervical cancer screening test should postpone their further diagnostic assessment for 6–12 months. For women who are presenting with high-grade cervical cancer screening test, further diagnostic assessment could be delayed up to 12 weeks^[15]
 2. Early-stage cervical cancer: Although in early-stage carcinoma cervix radical trachelectomy or radical hysterectomy is recommended, in this scenario, it may be managed accordingly:
 - a. Patients with low-risk or microscopic disease (<2 cm, low-risk histology) could be considered for conization or simple trachelectomy ± Sentinel Lymph Node Biopsy (SLNB)
 - b. High-risk patients should postpone their surgeries for a period of 4–6 weeks or till the crises is over^[2]
 - c. Chemoradiation may be started wherever appropriate.^[16,17]
 3. Locally advanced/metastatic carcinoma cervix
 - a. Chemoradiation should be used in curative setting (Stage 1B3-IVA stages) with an expected high success rate (>50%).^[18-20]
 - b. Hypofractionation may be offered to reduce hospital visits
 - c. As per the American Brachytherapy Society, brachytherapy procedures should not be delayed in non-COVID patients
 - d. Stage IVB – Chemotherapy regimens such as paclitaxel + cisplatin + bevacizumab, 3–4 weekly, may be started. Cisplatin may be replaced with Paclitaxel and Carboplatin.
 4. Recurrent carcinoma cervix
- In recurrent cases, chemotherapy should be offered selectively amidst the COVID crisis. Cisplatin and paclitaxel (TP, 3–4 weekly) is the preferred doublet regimen and has shown better results for relapse developed after 12 months. Symptomatic management and deferring the chemotherapy may be tried in poor performance status and high-burden recurrent disease.^[21]
- C. Carcinoma endometrium**
1. Postmenopausal bleeding:
 - a. Many patients are unlikely to have access to an examination by their physician, so those with a low-risk profile, normal cervical screening history, and an endometrial thickness <4 mm could be managed by patient-initiated follow-up over a 3–6-month period.^[22]
 2. Low-risk and low-burden disease: Disease confined to endometrium with Grade 1 features can be managed by conservative managements:
 - a. Systemic hormonal therapy (endometrioid type, low grade)
 - b. Levonorgestrel intrauterine devices (Mirena®).^[23,24]
 3. High-risk and low-burden disease: Patients with Grade 2–Grade 3 histology
 - a. Patients may be considered for total abdominal hysterectomy with bilateral salpingo-oophorectomy ± SLN biopsy
 - b. Laparoscopic hysterectomy could be considered with a safe, reproducible, and reliable filtering

and evacuation system for pneumoperitoneum gases.^[25] As per the European Society of Gynaecological Endoscopy, laparoscopic surgery for gynecological emergencies and cancer is beneficial for the health system and the society by reducing hospital stay and enabling quicker recovery, compared to open surgery. Laparoscopy might have some advantage over open surgery by confining the surgical smoke to a closed space, which gives the opportunity to control the release of smoke to the operating room more effectively and reduce the exposure of the operating team.^[26] Therefore, laparoscopic gynecological surgeries could be performed with all personal protective equipment (PPE) and reliable smoke evacuation measures.

4. Advanced endometrial cancer
 - a. For advanced endometrial cancer, especially low grade, consider megestrol acetate,^[27] or megestrol acetate alternating with tamoxifen^[28] for endometroid histology, and if hormone receptor is positive
 - b. Neoadjuvant chemotherapy can be attempted if surgery is not feasible upfront
 - c. If operated and surgically staged upfront, adjuvant chemotherapy \pm radiotherapy should be initiated. The regimen may include standard regimen (TP, 3–4 weekly) with growth factors for prophylaxis.

5. Recurrent
 - a. Symptomatic management.

- D. Carcinoma vulva
 1. Early disease:

Radiotherapy may be considered as a nonsurgical option in selected cases.

2. Locally advanced/metastatic disease
 - a. Locally advanced disease: Neoadjuvant chemoradiation should be considered in this scenario^[29]
 - b. Metastatic disease: First-line chemotherapy may be considered based on the symptoms. Symptomatic support should be the mainstay in relapsed cases.

Special considerations in vulnerable population:

- Decision for all the modalities of treatment, specially chemotherapy doses and schedules, must take into account high-risk vulnerable population, i.e., patients with age >65 years, those with associated cardiovascular comorbidities, and those with preexisting respiratory conditions.

PRINCIPLE FOR MANAGING SURGERY OF CANCER PATIENTS DURING THE COVID CRISIS

After the study of >4 million cancer patients, Turaga and Girotra have documented safe postponement period (SPP) very precisely.^[2]

Table 1: Society of Gynaecologic Oncology Guidelines for emergent, semi-urgent, and nonurgent gynecologic oncology surgeries

Urgent/emergent immediate	Semi-urgent 1-4 weeks	Nonurgent >4-12 weeks
Viscous perforation Closed-loop bowel or colonic obstruction Incarcerated hernia with gynecologic tumor Vaginal, uterine, or pelvic hemorrhage Molar pregnancy Pelvic mass with torsion or causing urinary or intestinal obstruction	Establishment of cancer diagnosis when high suspicion exists (e.g., diagnostic laparoscopy and D and C hysteroscopy) Grade 1 endometrial cancer when hormonal therapy is contraindicated or not possible High-grade uterine cancers, all stages (e.g., epithelial and sarcoma histotypes) Cervical and vulvar cancers – surgery with curative intent Cervical and vaginal malignancies requiring radiation applicators Cervical AIS or inadequate colposcopy and concern for invasive cancer Advanced ovarian cancer, particularly interval CRS Abdominopelvic masses concerning for malignancy Symptomatic gynecologic cancer in pregnancy requiring surgery Patients with recurrent disease without nonsurgical options Symptomatic patients with inoperable primary or recurrent cancer requiring palliative cancer procedures (e.g., diverting colostomy, venting PEG tubes, but not including exenteration) Moderate-to-severe anemia requiring repeated transfusion Consider postponing total pelvic exenteration	Risk reducing surgery for genetic predisposition to gynecologic cancer Benign-appearing ovarian cysts/masses Hysterectomy for benign disease VAIN/VIN 2–3 CIN 2–3 CAH/EIN; Grade 1 endometrial cancer when hormonal therapy is not contraindicated Completion surgery for early-stage ovarian cancer Recurrent cancer requiring palliative resection

*CRS: Cytoreductive surgery, PEG: Percutaneous gastrostomy surgery, VAIN: Vaginal intra-epithelial neoplasia, VIN: Vulvar intraepithelial neoplasia, CIN: Cervical intraepithelial neoplasia, CAH/EIN: Complex atypical hyperplasia/endometrial intra-epithelial neoplasia

“For cancers treated with surgery first, the median SPP was 3 weeks (0-12 weeks) which is 6 (3-12) weeks from diagnosis. For 48% of cancer types, the SPP was at least 4 weeks. For cancers treated with neoadjuvant therapy, the median SPP was 8 weeks (0-12) which was 26 weeks from diagnosis. In 76% of cancer types the SPP was at least 6 weeks.”

The above-mentioned SPP cannot be generalized. Therefore, highly aggressive tumors such as uterine sarcoma could be taken up for surgery on priority.

Decision to perform surgery should be taken very judiciously and based on:

- Availability of workforce, resources, PPE, and preparedness of hospital
- Alternative treatment options such as chemotherapy and radiotherapy
- Biology of the disease and impact of surgery on survival (risk–benefit ratio)
- Type of surgery (major/minor), expected complications, and postoperative stay.

The Society of Gynaecologic Oncology guidelines have also kept most of the surgeries in semi-urgent category, and they may be considered as reference in decision-making^[30] [Table 1].

OUTPATIENT DEPARTMENT TRIAGE

Tele-consultation/video consultations

Tele-consultations may play a very crucial role during COVID-19 crisis. It is important and safe to reduce hospital visits for general medical, surgical, and palliative issues. We can also direct follow-up patients to delay their visits and should provide them the option of tele-consultations.

CONCLUSION

As an oncologist, the time we are facing is full of confusion and ambiguity. In our regional territories, we are having different priorities, laws, resources, and patient burden. Therefore, considering all these facts, we should be focused in providing optimal cancer treatment to the large number of cancer patients in waiting. Precise triage of patients will play a pivotal role in preserving resources and protecting health-care workers and patients. We also recommend that the standard therapy should be resumed as soon as the situation improves.

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Conflicts of interest

There are no conflicts of interest.

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