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Impact of COVID-19 on gynecological cancer management

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Abstract
The coronavirus disease 2019 (COVID-19) pandemic has affected every aspect of health care, including the delivery of standard care to patients afflicted with cancer. Patients with cancer may be at higher risk for COVID 19 morbidity or mortality than general population. Whether one can delay cancer procedures remains an ethical issue and there is not much clarity on management in these critical situation. Currently available literature on impact of COVID-19 on gynecological cancer management was reviewed. COVID-19 poses more risks to cancer patients especially who are older and have medical co-morbidities. On the other hand, gynecological malignancies require radical surgical procedures, complex prolonged radiation techniques, and myelosuppressive chemotherapy which make these patients more susceptible for COVID-19. A virtual multidisciplinary tumour board should conducted to plan their management. To limit the hospital visit, teleconsultation should be used to advise patients for pretherapy evaluation and post therapy follow up. Surgical decision making may be categories into three categories: patients with low, intermediate, or high acuity. Assessment of the severity of disease, co-morbidites, and logistic challenges along with COVID-19 burden in their area are important variables for individualized decision making. Safety of healthcare personnel needs to be ensured at the same time.
Currently available evidence is limited by small sample size and unfamiliarity with the full impact of this pandemic on cancer. However, the ongoing crisis will strain resources needed to deliver cancer care in the future.

Keywords: COVID-19, gynecological, higher risk

Introduction
The coronavirus 2019 outbreak is a rapidly and dramatically evolving situation and it is placing unusual strain on health-care systems around the world. The impact of this pandemic to all health care delivery system will vary based on COVID-19 burden and available local resources. Decisions regarding cancer care delivery should be individualized based on locoregional factors. The recent Wuhan experience of 1524 patients reported in JAMA Oncology noted that the infection rate in cancer patients was double that of general population (OR, 2.31; 95% CI, 1.89–3.02) [1]. In addition, over 41% of COVID-19 infections were contracted in the hospital [2]. Traveling to treatment centers and interacting with the healthcare team inevitably increases the patients' risk of contracting COVID-19. Gynecological malignancies need radical surgical procedures, complex prolonged radiation techniques, and myelosuppressive chemotherapy making these patients more vulnerable to COVID-19. We know that leaving cancer untreated is life threatening; there are various guidelines to guide us for effective management of the gynaecological cancer which need to be tailored according to the local situation. Some procedures are urgent, while some can be deferred. COVID -19 infection related fatality rates were markedly higher in old age (≥85 years old, ranging from 10% to 27%, followed by 3% to 11% among persons aged 65–84 years) and among patients with comorbidities: 11% for cardiovascular disease, 7% for diabetes, 6% for chronic respiratory disease, and 6% for cancer [3]. Hence, we need to weigh the benefit of cancer treatment against the risk of getting infected with the novel coronavirus. Considering the unprecedented dynamic situation and uncertain epidemiological trends, new policies and recommendations continue to evolve on a daily basis. Currently routine surgical procedures are almost at a halt worldwide, but whether cancer procedures can be delayed remains an ethical issue. The present article explores the impact of the COVID-19 on the management of gynaecological cancer patients and suggests possible options for providing them with optimum care.

General considerations for the cancer patients

1. Establishing a non-covid-19 unit: it is preferable to develop Non-COVID unit and treat COVID-19 positive and negative patients separately.
2. Limit patient visits to the hospital; only patients with one attendant should be encouraged to visit the hospital for treatment.
3. Utilize telemedicine facility to limit the visit to hospital for evaluation for treatment or follow up.
4. Multidisciplinary virtual tumor board meetings should be conducted to reach a prompt decision whenever possible.
5. All patients to be tested for COVID-19 before admission or initiation of cancer treatment and if positive, should be kept in COVID-19 ward; cancer treatment should be initiated after COVID-19 negative.
6. Staging investigation with non-contrast CT (NCCT) scan thorax should be included to rule out any asymptomatic pneumonia in addition to chest metastasis.
7. All health care workers should use PPE for clinical examination or any procedure of patients as there is a risk of transmission from asymptomatic patient too.
8. Consider local administration of chemotherapy if a patient lives far from the current infusion site or it requires traveling to a COVID-19 "hotspot".
9. Try to limit frequency of infusions; avoid weekly infusions. Consider single agent therapy or holding cancer-directed therapy for patients > 65 years old, patients at any age with significant co-morbidity (DM, chronic lung disease and cardiovascular disease) or ECOG status ≥2.[4] Patients with these co-morbid conditions appear to be at higher risk for severe COVID-19.
10. Consider oral therapies over infusion-based treatments when appropriate.
11. Surgeries should preferably be performed by the open method, to avoid aerosols in minimal invasive surgery. Staging procedures should preferably use sentinel lymph node biopsy as a method of lymph nodal staging to reduce the postoperative morbidity.
12. Consider liberal use of granulocyte colony stimulating factor.
13. Consider outpatient management of neutropenic fever when clinically stable. Maintain close follow-up with daily phone contact for at least 3 days to ensure no clinical deterioration [5].
14. Delay imaging after completion of treatment to a post-COVID-19 surge time unless important to patient's immediate care.
15. Consent for potential risk of COVID-19 infection during investigation & treatment.
16. Supporting patient's emotional well being and adequate psychosocial support systems will be more important than ever in this pandemic.

Surgical Decision Making and Stratification

Surgery in cancer cases is time sensitive. The decision to perform or postpone surgery should be made based on the type and stage of the disease, medical condition of the patient, burden of COVID-19 cases, and available logistic support including adjuvant treatment services [6]. An acuity scale is suggested by American College of Surgeons to guide gynaecologic oncologists whether to postpone or perform surgical procedures during the COVID-19 pandemic in the current phase in India (Table 1). Surgery that is unlikely to require adjuvant treatment may be a better case for consideration (Table 2). However, cases that are likely to require ICU care are also best postponed as these facilities may be reserved for COVID-19 positive cases. Its advisable to hold cancer-directed therapy for patients > 65 years old, patients at any age with significant co-morbidity (diabetes, chronic lung disease and cardiovascular disease) as COVID-19 infection-related fatality is highest in persons ≥85 years old, ranging from 10% to 27%, followed by 3% to 11% among persons aged 65–84 years, 1% to 3% among persons aged 55–64 years, below 1% among persons aged 20–54 years, and no fatalities among persons aged ≤19 years [7].

Table 1: Acuity Scale for surgical decision making
(Adapted from American College of Surgeons COVID-19 recommendations for management of surgical procedures for gynaecological cancer)

Category	Examples	Suggested plan
Low acuity surgery (not life threatening)	Treatment of pre-invasive lesions of cervix or endometrium	Postpone surgery for few weeks or months e.g. conization to rule out invasion may be delayed for weeks but for HSIL may be delayed for months
Intermediate acuity surgery (Not life threatening but has potential for future morbidity and mortality)	Low-risk cancer (e.g. early cervical cancer, well differentiated endometrial cancer with comorbidities)	Postpone surgery if possible after informed decision making or consider early discharge. Cases with comorbidities should preferably be counselled for rescheduling surgery
High acuity surgery/ healthy patient (Life threatening)	Most cancers, highly symptomatic patients (Type II endometrial cancers, ovarian cancer, interval debulking surgery after 3–4 cycles of chemotherapy, uterine sarcoma, those in need of emergency procedures, GTN)	Do not postpone if COVID-19 burden low and resources permit. Virtual multidisciplinary tumor board discussion and planning of therapy is advisable prior to surgery.

(HSIL = High grade squamous intraepithelial lesion, GTN = Gestational trophoblastic neoplasia)

Table 2: Management of common gynecological cancers in COVID-19

Cervical cancer	Ovarian cancer	Endometrial cancer
1. Early stage (stage 1A, B1, B2, IIA1) = Radical hysterectomy with B/L pelvic lymph node dissection. Adjuvant chemotherapy if high risk factor. Avoid radiation for intermediate risk factors	1. Early Stage (stage I & II) = Staging laparotomy followed by adjuvant chemotherapy.	1. Stage I-III = Staging laparotomy, avoid radiation for low & intermeadiate risk factor, vault radiation for high risk factors.
2. Locally advanced cancer (stage1B3 IIA2 - IV) chemoradiation.	2. Advanced stage (III & IV) =NACT followed by IDS. Defer surgery as far as possible.	2. Advanced stage/inoperable = progesterone therapy, radical radiotherapy with brachytherapy
3. Relapse/Recurrent: single fraction radiation.	3. Relapse /Recurrent = chemotherapy with least myelosuppressive potential	3. Recurrent /Relapse = chemotherapy with least myelosuppresive potential
Performance Status 3 - 4 = Best supportive care		

(NACT= Neoadjuvant chemotherapy, IDS = Interval debulking Surgery)

Endometrial Cancer

A delay in surgery of more than 6 weeks was associated with the worst overall survival (OS) in type I endometrial cancers, with stages I and II only. High-dose progesterone has been shown to be effective in reversing the estrogenic effect on the endometrium in a good number of cases and has been used in fertility-preserving protocols [8]. Most cases of type I histology are estrogen/ progesterone-receptor positive and it would be worthwhile to start these patients on hormonal therapy to reduce progression if surgery is not possible within the 6 weeks in present resource-constrained settings. Adjuvant therapy in completely staged patients could be avoided, especially if the patient has co-morbidities and is elderly with a high risk of COVID-19 fatality. Adjuvant radiotherapy even in the presence of high and intermediate risk factors (age >or = 60, poor grade, presence of lymphovascular emboli) decreases the local recurrence rate, but has no impact on OS [9]. Hence, the risk and benefit of adjuvant radiation should be discussed can be deferred or omitted accordingly. Patients with high-risk factors (residual disease, positive resection margins, or aggressive histological subtype) should only be considered for vault brachytherapy [10] or can be deferred or omitted. Adjuvant treatment is given to decrease the chance of recurrence over the next 5 years [9]. If the disease recurs, it can be salvaged at a later date. This strategy will decrease the hospital visits of patients, thus limiting their exposure. In the PORTEC 3 trial, 4 cycles of paclitaxel-carboplatin led to an increase in the 5-year Overall Survival (OS) from 76.1% to 81.4%. Hence, this needs to be discussed [10].

Recommendation

Operable endometrial cancer surgery can be deferred for up to 6 weeks. Adjuvant radiation can be deferred in high-risk cases and omitted for the rest. In inoperable cases, either progesterone or radical radiation with brachytherapy can be administered.

In advanced disease, palliative therapy with chemotherapy with paclitaxel-carboplatin should be offered, except in the COVID-19 high-risk fatality cohort; in them, progesterone or palliative radiation can be offered.

Ovarian Cancer

Suspected early-stage ovarian cancer

Adenexal masses suspected to be cancerous should undergo immediate staging laparotomy as they constitute only 10%–15% of all ovarian cancer cases [11]. Primarily resected ovarian cancer mandates adjuvant therapy as per the guidelines, except for grade 1 or 2 stage I disease [11]. In the current situation of the COVID-19 pandemic, single-agent carboplatin can be considered a suitable option as there is limited evidence of benefit of combination therapy in early stage ovarian cancer. In patients over 60 years of age with co-morbidities, single-agent carboplatin can be considered to reduce the risk of neutropenia.

Advanced disease

Neoadjuvant chemotherapy followed by surgery has been shown to be no inferior to primary surgery and adjuvant chemotherapy in advanced-stage ovarian cancer [12].

During cytoreductive surgery, an optimal cytoreduction defined as no visible microscopic disease should be attempted [13]. However, ultraradical surgery, paraaortic lymph node dissection and extensive resection should be avoided [14]. It is worthwhile to withhold hyperthermic intraperitoneal chemotherapy in the centers where it is practiced, as the additive benefit of this procedure is minimal [15] and it delays postoperative recovery considerably. The choice of adjuvant or neoadjuvant therapy should be paclitaxel and carboplatin administered once in 3 weeks [16]. In patients at a high risk of COVID-19, single-agent carboplatin or metronomic chemotherapy can be considered to reduce the risk of immunosuppression. Delaying chemotherapy has an adverse impact in carcinoma ovary, and the OS decreases by 4% for each week of delay in initiating adjuvant chemotherapy [17]. Emergency procedures such as bowel obstructions should undergo treatment as required.

Recurrent

The intent of therapy based on the disease-free survival, the extent of disease and the symptoms of the disease will guide the promptness of therapy. The decision should be taken after discussion with the patient and the relatives by weighing the risk of getting COVID-19 and treatment of the disease. In case of asymptomatic recurrences or only CA-125 elevation, delaying treatment is a valid option [18]. In case of symptomatic recurrence, less intensive regimens such as single-agent carboplatin (platinum-sensitive disease) or single-agent paclitaxel [19] or metronomic combination [20] or poly (ADP-ribose) polymerase inhibitor [21] with growth factor support can be considered to minimize the risk of neutropenia and thrombocytopenia. Palliative care options for extensive disease, must be discussed with the patient and the caretakers.

Recommendation

Early stage ovarian cancer staging laparotomy should not be delayed and adjuvant chemotherapy should be offered with single-agent carboplatin (COVID-19 high-risk patient) or paclitaxel-platinum in others. For advanced disease, neoadjuvant therapy with single-agent carboplatin (COVID-19 high-risk patient) or paclitaxel-platinum in others, and cytoreduction should be performed after 3–6 cycles. If recurrent cases are symptomatic, only then systemic therapy should be offered. Single-agent therapy or metronomic combination should be preferred.

Cervical Cancer

Early Stage (stage I A1, 2, I B1, B2, IIA1)

Early-stage cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] 2018) should undergo surgery within 4 weeks of diagnosis. A delay beyond this time leads to a 1% per day decline in local control. Hence, early treatment initiation is necessary. Both surgery and radiation have equivalent control rates in early-stage cervical cancer [22].

Chemoradiation

For cervical cancers, pelvic radiotherapy with concurrent platinum-based chemotherapy remains the standard of care and should be initiated within 4 weeks, and treatment should be completed without any unnecessary delays or breaks [23]. A minimum number of fractions should be used. The use of concurrent cisplatin is associated with a 10% absolute improvement in the OS [24] and hence should be administered even in the current pandemic in early-stage cervical cancer.

Locally advanced stage (IB3, IIA2, IIB–IVA)

Radical chemoradiation should be administered without any delay. In a large population-based analysis by Nandakumar *et al.*, in 1,753 patients with locally advanced cancers, significantly better survival was observed with chemoradiation (70.2% vs. 47.3%; hazard ratio, 0.48; 95% CI, 0.41–0.56) over radiation alone [25].

Brachytherapy

Delay in brachytherapy procedures for cervical cancer patients may have a serious adverse effect on the outcomes and should not be delayed in non COVID-19 patients. In patients who have begun cancer treatment, including brachytherapy, and are COVID-19 negative should complete their treatment [26]. Patients from centers that cannot deliver brachytherapy because of limited availability of resources due to COVID-19 situations should be referred appropriately to higher facilities and should seek expert opinion if deviating from the protocol.

Recommendation

Early stage cervical cancer - If surgery alone can suffice, then radical hysterectomy with pelvic lymph node dissection should be performed. If not or in the presence of locally advanced cervical cancer, radical chemoradiation should be administered. The treatment should start within 4 weeks and should not be unnecessarily delayed. Concurrent cisplatin is necessary and should be administered unless the patient has a high risk of COVID-19 infection-related fatality. Palliative treatment in recurrent-relapsed cancer can be offered in single-fraction radiation schedules.

Vulval Cancers

Early stage-Surgery can be avoided for 4–6 weeks, considerations should be given for sentinel node biopsy to avoid groin wound complications as only 25%–30% of early-stage vulvar cancers have nodes harboring disease [27]. Locally advanced disease - Surgery is urgent and should be performed as early as possible. Adjuvant radiation should be limited to settings with proven benefit as mentioned above. Locally advanced unresectable or metastatic disease-Palliative single-fraction radiation can be used.

Gestational Trophoblastic Neoplasia

Gestational trophoblastic neoplasia (GTN) is a rare tumor which originates from the placental tissues and is a highly curable malignancy. Immediate treatment is required, since a delay in the treatment may lead to the occurrence of tumor chemoresistance or even metastatic disease, necessitating multiple agent chemotherapy [28].

GTN needs to be considered urgent, and treatment should be done in accordance with standard guidelines, irrespective of the COVID-19 pandemic situation.

Germ Cell Tumor

Germ cell tumors, a disease of young individuals and being chemo-sensitive, the treatment must be considered urgent. Malignant ovarian germ cell tumors are rare but curable at all stages of disease. Appropriate chemotherapy must be initiated as per the standard guidelines for treatment, and delay should be avoided.[29] Surgery for residual disease should be delayed for 6–8 weeks post chemotherapy but should be performed on an urgent basis if required [30].

Germ cell tumor management needs to be considered urgent, and should be done in accordance with the standard guidelines [31] irrespective of the COVID-19 pandemic situation.

Discussion

- Neoadjuvant chemotherapy for ovarian cancer compared with primary surgical debulking can reduce morbidity and reduce risk of hospitalization over primary surgical debulking especially in high COVID-19 burden areas [32].
- Delaying interval debulking surgery beyond 3–4 cycles of neoadjuvant chemotherapy can reduce morbidity and hospitalization for patients with ovarian cancer.
- Choose regimens that necessitate the less infusion visits (i.e., 3 week paclitaxel/carboplatin). Consider avoiding/ limiting the prescription of dose-dense, intraperitoneal, and HIPEC regimens.
- Consider oral hormonal mono-therapy in patients with low-grade serous ovarian cancers [33].
- For early endometrial cancer, treatment with progesterone therapy or a progesterone containing IUD may decrease bleeding and provide temporizing benefit if primary surgery is delayed for lower grade cancers [34].
- For advanced /recurrent endometrial cancer consider the use of megestrol acetate, or megestrol acetate alternating with tamoxifen for endometrioid endometrial cancer or if estrogen/progesterone receptor status positive [35]. Oral letrozole may have a better response rate compared to hormonal therapy alone but the impact of the increased toxicity and possible immunosuppression should be considered [36].
- Avoid radiation if possible unless for curative intent (i.e., locally advanced cervical cancer)
- For patients with recurrent cervical cancer who have received prior cisplatin, consider paclitaxel /carboplatin over paclitaxel/cisplatin based regimen due to shorter total time in infusion center and less toxicity [37].
- For Stage IV primary high grade endometrial and cervical cancers, consider delaying/deferring non-curative treatment, especially if patients are older or possess significant co-morbidity unless to control symptoms that may necessitate/lead to hospitalization.

Conclusion

During the COVID-19 pandemic, patients with cancer should be treated with careful utilization of resources and with an effort to reduce the chance of progression and the risk of getting infected with COVID-19. All care should consider the risks of cancer care balanced against the risk of COVID-19 infection with special consideration to older age and patients with co-morbidities.

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Compliance with Ethical Standards

Conflict of interest the authors declare that there is no conflict of interest.

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