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COVID-19 and gynecological cancers: Asia and Oceania Federation of Obstetrics and Gynecology oncology committee opinion

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Abstract

Since the outbreak of COVID-19, there have already been over 26 million people being infected and it is expected that the pandemic will not end in near future. Not only the daily activities and lifestyles of individuals have been affected, the medical practice has also been modified to cope with this emergency catastrophe. In particular, the cancer services have faced an unprecedented challenge. While the services may have been cut by the national authorities or hospitals due to shortage of manpower and resources, the medical need of cancer patients has increased. Cancer patients who are receiving active treatment may develop various kinds of complications especially immunosuppression from chemotherapy, and they and their carers will need additional protection against COVID-19. Besides, there is also evidence that cancer patients are more prone to deteriorate from COVID-19 if they contract the viral infection. Therefore, it is crucial to establish guidelines so that healthcare providers can triage their resources to take care of the most needed patients, reduce less important hospitalization and visit, and to avoid potential complications from treatment. The Asia and Oceania Federation of Obstetrics and Gynecology (AOFOG) hereby issued this opinion statement on the management of gynecological cancer patients during the COVID-19.

Key words: AOFOG opinion, COVID-19, gynecological cancer.

Introduction

The COVID-19 pandemic has become a global problem with more than >26 million confirmed cases and >0.8 million deaths.[1] Although the situation is being settled in certain countries, there are still transmission from overseas countries. Cancer patients are found to be more susceptible for deterioration from

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COVID-19 and overall deaths than those without cancer.[2,3] Cancer survivors also remain an important at-risk population for COVID-19. Yet with the limited resources, cancer services can be significantly interrupted due to limited sanitary materials and manpower. Many academic societies have already published their guidelines on cancer care during the COVID-19 pandemic. Here, the Asia and Oceania Federation of Obstetrics and Gynecology (AOFOG) would like to make a general recommendation for gynecological cancer care in Asia.

General Principles

All patients, care providers and staff who have symptoms like fever, cough, or other respiratory symptoms and travel history must be screened for covid-19. Those who have travel history should be self-isolated according to national guidelines.

Patients and their carers should be educated with the knowledge about the signs and symptoms of COVID-19, as well as the general hygienic measures.[4] This includes, but not limited to, frequent and proper hand washing, wearing masks, proper handling of used masks, avoiding contacting eyes and noses, physical distancing and avoiding travels. Cancer patients and survivors should use stronger personal protection.

Patients who have symptoms should not attend oncology clinics or ward, but to consult their family doctors or Emergency Department and rule out COVID-19. Measures should be taken to restrict the duration of visiting hours and limit the number of people accompanying the patients. Communication with patients' family or friends should be maintained by phone or other video systems upon patients' agreement.

Medical care providers have to be equipped with qualified protection goggles, masks, surgical gowns and gloves. As they may need to help with critical care patients, resuscitation training may need to be refreshed and back-up duty roster should be in place. A national centralized reporting system should be available, and updated and accurate news should be disseminated to the public on time. However, as the situation is evolving from time to time and different centers have different capacity, the management has to be individualized and well-documented.

New Case Referral

Patients should be triaged according to severity of symptoms, nature of the disease, availability of shared care with family physician, chance of cure and physical fitness of the patients. As there was evidence that cancer patients undergoing surgery and/or chemotherapy were at risk of developing severe complications of COVID-19, decision has to be made whether elective surgery or adjuvant chemotherapy for certain cancer patients especially those with stable disease can be postponed (see Sections 4 and 5). The AOFOG recommendation is modified from the Asian Society of Gynecologic Oncology (Table 1).[5]

Surgery

Triage of the operations should be performed where resources are restricted, and should be based on factors such as patients' symptoms, biology of the diseases, expected life expectancy, intent of the operations, complexity of the operations and the likelihood of intensive care unit /high dependency unit requirement.[6] The decision should be fully discussed in multidisciplinary team and communicated to the patients and their family. One example of recommendations on the triage of operation by British Gynaecological Cancer is listed in Table 2.[7]

The number of operation room staff should be kept to the minimum that can maintain the normal services, and an alarm or other system should be available that can call for help immediately during emergency situation. In addition, centers which have experience in sentinel lymph node biopsy should utilize this to replace full lymphadenectomy to shorten the operation duration, reduce intra-operatively bleeding and post-operative complications. Enhanced recovery pathway should be adopted to reduce hospital stay.

Minimally invasive surgery include robotic surgery can shorten patients' hospital stay, and can minimize spillage of body fluid and number of directly-exposed medical staff.[8] There is no evidence of aerosolization of the COVID-19 during minimally invasive surgery. However, it is recommended to take the below measures to prevent gas dispersal[8–11]:

1. Close the taps of the ports to avoid escape of gas during insertion.

Table 1 Prioritization of new case referral[5]

Priority	Examples
A	Condition is life-threatening or needs emergency care
Cancer (CA) cervix	Severe symptoms like massive and/or persistent bleeding, pain, bowel perforation and thromboembolism; stage Ia2–IIa1
CA corpus	Severe symptoms like massive and/or persistent bleeding, pain, ascites
CA ovary	Suspected ovarian cancer with symptoms like bowel obstruction/perforation, massive ascites, or peritonitis; suspected post-treatment complications like anastomotic leak, neutropenia; aggressive histology like high-grade serous/endometrioid
B	Condition is non-life threatening and could be deferred 6–8 weeks during the COVID-19 pandemic
CA cervix	Suspected of invasive cervical cancer on cervical smears; stage IIa2 and above; post-treatment with intermediate/high risk of recurrence like occult cervical cancer after simple hysterectomy; recurrent diseases
CA corpus	Early stage/high risk and advanced stage requiring primary treatment; post-treatment requiring adjuvant therapy like stage II requiring adjuvant radiotherapy; recurrence diseases
CA ovary	Suspected early stage asymptomatic ovarian cancer; more indolent histology like non-high-grade serous/endometrioid; symptomatic platinum-sensitive recurrence
C	Condition is stable even in the discontinuation of treatment during the current COVID-19 crisis
CA cervix	Stage Ia1 based on large loop excision of eransformation zone pathology; post-treatment with low risk of recurrence
CA corpus	Post-treatment with low risk of recurrence; distant recurrence without symptoms
CA ovary	Post-treatment ± maintenance therapy; symptomatic platinum-resistant recurrence; symptomatic slow recurrent diseases; asymptomatic recurrent diseases

2. Care should be taken not to make a big incision to avoid dislodgement of the port and hence air leakage during the operation.
3. Use the minimally required intra-abdominal pressure to 8 mmHg.
4. Connect one of the ports to an Ultra-Low Particulate Air suction device that can filter 99.999% of particles with penetration size of 0.05 μ, where the size of SARS-CoV-2 virus is 0.06–0.14 μ.[12]
5. Avoid using ultrasonic sealing devices but to use electro-thermal bipolar cautery with the lowest required power.
6. Do not open the taps of any ports that are not used for insufflation or deflation.
7. Minimize the change of instrument if possible.
8. If the insufflation port needs to be changed to another port, close the insufflator, close the tap of the port and then reconnect the tubing from the

Table 2 Prioritization of gynecological cancer surgery[7]

Level	Type	Best timing	Examples
1a	Emergency	≤24 h	Anastomotic leak, bowel perforation, peritonitis, burst abdomen, torsion or rupture of suspected malignant pelvic masses, heavy bleeding from molar pregnancy requiring initial or hysterectomy
1b	Urgent	≤72 h	Acute mechanical intestinal obstruction, impending bowel perforation, life-threatening bleeding from cervical or uterine cancer where benefit outweigh urgent radiotherapy
2	Elective – early	≤4 week	Suspected germ cell tumors, early-stage cervical cancer, high grade/high risk uterine cancer, suspected early-stage ovarian cancer, delayed debulking surgery (timed to chemotherapy schedules) for advanced epithelial ovarian cancer where intensive care unit /high dependency unit capacity permits, resection of primary vulval tumor
3	Elective – delayed	≤10–12 week	Early-stage /low-grade uterine cancer, microinvasive cervical cancer completely excised at loop excision

original port to a new port. Turn on the insufflator first before opening the tap of the new port to avoid back-flowing of the gas into the insufflator.
9. Deflate the abdomen into the suction device first before retrieving specimens from the abdominal wound or removing the uterus out of the vagina to avoid sudden gas dispersal.
10. Release the pneumoperitoneum in a controlled manner at the end of the operation before removing the ports.

Chemotherapy, Radiotherapy, Targeted Therapy and Immunotherapy

If cancer facility has to be interrupted, prioritization should be considered. The UK has provided a guidance on the prioritization of systematic anti-cancer treatment and radiotherapy Tables 3 and 4).[13]

Patients receiving certain anti-cancer treatment are at risk of neutropenia and immunosuppression. Lee *et al*. reported that among 281 patients who received chemotherapy within 4 weeks before their positive COVID-19 results, the use of chemotherapy in the past 4 weeks had no significant impact on the mortality from COVID-19 compared with those who did not receive recent chemotherapy (1.18, 95% confidence interval (CI) 0.81–1.72; $P = 0{\cdot}380$).[14] However, Zhang *et al*. showed that severe complications from COVID-19 was significantly associated with the use of anti-cancer therapy in the past 14 days among their 28 patients (hazard ratio [HR] 4.079, 95% CI 1.086–15.322, $P = 0.037$).[15] With limited data, it is legitimate to withhold anti-cancer treatment during active COVID-19 infection as further anti-cancer treatment may potentially lead to immunosuppression and aggravate COVID-19.

For those who have recovered from COVID-19, it is uncertain when is the best time to resume the anti-cancer therapy. The ASCO considers it is reasonable to resume anti-cancer treatment once transmission-based precautions can be considered based on Centers for Disease Control and Prevention guideline.[16,17] For example, for those with laboratory-confirmed COVID-19, they should be at least 10 days from the date of their first diagnosis of COVID-19 or first appearance of symptoms, or two consecutive negative SARS-CoV-2 RNA results from their respiratory specimens collected ≥24 h apart.

The medical carers should educate the patients and their carers to watch out for symptoms of COVID-19, their cancer and complications, as well as flare-up of their underlying co-morbidities. They should also provide enough medications, reduce non-urgent hospital visits, consider replacing parental medications with oral drugs and use shorter treatment regimens. For example, for platinum-sensitive recurrent ovarian cancer patients who are either breast cancer susceptibility gene (BRCA)

Table 3 Prioritization of systemic anti-cancer treatment[13]

Priority	Treatment
1	• Curative treatment with a high (more than 50%) chance of success • Adjuvant or neoadjuvant treatment which adds at least 50% chance of cure to surgery or radiotherapy alone or treatment given at relapse
2	• Curative treatment with an intermediate (20–50%) chance of success • Adjuvant or neoadjuvant treatment which adds 20–50% chance of cure to surgery or radiotherapy alone or treatment given at relapse
3	• Curative treatment with a low (10–20%) chance of success • Adjuvant or neoadjuvant treatment which adds 10–20% chance of cure to surgery or radiotherapy alone or treatment given at relapse • Non-curative treatment with a high (more than 50%) chance of more than 1-year extension to life
4	• Curative treatment with a very low (0–10%) chance of success • Adjuvant or neoadjuvant treatment which adds less than 10% chance of cure to surgery or radiotherapy alone or treatment given at relapse • Non-curative treatment with an intermediate (15–50%) chance of more than 1-year extension to life
5	• Non-curative treatment with a high (more than 50%) chance of palliation or temporary tumor control and less than 1 year expected extension to life
6	• Non-curative treatment with an intermediate (15–50%) chance of palliation or temporary tumor control and less than 1 year expected extension to life

mutated or whose tumor are homologous recombination deficient, PARP inhibitor can be considered instead of non-platinum chemotherapy based on the SOLO-3 and QUADRA trials.[18,19] For platinum-resistant/refractory recurrent ovarian cancer patients, one may choose 4-weekly liposomal doxorubicin, oral chemotherapy like cyclophosphamide or etoposide, instead of weekly gemcitabine, 5-day topotecan or weekly paclitaxel as second-line chemotherapy. The frequency of immunotherapy can be lengthened, such as pembrolizumab 400 mg every 6 weeks, nivolumab 480 mg every 4 weeks and atezolizumab 1680 mg every 4 weeks.[20] G-CSF should be administered promptly for those who are at risk of developing neutropenia.

Summary of Care for Gynecological Cancers

A summary based on recommendations from other groups is listed in Table 5.[20–24]

Special High-Risk Groups

Elderly patients are a major group in gynecological cancer. An Italian study showed that the average age of death from COVID-19 was 80 years old, and most of them had other co-morbidities such as diabetes and cardiovascular diseases.[25] Other high-risk patients, other than cancer, also includes those with organ transplantation, bone marrow/stem cell transplantation, hematological malignancies, severe lung diseases, immunocompromised conditions, pregnancy, obesity, diabetes, chronic cardiovascular, kidney and liver diseases.[26]

Physical distancing of at least 2 m away from the others, staying at home, avoiding too many home visitors, ordering food and groceries through delivery services, frequent hand washing with soap and water for at least 20 s should be discussed with the high-risk group.[27] It is important to keep engaging the elderly with social relationship, and this can be maintained by teaching them how to use phone, video calls and internet.

Multidisciplinary Meeting

Multidisciplinary meeting should be continued on regularly basis, especially treatment may need to deviate from the usual practice and prioritization of treatment may need to be adapted. Instead of face-to-face meeting, online meeting should be considered using Zoom,

Table 4 Prioritization of radiotherapy[13]

Priority	Treatment
1	• Patients with category 1 (rapidly proliferating) tumors currently being treated with radical (chemo)radiotherapy with curative intent where there is little or no scope for compensation of gaps. • Patients with category 1 tumors in whom combined External Beam Radiotherapy (EBRT) and subsequent brachytherapy is the management plan and the EBRT is already underway. • Patients with category 1 tumors who have not yet started and in whom clinical need determines that treatment should start in line with current cancer waiting times.
2	• Urgent palliative radiotherapy in patients with malignant spinal cord compression who have useful salvageable neurological function.
3	• Radical radiotherapy for Category 2 (less aggressive) tumors where radiotherapy is the first definitive treatment. • Post-operative radiotherapy where there is known residual disease following surgery in tumors with aggressive biology.
4	• Palliative radiotherapy where alleviation of symptoms would reduce the burden on other healthcare services, such as hemoptysis.
5	• Adjuvant radiotherapy where there has been compete resection of disease and there is a < 20% risk of recurrence at 10 years.

Webex or equivalent. If face-to-face meeting is deemed necessary, it is advised to limit to one representative from each team. And importantly, patients and family members should be adequately informed about the benefit and risk of each intervention in order to make a consensus of the treatment plan.

Follow-Up

Patients who are in disease remission should be deferred from routine follow-up, and those with stable active disease should have less frequent hospital visits. Follow-up by phone or video should be

Table 5 Summary of the management approach in carcinoma of cervix, corpus and ovary

Diseases	Alternative strategies
CA cervix	
Early stage	Defer those potentially long operations like radical hysterectomy till resources become available. Neoadjuvant chemotherapy can also be considered.
Locally advanced	Consider hypofractionation.
Recurrent	Consider carboplatin/paclitaxel instead of cisplatin / paclitaxel. Consider delaying non-curative treatment.
CA corpus	
Early-stage low-risk	Defer operations for 1–2 months and use progestogen at the meantime.
Early-stage high-risk	Hold radiotherapy unless this is for curative intent.
Advanced stage	Consider to use chemotherapy first instead of upfront surgery.Hold radiotherapy unless this is for curative intent or severe symptoms like heavy bleeding.
Recurrent	Consider to use megestrol acetate, or megestrol acetate alternating with tamoxifen if estrogen/progesterone receptors are positive. Consider delaying non-curative treatment.
CA ovary	
Early-stage low-risk	If restaging surgery is required, it should be deferred from 1–2 months. Hold chemotherapy for controversial histology groups, such as stage 1c1 mucinous carcinoma.
Advanced stage	Consider neoadjuvant chemotherapy instead of upfront surgery, and administer 6 cycles instead of 3.Choose 3-weekly carboplatin/ paclitaxel instead of dose-dense therapy.Reduce the use of hyperthermic intra peritoneal chemotherapy or intraperitoneal chemotherapy.For those BRCA/high dose rate (HRD) positive and platinum-sensitive patients, consider to use oral poly (adenosine diphosphate-ribose) polymerase inhibitor (PARPi) instead of bevacizumab for maintenance.For those not eligible for PARPi, need to balance the benefit of bevacizumab and the need of frequent hospital visit and risk of COVID-19.
Progressive/recurrent	For those BRCA/HRD positive and platinum sensitive patients, consider to use oral PARPi instead of bevacizumab for maintenance. For those not eligible for PARPi, need to balance the benefit of bevacizumab and the need of frequent hospital visit and risk of COVID-19.Consider delaying non-curative treatment.
Rare tumors	
Uterine leiomyosarcoma	Hold chemotherapy for stage I disease.Choose doxorubicin, or oral aromatase inhibitors if estrogen receptor is positive, or pazopanib, instead of combination chemotherapy
Gem cell tumor	Hold bleomycin in dysgerminoma.
Low-grade serous CA ovary	Consider aromatase inhibitor monotherapy instead of chemotherapy in advanced/recurrent patients.
Gestational trophoblastic neoplasia	Low risk: Consider pulse actinomycin-D instead of methotrexate.High risk: Consider immunotherapy instead of combination chemotherapy.
Vulvar cancers	Postpone treatment for a few weeks if a tumor is not progressing much in elderly patients.Consider neoadjuvant chemo-irradiation in advanced diseases.

considered. They should be given a contact number so that they can advance their appointment if they develop any symptoms.

Clinical Trials

The number of active trials should be limited and priority should be given to those trials that are curative intent, and those that offer drugs where there are limited effective therapies.[20,21] The local ethics committee and sponsors should be informed about the potential deviation of the study drugs and monitoring from study protocol. Toxicity review by video or phone, and mail delivery of oral medicine should be considered. Those who are positive for COVID-19 should stop the trial intervention and obtain the standard care of the COVID-19.

Disclosure

None declared.

Resources

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