Recommendations on management of gynecological malignancies during the COVID-19 pandemic: perspectives from Chinese gynecological oncologists

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ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 has rapidly spread globally. Cancer patients are at a higher risk of being infected with the coronavirus and are more likely to develop severe complications, as compared to the general population. The increasing spread of COVID-19 presents challenges for the clinical care of patients with gynecological malignancies. Concerted efforts should be put into managing gynecological malignancies in an orderly manner by strictly implementing the measures that are specifically developed for controlling the spread of COVID-19. We have drafted Recommendations on Management of Gynecological Malignancies during the COVID-19 Pandemic based on our experience on controlling COVID-19 pandemic in China. We recommend that patients with gynecological malignancies should be managed in hierarchical and individualized manners in combination with local conditions related to COVID-19. Medical care decision should be balanced between controlling COVID-19 pandemic spread and timely diagnosis and treatment for gynecologic oncology patients.
INTRODUCTION

Since its first identification, coronavirus disease 2019 (COVID-19) has spread over 200 countries with 2,544,792 cases and a total of 175,694 deaths worldwide (as of April 24, 2020), according to the World Health Organization reports (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports). COVID-19 is a severe disease caused by a newly discovered virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 belongs to the β genus family of coronavirus, to which human are susceptible [1,2]. Unlike healthy subjects in general public, patients with malignancy are in a hypo-immune state. They are therefore more susceptible to SARS-CoV-2 infection and prone to develop severe COVID-19, especially those undergoing surgery, chemotherapy or radiotherapy [3]. In China, the situation has improved significantly since the COVID-19 outbreak, with both new cases and case fatality reducing markedly. However, the risk posed by imported cases and viral rebound is significant and high vigilance is thus required to contain the spread of the infection. There have been significant needs for a well-organized and managed medical infrastructure to safe-guard the basic health care of patients during COVID-19 pandemic. It is in this realization that we have developed Recommendations on Management of Gynecological Malignancies during the COVID-19 Pandemic to share our experience in the management of patients with gynecological malignancies during the pandemic.

CLINICAL PRESENTATION AND DIAGNOSIS OF COVID-19

Fever, cough, and fatigue are the main symptoms of COVID-19. Nasal congestion, runny nose, sore throat, and/or diarrhea present in a minority of patients. The incubation period between the SARS-CoV-2 infection and the development of COVID-19 ranges from 1 to 14 days, but mostly in 3 to 7 days. At present, patients with COVID-19 are the primary source of contagion, but asymptomatic carriers of SARS-CoV-2 can also be contagious [4]. SARS-CoV-2 spreads primarily through respiratory droplets and close contacts, but high concentration aerosol in a relatively closed environment could also be potentially transmissible, but evidence remains preliminary. SARS-CoV-2 has also been isolated from feces and urine, which can also be a source of contagion. As such, preventive measures should include avoiding environmental contamination and related aerosol or contact transmission caused by feces and urine [5-7]. The COVID-19 diagnosis and treatment protocol developed and updated by the National Health Committee of the People’s Republic of China (trial version 7) recommends classifying patients into 1) suspected patients, who present either 2 main clinical manifestations and epidemiological history, as discussed above or have all three main clinical manifestations without epidemiological history, and 2) confirmed COVID-19 patients, who were suspected cases and present positive results from one of the etiological or serological tests listed in Table 1 (http://en.nhc.gov.cn/2020-03/29/c_78469.htm).

CARE FOR PATIENTS WITH GYNECOLOGICAL MALIGNANCIES DURING COVID-19 PANDEMIC

1. Containment team
A COVID-19 containment team for gynecological malignancies (CoCTGM) should be established to evaluate not only the needs for the treatments of patients with gynecological...
malignancies, but also the risk for COVID-19 during this pandemic. This team is responsible for developing strategies and procedures for the care of patients with gynecological malignancies during the period, as well as for implementing developed strategies, providing COVID-19 related trainings, and responding to public health emergencies.

2. Dual experts evaluation system

During the COVID-19 pandemic, all patients should be evaluated by at least 2 gynecology oncologists for not only the severity of gynecological malignancies, but the risk of COVID-19, in consultation with an infectious disease specialist. This physician team is responsible for developing individualized treatment plan for each patient based on results from initial evaluation, to avoid "either panic or indifference" for both doctors and patients toward to COVID-19.

3. Education of patients and their companies

Patients and their companies or guardians should receive training on COVID-19 and the needs of social distancing, wearing face mask, checking temperature and frequent washing hands. During hospitalization, constant company is recommended. The hospital should also develop polices to reduce patients visits during the pandemic.

4. Patient triage system

Patients should then be triaged based on the severity of gynecological malignancies and the risk of COVID-19. Life-saving procedures should be immediately performed if patients in life-threatening situations caused by gynecological malignancies. Otherwise, COVID-19 screening should always be performed first.

Outpatient

Patients are required to make appointments before visiting outpatient centers, where their levels of risk for COVID-19 should first be carefully evaluated before entering the outpatient department. In general, a dedicated area at the entrance of an outpatient center should be specifically designated for preliminary screening of high-risk patients, where trained staff
collects epidemiological history and records clinical symptoms, and takes body temperatures from these patients. This information will be used to stratify the level of COVID-19 risks.

Patients with minimal risk of COVID-19 can be directed to go to the clinic. After professional consultation of gynecology oncologists, whether the patients need to be hospitalized or not will be evaluated carefully. On the other hand, those with a high risk should be transferred to the fever clinic accompanied by medical staff for further examination. The fever clinic has been set up as independent unit that is equipped for patients with infectious diseases such as COVID-19.

**Inpatient**

Patients should be triaged according to the urgency and severity between gynecological malignancies and COVID-19. First-aid measures should be given to patients with gynecological malignancies in emergency situation. COVID-19 should be screened for patients in non-emergency situations to be hospitalized for elective operation, chemotherapy, target therapy or radiotherapy.

Patients to be admitted for their gynecological malignancies should provide blood samples for blood cell counts and C-reactive protein measurements, receive computerized tomography scans, and have mucosal swap SARS-CoV-2 nucleic acid test, if necessary. The test could also be administered to patients’ companies or guardians.

Patients should then be triaged into different area zones according to their levels of risk for COVID-19: green zone for general wards to accommodate patients with negative screening results; yellow zone (insulation rooms) for patients with elevated risks for COVID-19, but do not meet the criteria for suspected cases and for those without screening result; and red zone should be a dedicated insulation unit to accommodate patients with suspected COVID-19. In China, all patients who were diagnosed as COVID-19 have been treated only in government designated hospitals.

1) Patients with a minimal risk

These patients should be admitted to green zone. Medical staff should wear surgical mask, as needed.

2) Patients with elevated risk

Patients with fever or epidemiological history but do not meet the criteria of suspected COVID-19 should be transferred to yellow zone, where they will wait for test results while being monitored for medical conditions. Medical staff in this zone should wear surgical masks, eye protection, gloves, and disposable medical isolation gowns or disposable coveralls to prevent the clustering of nosocomial infections caused by patients assigned to this zone.

3) Suspected patients

Insulation wards in red zone are designated for patients with suspected COVID-19. There, medical staff should be equipped with N95 respirator, eye protection, gloves and disposable medical isolation gowns or disposable coveralls.

4) Confirmed cases

In China, the governmental guideline requires that patients who have been diagnosed as COVID-19 should be transferred to hospitals designated by the local governments for treatments. Medical staff there should have the same personal protection equipment as those receiving suspected patients.
PRINCIPLES OF MANAGING PATIENTS WITH GYNECOLOGICAL MALIGNANCIES DURING COVID-19 PANDEMIC

1. Surgery

Emergent surgery
Emergent surgery should only be performed on patients in life-threatening situations, such as tumor rupture, torsion and uncontrolled bleeding. Appropriate insulation and preventive measures should be taken during the surgery, and screening of COVID-19 should be completed as soon as a patient’s condition becomes stable.

Elective surgery
The physical condition of patients should be evaluated for the risk of COVID-19 and the needs of surgery. The latter should be based on pathological and radiological findings of the cancer in order to determine whether surgery is needed during the pandemic or can be postponed. Timely surgery may be needed for patients with rapidly progressing tumor. Patients with less aggressive early stage tumor are recommended scheduled surgery after comprehensive evaluation of both tumor characteristics and risk of SARS-CoV-2 infection. For patients with precancerous lesions, we recommend postponing surgery moderately according to local COVID-19 pandemic.

1) Preparation for elective surgery
Patients with negative COVID-19 results could then undergo a preoperative assessment, as routinely performed. Specialists in a multi-disciplinary team (MDT) should be consulted to assess risks of comorbidities and underline conditions for surgery. Other conditions that may develop during surgery should also be carefully considered, such as potential blood loss and need for transfusion.

2) Postoperative management of fever
Fever is one of the most common symptoms after surgery. During the outbreak of COVID-19, it is critical to identify whether the fever is caused by COVID-19, by surgery related infection, or by surgery induced acute phase reaction. Clinical examination and laboratory test should be performed excluding surgery related infection. If COVID-19 is highly suspected, it is necessary to test the patient again, even though patient has undergone preoperative evaluation for COVID-19. It is also recommended that patients should be transferred into insulation wards in yellow zone. Medical staff there should be equipped with the same personal protective equipment (PPE) required for the staff who interact with confirmed COVID-19 cases. The epidemiological history of patients, companies and family members should be checked again. Once COVID-19 was confirmed, the patients should be transferred to government designated hospitals.

2. Principals of managing patients receiving chemotherapy, target therapy, radiotherapy for gynecological malignancies
Patients should be screened for COVID-19 before they receive chemotherapy, target therapy, and radiotherapy. Since chemotherapy and radiotherapy are primary treatment for some gynecological malignancies, postponing may lead to tumor progress and compromise patients’ prognosis. Patients with minimal risk of COVID-19, timely implement of above therapy are recommended. Once COVID-19 is diagnosed or suspected, MDT consultations should be assembled to develop a plan for the follow-up treatments.
Chemotherapy and target therapy
Before chemotherapy, patients should be screened for COVID-19. For patients with no contraindications, chemotherapy or target therapy can be administered. During treatments, patients should be monitored for general health and complications (e.g., severe myelo-suppression) through clinical evaluations and laboratory tests. For elderly and frail patients who have preconditions or complications and those in hypo-immune state due to repeated chemotherapy, monitoring for chemotherapy-induced complications is critically important in order to take early prophylactic measures and treat patients early. In principle, chemotherapy or target therapy should be provided only to patients who have been determined to have a relatively stable condition thus likely tolerate the treatment. Minimal effective dosage of chemotherapy and reasonably extended interval could be considered for elderly and frail patients.

Some patients may develop fever during the treatment. It is therefore very important to determine whether the fever is caused by COVID-19 or adjuvant therapy that patients received. Clinical examinations and laboratory tests should be performed to exclude adjuvant therapy related infection. Patients who have severe myelo-suppression from previous chemotherapy should be closely monitored for the progress of the condition, with laboratory tests. Granulocyte-colony stimulating factor (CSF) and Granulocyte-macrophage CSF should be considered on the basis of individual evaluation of patients.

Radiotherapy
Before radiotherapy, patients should be screened for COVID-19. For patients with suspected or confirmed COVID-19, radiotherapy should not start or continue until COVID-19 is cured and individual status permits. Since radiotherapy is the primary treatment for some patients with cervical cancer and endometrial cancer, postponing radiotherapy may impact curative effect and prognosis. For patients with minimal risk of COVID-19, treatment is recommended to be continued if the medical condition and individual status permit. Patients who need radiotherapy after surgery should consult with radiation oncologist. Radiotherapy could be moderately postponed within 12 weeks after surgery. If radiotherapy is urgently needed, patients can choose the nearest radiotherapy center as appropriate. For patients with locally advanced cervical cancers, neo-adjuvant chemotherapy regimen could be the preferred option which offers the possibility of an appropriate delay of brachytherapy during COVID-19 pandemic. The radiation treatment room and nearby areas should be thoroughly disinfected during treatment intervals [8].

Management of patients who are suspected or confirmed COVID-19
MDT that consists of gynecology oncologists, respiratory physicians, infectious diseases specialists, intensive care unit specialists, anesthesiologists should be assembled to evaluate patients with gynecological malignancies who are suspected or confirmed COVID-19. The treatments for gynecological malignancies should be considered on an emergency basis after careful evaluation of the patients. These patients should also be insulated from other patients and closely monitored during hospitalization and treatments.

1. Emergent surgery
Patients with gynecological malignancies and suspected or confirmed COVID-19 should undergo emergent surgery only when life-threatening conditions (e.g., severe bleeding and
rupture of tumor) have developed. All medical staff dealing with these patients should always be equipped with the same PPE required for dealing with patients with confirmed COVID-19. A patient in this status should be reported to the hospital epidemic containment team in order to initiate COVID-19 algorithm immediately as follows.

Pre-operation
Areas where the patients have used (passages, elevators, insulation zones) are specially designated. Operation rooms should be under negative-pressure. Protective equipment in operation rooms should be disinfected periodically to minimize cross-infections. Medical staff in close contact with these patients should be well-trained for COVID-19 and equipped with required PPE.

Intra-operation
Operation room should be clearly marked as “COVID-19 OR”. Minimal medical staff and equipment are preferred to reduce the risk of infection and contamination. The COVID-19 OR should maintain its own disposable and medicines, which shall not be taken to outside of designated areas under any circumstances.

Post-operation
After surgery, these patients should be transferred to insulation wards in red zone through passages specifically designated for COVID-19 patients. The pathological tissue bags should be specifically labeled (e.g., novel coronavirus-2019) to clearly distinguish them from those used by other patients. The medical staff should leave the operation room through the special passage and follow the standard protocol to remove PPE. The “COVID-19 OR” and equipment should be disinfected completely. Medical wastes should be disposed appropriately according to the disinfection and management specifications. Once a COVID-19 patient is in a stable condition after surgery, she should be transferred to government designated hospitals for treatment of COVID-19.

2. Adjuvant therapy or postoperative monitoring
Patients with gynecological malignancies and COVID-19 are prone to developing severe complications because these cancer patients are in a hypo-immune state, especially during the postoperative period or during (or after) adjuvant therapy. The gynecological oncologist who administers post-surgery adjuvant therapy should consult with an infectious disease specialist regarding the impact of COVID-19 on the adjuvant therapy and necessary prophylactic measures necessary to reduce the risk of developing complications. Priority should be given to COVID-19 treatment, if patients have no life-threatening issue related to the malignancy.

FOLLOW-UP
“Digital hospital” or telemedicine is recommended for following-up patients and mental health care during the COVID-19 pandemic. It provides online consultation, prescription, and in some incidences, medicine delivery. Digital hospital is not only the choice for outpatients but could also minimize the cross-infection of COVID-19 among hospitalized patients. However, for patients with tumor progression or complex medical condition, we recommend that patients should visit an oncologist instead of seeking care through online consultation. Furthermore, patients with gynecological malignancies often become emotional (e.g., panic and depression) and the condition can deteriorate during the pandemic. Online medical service is a good option for patient’s emotional support.
CONCLUSION

The current COVID-19 pandemic has added additional burdens to the doctors and healthcare delivery system worldwide. It affects how we see patients and treat them. This is particularly true for patients with gynecological and other malignancies whose immune system is severely compromised by the underlying disease and extensive treatments. As first line physicians, we have treated patients with gynecological malignancies who are also suspected or diagnosed COVID-19 during an extended period of COVID-19 pandemic and developed a system of dealing with the pandemic. The recommendations discussed here are developed based on our experience from several major metropolitan hospitals. Hierarchical and individualized management of gynecological malignancy should be conducted to balance the need for COVID-19 pandemic containment and for management of gynecological malignancy. Priority should always be given to the life-threatening circumstance. MDT strategy could provide a comprehensive management plan for gynecological malignancy patients. Digital hospital or telemedicine is an effective and convenient communication platform during the pandemic. We hope these recommendations could provide reasonable references for gynecology oncologists worldwide facing COVID-19 epidemic. We support and encourage information sharing and international cooperation during pandemic containment.

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REFERENCES

1. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020;5:536-44.  
https://doi.org/10.1038/s41564-020-0744-9  
PUBMED | CROSSREF

2. Chang L, Yan Y, Wang L. Coronavirus disease 2019: coronaviruses and blood safety. Transfus Med Rev 2020;34:75-80.  
https://doi.org/10.1016/j.tmr.2019.12.006  
PUBMED | CROSSREF
3. Al-Shamsi HO, Alhazzani W, Alhuraiji A, Coomes EA, Chemaly RF, Almuhanna M, et al. A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: an international collaborative group. Oncologist. Forthcoming 2020.

4. Del Rio C, Malani PN. COVID-19-new insights on a rapidly changing epidemic. JAMA 2020;323:1339-40.

5. Chen Y, Chen L, Deng Q, Zhang G, Wu K, Ni L, et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J Med Virol. Forthcoming 2020.

6. Zhang T, Cui X, Zhao X, Wang J, Zheng J, Zheng G, et al. Detectable SARS-CoV-2 viral RNA in feces of three children during recovery period of COVID-19 pneumonia. J Med Virol. Forthcoming 2020.

7. Ling Y, Xu SB, Lin YX, Tian D, Zhu ZQ, Dai FH, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J (Engl) 2020;133:1039-43.

8. Wei W, Jiang H, Chen W, Zhou Y, Guo S, Zhong G, et al. How should we implement radiotherapy for cancer patients in China during the endemic period of COVID-19? Radiother Oncol 2020;147:100-2.