

What to do as a gynecologic oncologist during the COVID-19 pandemic?

David Atallah and Yara Abdelkhalek



David ATALLAH, M.D., M.Sc.

Chairman, Department of Obstetrics and Gynecology
Professor of Obstetrics and Gynecology
Gynecologic and Breast Oncologic Surgery
Urogynecology
Hôtel Dieu de France University Hospital
Saint Joseph University
Beirut, Lebanon.

Yara Abdelkhalek, M.D.,

Fellow
Gynecologic and Breast Oncologic Surgery
Hôtel Dieu de France University Hospital
Saint Joseph University
Beirut, Lebanon.

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Introduction

In December 2019, an outbreak of a novel beta coronavirus occurred in Wuhan, China. The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2; COVID-19) spreads rapidly causing severe symptoms, multiple organ failure and thousands of death worldwide. The WHO declared COVID -19 pandemic a public health emergency of international concern, and most countries are on lockdown in an effort to stop the spread of the disease and its fatal consequences.

All the medical and para-medical staff are requisitioned to work with patients infected by the COVID-19, meanwhile gynecological cancers and emergencies continue to occur requiring a management strategy to provide affected women with the highest quality of medical care and at the same time, safety for the patients, their families and the working medical teams.

Surgery in Gynecology – The Triage

Surgical procedures in gynecology can be divided according to a priority level. Some needs urgent interventions while others may be postponed for months after the resolution of the crisis, without compromising the patient's safety and quality of life. Therefore multiple societies classified the indications of the gynecological procedures according to the degree of urgency. The Society of Gynecologic Oncology used the Elective Surgery Acuity Scale (ESAS), modified for gynecologic oncology procedures, to classify indications for surgery into elective/non-urgent, semi-urgent, and urgent/emergent (1). According to their scale, gynecologic oncology procedures fall into high acuity surgery for healthy/unhealthy patient (Tier 3a/b) category, which means semi-urgent surgeries that cannot be postponed (table 1). Likewise the American College of Surgeons considered gynecologic cancers or suspected cancer cases (ovarian, tubal, peritoneal, endometrial, cervical, vulvar, vaginal, gestational trophoblastic neoplasm) as non-urgent surgeries but needing interventions with no delay to prevent significant harm (2).

Surgery, Adjuvant Treatment and Mortality in COVID-19 Infected Patients

One retrospective study, conducted in multiple centers in Wuhan, China, showed that all patients operated during the incubation period of the COVID-19 infection developed pneumonia shortly after surgery, 44.1% required ICU admission and 20.5% died (3).

Gynecologic oncology team should ensure that its patients are not carriers of the infection, even if asymptomatic, before ongoing any surgery. Therefore, screening for COVID-19 infection must be done

before any intervention if available, depending on local resources and priorities (4). If the patient tests positive, surgery should be postponed, if possible, until recovery (4).

Furthermore, oncologic surgeries and treatments make patients immunosuppressed thus prone to infections. Multiple studies showed that compared to the healthy population, this group of patients is at greater risk of having the COVID-19 infection and developing more severe complications of it. A nationwide prospective cohort showed that 1% of all the cases of COVID-19 collected in China, until January 31, had cancer (higher than the incidence of cancer in the Chinese population: 0.29%). Patients with cancer were at higher risk of severe complications (39% vs. 8%, p value=0.0003), especially those who received chemotherapy or underwent surgery in the past month (75% vs. 43%) (Figure 1) (5). Similarly, He et al showed in his study a statistically significant increased risk of severe complications of the COVID-19 infection in patients with a history of cancer, with a hazard ratio of 3.56 (Figure 2) (6).

Another nationwide analysis in China showed an increased risk of intubation and death in patients with cancer infected with COVID-19 (7). The Chinese Center for Disease Control reported a mortality rate of 5.6% among cancer patients compared with 0.9% in those without any pre-existing condition (Table 2).

The majority of these studies were conducted on small patients groups. In an effort to precisely estimate the risk of death in cancer patients undergoing treatment and infected with COVID-19, a model study regrouping data from the Chinese Center for Disease Control, the Italian Public Health authorities and the Diamond Princess cruise ship was conducted (7). The case fatality rates and risks of infection were inspired from and compared to previous viral respiratory pandemics.

The results suggested that COVID-19 infection is associated with a doubling risk of death in this population group (8). It was unclear whether the increased risk is only related to the primary oncological disease or receiving chemotherapy enhanced it, but the risk of death was $> 5\%$ (table 2) therefore greater than most benefits of adjuvant treatment (7). Thus indications of treatment in this pandemic must be adequately chosen to limit its additional negative consequences.

In the oncology patients group, risk factors of greater vulnerability are (9):

- Age \geq 65 years old.
- Significant co-morbidity (cardiovascular disease, pulmonary disease, diabetes mellitus).
- ECOG performance status \geq 2.
- Cytotoxic chemotherapy.

Cancer patients are more vulnerable to COVID-19 infection and its complications, thus the gynecologic oncology team should pay a more intensive attention to their patients during this period of crisis. Limitation of hospital visits should be applied, and surgical and treatment indications must be chosen with caution.

Outpatient Visits

- Screen patients for symptoms of COVID-19 by phone one day prior to the visit. Repeat at check in (symptoms +/- temperature) (9).
- Restrict visits to new diagnosed cancer patients, or those presenting acute symptoms and recurrent / active disease (9,10).
- Restrict accompanying visitors (one visitor can be allowed if necessary, for physical/psychological patients limitations, providing that this person is not suspected of being infected) (9,10).
- Limit the number of healthcare providers in the room to minimize the risk of exposure (physician, resident, nurse) (10).
- Schedule the appointments to minimize the number of patients in the waiting area, to encourage physical distancing (9).
- Postpone routine visits, and schedule telemedicine appointments for postoperative visits, if feasible (9,10).
- Educate patients on symptoms of COVID-19 infection and on best practices to limit its transmission (hand washing, social distancing).

Inpatient Management

When indicated, perform cancer surgeries only in centers free of COVID-19, if possible, to limit the risk complications for both the patients and the medical staff.

During inpatient interventions, for safety reasons, some practices must be encouraged:

- Avoid surgeries with prolonged operative time, associated with major intraoperative and postoperative complications, risks of blood loss and admission to intensive care units.
- Reduce hospital stay.
- Minimize the number of healthcare providers working with each patient (9).
- Opt for minimally invasion techniques. However, laparoscopic surgery may be associated with risks of aerosol exposure to the medical staff. Till now, no data confirm the presence of COVID-19 in the surgical smoke, but like HPV and HIV, the novel coronavirus particles may be present in the body cavity thus disseminates through CO2 release during laparoscopy (4). Open surgeries should be promoted, otherwise use laparoscopy with caution to minimize gas dispersal during interventions (insertion and removal of ports, instruments, specimen, abdominal deflation) (4).
- Avoid inpatient chemotherapy (9).

When the indication of surgery/treatment of cancer is present, some guidelines may be followed, if feasible according to each hospital local resources.

Cervical cancer

- a. Pre-invasive disease:

The American Society of Colposcopy and Cervical Pathology (ASCCP) divided pre-invasive disease into low grade and high grade according to screening tests. The diagnostic evaluations of low grade disease may be postponed for 6-12 months, while it should be scheduled within 3 months for high grade lesions (9,10).
- b. Early-stage disease:

Surgical intervention is recommended whenever feasible. In hospitals where oncologic surgeries are suspended, consider postponing localized disease for 6-8 weeks. Low risk /microscopic disease (<2cm, low grade) can benefit from conization or simple trachelectomy +/- sentinel lymph nodes, while prolonged procedures associated with intra and postoperative complications should be postponed (10). Consider neoadjuvant treatment for gross visible tumors.
- c. Locally advanced disease:

According to the American Brachytherapy Society, treatment should be offered with no delay for asymptomatic patients (COVID-19 negative).
Stage IB3, IIB-IVA chemotherapy + radiotherapy. Stage IVB first line and first recurrence after more than one year from primary treatment: Cisplatin/paclitaxel + bevacizumab (if contraindication for cisplatin replace with carboplatin or topotecan) (11).
Consider hypofractionation (increase dose, reduce number of fractions) and weekly telemedicine visits to minimize patients visits to the hospital (10).
Radiotherapy for symptomatic localized recurrence or inoperable asymptomatic recurrence (11).

Endometrial cancer

- a. Low-risk disease:

Consider conservative management (systemic/intrauterine hormonal therapy) in atypical hyperplasia / grade 1 endometrial disease (8,9,10).
- b. High-risk disease:

Consider simple hysterectomy + bilateral salpingo-oophorectomy +/- sentinel lymph nodes if feasible in grade 2/3 or high risk histology disease (10).
Consider brachytherapy in intermediate-high risk disease (12).
- c. Advanced disease:

Consider systemic treatment after tissue biopsy (10).
Consider radiotherapy for isolated vaginal relapse (curative) or asymptomatic pelvic recurrence (12).

Ovarian cancer

- a. Suspected early disease:
Consider risk factors (age, family history, genetic predisposition), physical examination and radiological and biological tests to determine the risk of malignancy and the benefits of direct intervention (10).
In early stage disease, in women with low or moderate risk factors (pre-menopause), it is safer to postpone the surgery (8).
- b. Advanced disease:
Consider neoadjuvant treatment after tissue biopsy until resolution of the pandemic (10). Carboplatin/paclitaxel every 3-4 weeks for 4-6 cycles (4-5 cycles if response before adding PARP inhibitor +/- early discontinuation of paclitaxel if toxicity) (13).
Consider GCS to prevent leucopenia and limit dexamethasone to prevent immunosuppression (13).
- c. Patients under neoadjuvant chemotherapy:
Consider administration of four to six cycles of chemotherapy, rather than three, before proceeding to cytoreductive surgery, if feasible (8,10).
Consider chemotherapy agents and doses with minimal complications (lymphopenia/neutropenia) to limit the need of hospitalization (9)
- d. Patients who completed up-front platinum-based chemotherapy:
Consider no more treatment, but repetitive toxicity evaluations via telemedicine appointments if possible (10).
- e. Patients who progresses on current treatment:
Consider additional chemotherapy if potential benefits are expected (10).

Vulvar cancer

The main symptom in these cancers is the pain. Perform resection, if possible, because it is the most successful method to relief the pain. Consider surgery under local anesthesia if feasible. Remove sentinel lymph nodes when possible but postpone groin lymphadenectomy until the end of the crisis (8).

Treatment delay, especially for cancer cases, is psychologically unacceptable. Both the patient and the surgeon fear disease progression and a worsening prognosis. Whereas all oncologic data show that a 3 to 8 weeks delay may be acceptable, unless urgent indication, without associated negative outcomes (1).

Follow-Up

Despite the primary tumor, complications are common after oncologic surgeries and treatment, some require urgent diagnosis (imaging using CTscan/US) and urgent interventions with no delay such as (11,12,13):

- Bowel perforation, peritonitis
- Fistulisation
- Anastomotic leak
- Intestinal or urinary obstruction
- Pelvic bleeding
- Pulmonary embolism
- Abscess

If a delay in the treatment is chosen, consider follow-up for symptoms re-evaluation every 2 to 4 weeks to avoid disease progression and worsening outcomes (1)

Informed Consent

Even in this critical situation, the clinician should discuss with the patient all the available treatment modalities (surgery/medical treatment – immediate/delayed procedure) with the risks and benefits of each intervention, finally a shared decision should be taken based on different factors: local resources, COVID-19 prevalence in the hospital, patient performance status and co-morbidities, tumor characteristics and outcomes expected from delay (1). An informed consent should be signed before any intervention.

Academic Activities and Studies

In order to maintain the best quality of medical services, transparent communication should be encouraged to benefit from other institutions experiences in this outbreak. Academic activities must be maintained, such as morning meetings, journal clubs, tumor boards and multidisciplinary conferences, via web-based systems (6,10).

As for clinical trials, only those with curative intents or life prolonging opportunities must be remain active (10). All other trials may expose patients and health care providers to unnecessary risks, thus

must be closed until the end of the crisis. If toxicity evaluation visits are needed, consider telemedicine appointment. However, every patient that tests positive for COVID-19 must be removed from the study and oriented for appropriate treatment (10).

COVID-19 Burden on Health Care Systems

Nowadays COVID-19 infection is causing a heavy burden on the health systems worldwide, but its effect will continue months after the resolution of the crisis.

Due to limited resources and high risks of contamination, the health care providers are focusing their activity on COVID-19 patients, postponing all other clinical practices.

Delaying proper management of other patients will lead to their disease progression, especially for those diagnosed with cancer and should have been operated or received neoadjuvant treatment, leading to worse survival outcomes (6).

In parallel, stopping screening activities (mammography, pap smear) will increase the disease morbidity and mortality. That is why scheduled appointments should be maintained if feasible, or otherwise adequately rescheduled after the resolution of the crisis (6).

Moreover, diverting all follow-up and screening activity until the end of the pandemic will lead to excessive accumulation of visits, risking a greater burden on the health care system (6).

This is the distraction effect of the COVID-19 and we should fear its menaces for the coming months (6).

Local Prevalence and Resources

On the 8th of December 2019, the first case of COVID-19 infection was identified in Wuhan, China. Rapidly the virus had spread worldwide with over one million cases on April 2 and more than two millions on April 15 with thousands of deaths.

With the rapid increase in the number of cases, the prevalence of the disease varies from one country to another. Likewise, the infra-structures of health care services vary around the globe. The difference in the prevalence of the disease and the local resources means that there is no global guideline that can fit and be used everywhere.

Benefits and risks must be weighed and the decision of gynecologic oncology disease management should be taken according to the local prevalence of the disease and the available resources, to guarantee the highest quality of medical care.

Conclusion

The COVID-19 infection is a serious disease, causing severe morbidity and mortality particularly in the group of cancer patients. In order to maintain the best quality of medical services for gynecologic cancer patients, accurate triage of cases according to the level of urgency is required to prevent delay in the treatment administration and preserve patient's and health care providers' safety on the other hand. The disease is worldwide but locoregional circumstances vary; thus practice guidelines must be individualized according to available resources.

Table 1: Modified Elective Surgery Acuity Scale (1)

Tiers/ Description	Definition	Locations	Examples	Action
1a	Low acuity surgery/ healthy patient Outpatient surgery Not life threatening illness	ASC Hospital with low/no COVID-19 census	Surgery for benign-appearing ovarian cysts Hysterectomy for menorrhagia without anemia	Postpone surgery or perform at ASC
1b	Low acuity surgery/ unhealthy patient	ASC Hospital with low/no COVID-19 census		Postpone surgery or perform at ASC
2a	Intermediate acuity surgery/healthy patient Not life threatening but potential for future morbidity and mortality May require in-hospital stay	ASC in select cases Hospital with low/no COVID-19 census	Hysterectomy for pre-cancerous conditions or low risk endometrial cancer	Postpone surgery or consider ASC
2b	Intermediate acuity surgery/ unhealthy patient	ASC Hospital with low/no COVID-19 census		Postpone surgery if possible or consider ASC
3a	High acuity surgery/ healthy patient Potentially life threatening or patient is highly symptomatic Requires in-hospital stay	Hospital	Surgery for most cancers Resection of masses resulting in significant end-organ damage or quality of life impairment	Do not postpone
3b	High acuity surgery/ unhealthy patient	Hospital		Do not postpone

ASC: Ambulatory surgical center

Table 2: Death rate according to pre-existing conditions. Chinese CDC and prevention 2020.

Pre-existing Condition	Death Rate confirmed cases	Death Rate all cases
Cardiovascular Disease	13.2%	10.5%

Diabetes	9.2%	7.3%
Chronic Respiratory Disease	8.0%	6.3%
Hypertension	8.4%	6.0%
Cancer	7.6%	5.6%
No Pre-existing Conditions		0.9%

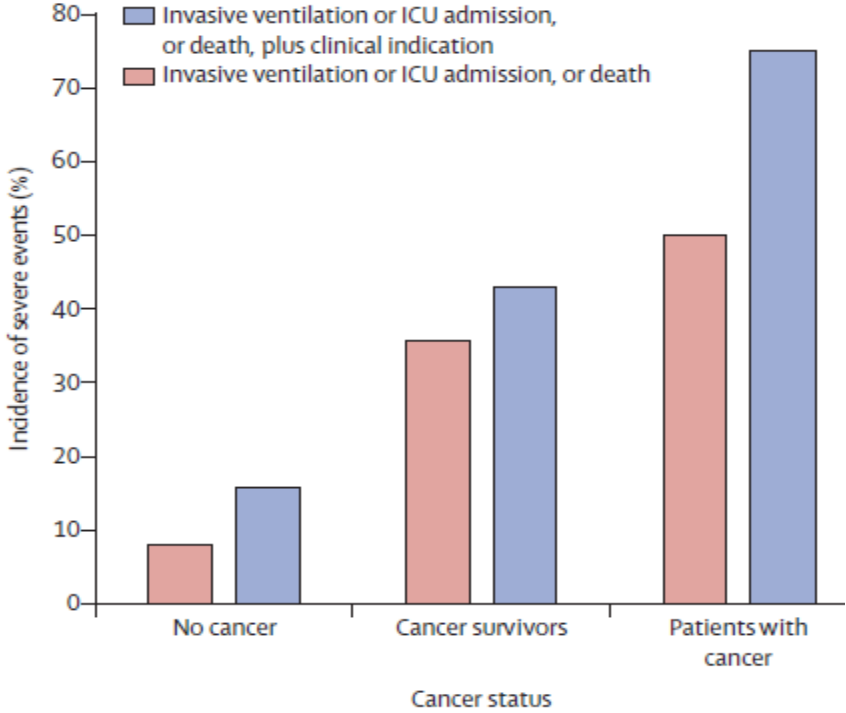


Figure 1: Severe events in patients without cancer, cancer survivors, and patients with cancer (5).

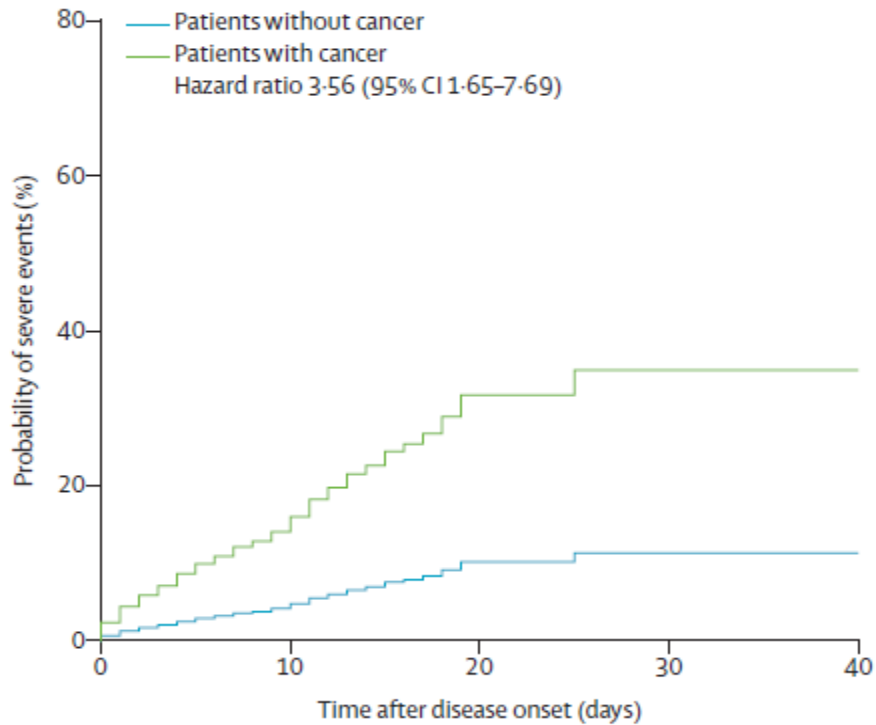


Figure 2: Probability of developing severe events for patients with and without cancer (5).

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