

## COVID-19 PANDEMIC

### WHAT TO DO AS A GYNECOLOGIC ONCOLOGIST DURING THE COVID-19 PANDEMIC?

#### MEMAGO Statement

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**ABSTRACT** • The SARS-Cov-2 virus pandemic causes an acute public health emergency with millions of infected patients and thousands of deaths. The infection makes adults prone to severe and fatal consequences, especially when they suffer several comorbidities. Our oncologic patients are the most susceptible to its severe repercussions because of their initial diagnosis and the immunosuppressive adjuvant and neoadjuvant treatments they receive. The Chinese CDC reported a 5.6% risk of mortality among cancer patients compared to 0.9% in the general population; likewise, other studies showed a twofold higher risk of death in this patients' subgroup. In order to maintain the best quality of medical services during this crisis, along with the safety of health-care providers, accurate triage of our oncologic patients must be done before any medical or surgical intervention to decide whether or not postponing treatments may be considered, without risking the disease progression and patients' worsening outcomes, otherwise inpatient and outpatient special precautions must be followed whenever interventions are currently scheduled, according to each gynecologic cancer type. The disease is worldwide but local and regional circumstances vary, thus practice guidelines must be individualized according to each country virus prevalence and available medical resources, in order to limit the burden of the COVID-19 infection on the health system during the crisis and the upcoming months after its resolution.

Keywords: COVID, gynecologic oncology management

#### INTRODUCTION

In December 2019, an outbreak of a novel beta coronavirus occurred in Wuhan, China. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19) spreads rapidly causing severe symptoms,

multiple organ failure and thousands of deaths worldwide. Two months later, the WHO declared the COVID-19 pandemic and a public health emergency of international concern; most countries were on lockdown in an effort to stop the spread of the disease and its fatal consequences.

All medical and paramedical staffs were requisitioned to work with patients infected by the COVID-19, meanwhile gynecological cancers and emergencies continued 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 need 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 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 I).

Similarly, 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].

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**TABLE I**  
MODIFIED ELECTIVE SURGERY ACUITY SCALE [1] FOR PATIENTS WITH CANCER IN THE ERA OF COVID-19 [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 precancerous 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

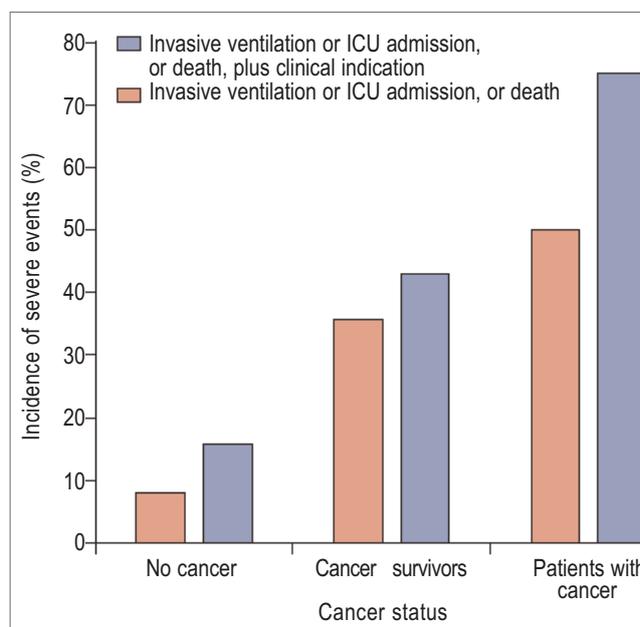
#### SURGERY, ADJUVANT TREATMENT & MORTALITY IN COVID-19 INFECTED PATIENTS

In Wuhan, China, a multicenter retrospective study showed that all patients operated during the incubation period of the COVID-19 infection developed pneumonia shortly after surgery, and that 44.1% of them required ICU admission and 20.5% of them died [3].

The gynecologic oncology team must ensure that their patients are neither carriers nor infected with COVID-19, even if asymptomatic, prior to any surgery. Screening for COVID-19, if available, must be performed before any intervention, depending on local resources and priorities [4]. If the patient tests positive, surgery should be postponed, if possible, until recovery [4].

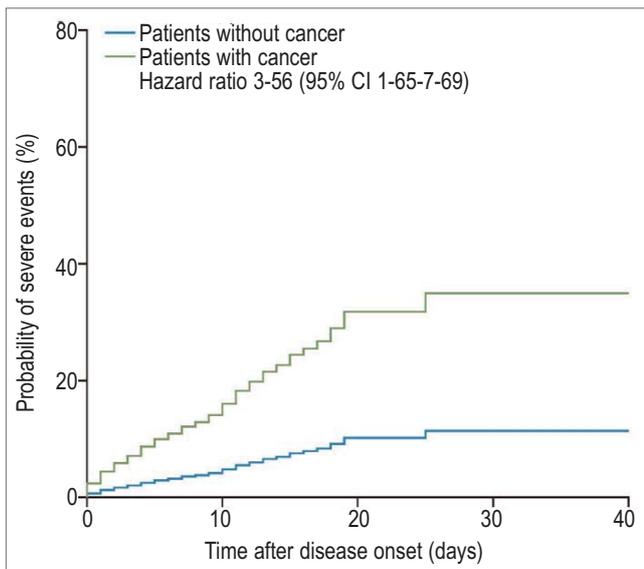
Furthermore, oncologic surgeries and any additional medical or radiotherapy treatments may result in immunosuppression and increase the patients' risk for infections. Studies show that, compared to the healthy population, patients are at a greater risk of acquiring the COVID-19 infection and developing severe complications. Until January 31, 1% of all the cases of COVID-19 in China had cancer, which is higher than the incidence of cancer in the general population (0.29%). These cancer patients were at higher risk of severe complications (39% vs. 8%,  $p$ -value = 0.0003), especially those who received chemotherapy or underwent surgery in the prior month (75% vs.

43%) (Figure 1) [5]. Similarly, He et al. showed a statistically significant increased risk of severe complications in the COVID-19 infected patients with cancer, with a hazard ratio of 3.56 (Figure 2) [6].



**Figure 1**

Severe events in patients without cancer, cancer survivors, and patients with cancer during the COVID-19 pandemic [5].



**Figure 2**

Probability of developing severe events for patients with and without cancer during the COVID-19 pandemic [5].

Another nationwide analysis in China showed an increased risk of intubation and death in patients with cancer who were 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 the rest of the population (Table II).

The problem is that the majority of these studies included a small number of patients. In an effort to precisely estimate the risk of death in cancer patients undergoing treatment and infected with COVID-19, data from the Chinese Center for Disease Control, the Italian public health authorities and the Diamond Princess cruise ship were combined, analyzed and compared to previous viral respiratory pandemics [7-8]. COVID-19 infection was associated with a twofold higher risk of death. However, it was not clear whether this higher risk was due to the cancer itself or increased with chemotherapy. Further, the risk of death in these patients was > 5% (Table II),

**TABLE II**

DEATH RATE OF PATIENTS WITH COVID-19 INFECTION ACCORDING TO PRE-EXISTING CONDITIONS. DATA FROM THE CHINESE CENTER FOR DISEASE CONTROL AND PREVENTION 2020

Pre-existing Condition	Death Rate	
	Confirmed cases	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%

which may be higher than the most benefits of adjuvant treatment [7]. Therefore, any benefit from gynecological, surgical or medical treatment during this pandemic, must be appropriately balanced against any increase in the risk of complications and death.

In the oncology patients the risk factors of greater vulnerability include [9]:

- Age ≥ 65 years old.
- Significant comorbidity (cardiovascular disease, pulmonary disease, diabetes mellitus).
- Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2.
- Cytotoxic chemotherapy.

#### OUTPATIENT VISITS

The following precautions are recommended in relation to outpatients visits of gynecologic cancer patients.

- i. Screen patients for symptoms of COVID-19 by phone one day prior to the visit. Repeat at check-in (symptoms ± temperature) [9].
- ii. Restrict visits to new diagnosed cancer patients, or those presenting acute symptoms and recurrent/active disease [9,10].
- iii. 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].
- iv. Limit the number of healthcare providers in the room to minimize the risk of exposure (physician, resident, nurse) [10].
- v. Schedule the appointments to minimize the number of patients in the waiting area, to encourage physical distancing [9].
- vi. Postpone routine visits, and schedule telemedicine appointments for postoperative visits, if feasible [9,10].
- vii. Educate patients on symptoms of COVID-19 infection and on the 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 feasible, to limit the risk of complications for both patients and medical staff.

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

- i. Avoid surgeries with prolonged operative time, associated with major intraoperative and postoperative complications, risks of blood loss

- and admission to intensive care units.
- ii. Reduce hospital stay.
- iii. Minimize the number of healthcare providers working with each patient [9].
- iv. Opt for minimally invasive techniques. However, laparoscopic surgery may put medical staff at risk of aerosol exposure. Till now, no data confirmed 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 disseminated through CO<sub>2</sub> 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].
- v. Avoid inpatient chemotherapy [9].

These guidelines may be followed, according to each hospital local resources and the presence of COVID-19 specialized centers.

In hospitals, as well as the lack of masks, gloves, hand sanitizers, ventilators and available beds, the healthcare staff is facing during this pandemic a shortage of blood supplies. Many blood donation centers are closed, donors are either sick or following social distancing measures, and most blood components have short expiration time, thus obtaining blood supply for transfusions during this crisis has become a real challenge [11]. One example is from New York City, where blood centers reported a 75% decrease in the number of donors [12].

Currently, the postponement of elective surgical interventions may reduce the need of blood products, but the possible progression of untreated cases may result in additional needs for transfusions during the upcoming period [11].

Although it is confirmed that the COVID-19 transmission occurs via respiratory droplets, more studies are needed to rule out its possible transmission via blood components [11].

Therefore, other strategies are crucial to optimize our patients' own blood supply. They can be classified into preoperative, intraoperative and postoperative practices:

#### **[a.] Preoperative practices**

On March 2020, both the WHO and the European Center for Disease Prevention and Control strongly recommended the implementation of "Patient Blood Management" measures to guaranty an effective treatment of all patients [11]. Meanwhile, for patients scheduled for delayed interventions, practices that must be undertaken are:

- i. Early diagnosis and treatment of anemia:

Anemia is a contraindication for elective surgery [13], especially during the current crisis. A large meta-analysis by Fowler et al. including almost one million patients showed that preoperative anemia is associated with higher probability of mortality (OR = 2.9,  $p < 0.001$ ) [14], infections (OR = 1.93,  $p = 0.01$ ) [14], kidney injuries (OR = 3.75,  $p < 0.001$ ) [14], needs for transfusion (OR = 5.04,  $p < 0.001$ ) [14], and 22% of longer hospital stays (11 vs. 9 days,  $p = 0.0001$ ) [15]. Iron deficiency is the major cause of anemia, thus oral or intravenous supplementation is essential while waiting for the planned delayed surgery. Other anemia related deficiencies must also be addressed via folate or vitamin B12 supplementation while chemotherapy induced bone marrow suppression can be treated via erythropoiesis stimulating agents administration [11,13].

- ii. Early diagnosis and management of coagulopathy: When available, perform coagulation and platelet function testing to adequately diagnose coagulation disorders, and treat via administration of clotting factors and antifibrinolytic agents that may prevent the need of plasma and platelets transfusion [11,13].

#### **[b.] Intraoperative practices**

- i. Meticulous surgical techniques and hemostasis [13].
- ii. Cell salvage techniques [11,13].
- iii. Antifibrinolytic agents [11,13].
- iv. Topical hemostatic agents [11,13].
- v. Local vasoconstrictive agents [11,13].
- vi. Acute normovolemic hemodilution [11,13].

#### **[c.] Postoperative practices**

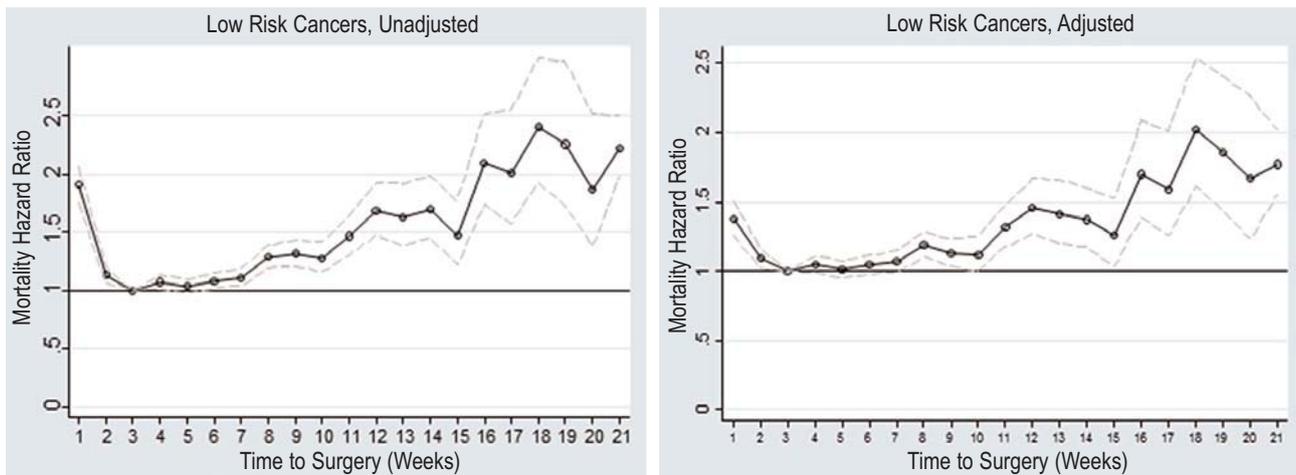
- i. Rapid surgical intervention or embolization when interventional radiology is available to address postoperative bleedings [11].
- ii. Prophylaxis of upper GI hemorrhage [13].

The accurate management of anemia leads to lower transfusion rates, fewer hospital acquired infections, reduced hospital stays thus better clinical outcomes [11].

Below, we list the management of each gynecological cancer separately.

#### **Specific types of gynecological cancers**

- a. Pre-invasive cervical neoplasia:  
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



**Figure 3.** Hazard ratios for mortality of low grade endometrial cancer.

Dashed lines indicated 95% confidence interval. (Unadjusted/adjusted for patient's age, race, insurance status, stage, ...) [17].

can be postponed for 6-12 months, while it should be scheduled within 3 months for high grade lesions [9,10]. Patients with AIS should be individualized.

- b. Early-stage cervical cancer: 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 (< 2 cm, low grade) can benefit from conization or simple trachelectomy ± sentinel lymph nodes, while prolonged procedures associated with intra- and post-operative complications should be postponed [10]. Consider neoadjuvant treatment for gross visible tumors.
- c. Locally advanced cervical cancer: According to the American Brachytherapy Society, treatment should be offered with no delay for asymptomatic patients (COVID-19 negative).
  - i. Patients with stages IB3, IIB-IVA should receive the standard treatment with concurrent chemotherapy and radiotherapy [16].
  - ii. Patients with stage IVB: For the first line and/or for the first recurrence after more than one year from primary treatment, use cisplatin/paclitaxel + bevacizumab (if there is a contraindication for the use of cisplatin, it can be replaced with carboplatin or use GOG 240 protocol of paclitaxel, topotecan and bevacizumab) [16].
  - iii. Consider hypofractionation of the radiotherapy sessions (increase dose, reduce number of fractions) and weekly telemedicine appointments to minimize the patient's visits to the hospital [10].
  - iv. Radiotherapy for symptomatic localized recurrence or inoperable asymptomatic recurrence [16].

### **Endometrial cancer**

- a. Low-risk endometrial cancer:
  - i. Low grade cancers are usually cured by surgery. This subtype of endometrial cancer is the most sensitive to delay [17]. One large study on the relation between surgical timing and survival outcomes was published in 2017. Low grade and high grade endometrial cancers cases from 2003 to 2012 recorded in the American National Cancer Database were collected. The results showed that 5-years survival rates are higher when surgery for low grade endometrial cancer is performed between week 3 and week 8 after the diagnosis, after that mortality rates are significantly higher (Figure 3) [17]. Thus, surgery must be the first line therapy for low grade endometrial cancers, whenever possible, according to local resources and the virus prevalence.
  - ii. Consider conservative management (systemic/intrauterine hormonal therapy) in patient with atypical hyperplasia or grade 1 endometrial disease [8-10], when surgery is not feasible.
- b. High-risk endometrial cancer: 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 [18].
- c. Advanced endometrial cancer: Consider systemic treatment after tissue biopsy [10]. Consider radiotherapy for isolated vaginal relapse (curative) or asymptomatic pelvic recurrence [18].

### **Ovarian cancer**

- a. Suspected early ovarian cancer:  
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 (premenopause), it is safer to postpone the surgery [8].
- b. Advanced ovarian cancer:
  - i. Consider neoadjuvant treatment after obtaining tissue biopsy [10].
  - ii. Use 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) [19]. Consider adding bevacizumab if there is significant ascites and or no response to treatment.
  - iii. Consider GCS to prevent leucopenia and limit dexamethasone to prevent immunosuppression [19].
- c. Patients undergoing neoadjuvant chemotherapy:
  - i. If feasible, consider administration of four to six cycles of chemotherapy, rather than three, before proceeding to cytoreductive surgery [8,10].
  - ii. Consider chemotherapy agents and doses that have minimal complications (lymphopenia/neutropenia) in order to limit the need of hospitalization [9]
- d. Patients who have completed up-front platinum-based chemotherapy:  
Consider stopping treatment; however, continue monitoring toxicity via telemedicine if available [10].
- e. Patients who progress on current treatment:  
Consider additional chemotherapy if potential benefits are expected [10].

### **Vulvar cancer**

The main symptom of vulvar cancers is pain. Perform resection, if possible, because it is the most successful method to relieve the pain. Consider surgery under local anesthesia if feasible. Remove sentinel lymph nodes but postpone groin lymphadenectomy until the end of the crisis [8].

#### PSYCHOLOGICAL IMPACT OF TREATMENT DELAY

Any delay in the treatment of a patient with cancer can result in significant anxiety and depression. Both the patient and her physician may be concerned about disease progression resulting in a worse prognosis. However, data show that, in most cancers, a 3 to 8 weeks delay is acceptable [1].

If a delay in the treatment is chosen, consider reevaluation every 2 to 4 weeks to avoid disease progression and a worse outcome [1].

#### FOLLOW-UP

Complications are common following cancer surgery and treatment, and these may require urgent attention (such as examination, blood tests, imaging) and urgent interventions [16,18,19]. These complications include, but are not limited to:

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

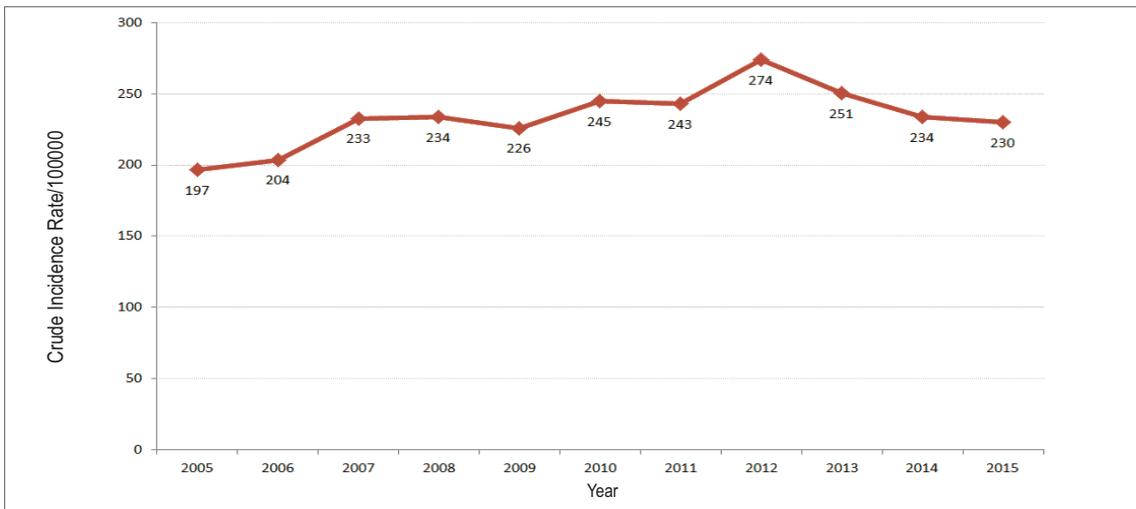
#### INFORMED CONSENT

Even in this critical situation, the clinician should discuss with the patient all the available treatment modalities (surgery/medical treatment – immediate/delayed procedure) and the resulting risks and benefits of each intervention or the delay of such intervention. A shared decision should be taken based on different factors: the local resources, the local prevalence of COVID-19, the patient's performance status and comorbidities, the cancer characteristics and stage and the possible adverse outcomes that may result from any delay in the treatment [1]. As usual, a detailed informed consent should be signed before any intervention, with particular reference to the status of the COVID-19 infection in the community.

#### 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 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 doing them via telemedicine. However, patients who test positive for COVID-19 must be removed from the study and referred for appropriate treatment by their physicians [10].



**Figure 4.** All cancers, crude incidence rates/100000, females, Lebanon, 2005-2015 [21]

#### COVID-19 BURDEN ON HEALTH CARE SYSTEMS

COVID-19 infection has caused a heavy burden on health systems all over the world, and it is expected that these repercussions will continue months after the resolution of the immediate crisis.

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

Delaying proper management, especially of cancer patients may lead to disease progression and possible worse survival outcomes [6].

Moreover, stopping screening activities such as mammography, pap smear, colonoscopies, etc., may lead to increase morbidity and mortality. That is why scheduled appointments should be maintained whenever feasible and safe for both patients and health practitioners, otherwise they should be timely rescheduled after the resolution of the immediate crisis [6].

However, diverting all follow-up and screening visits until the end of the pandemic will lead to excessive accumulation of visits, which will result in a greater

burden on an already overstretched health care system [6].

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

#### LOCAL PREVALENCE AND RESOURCES

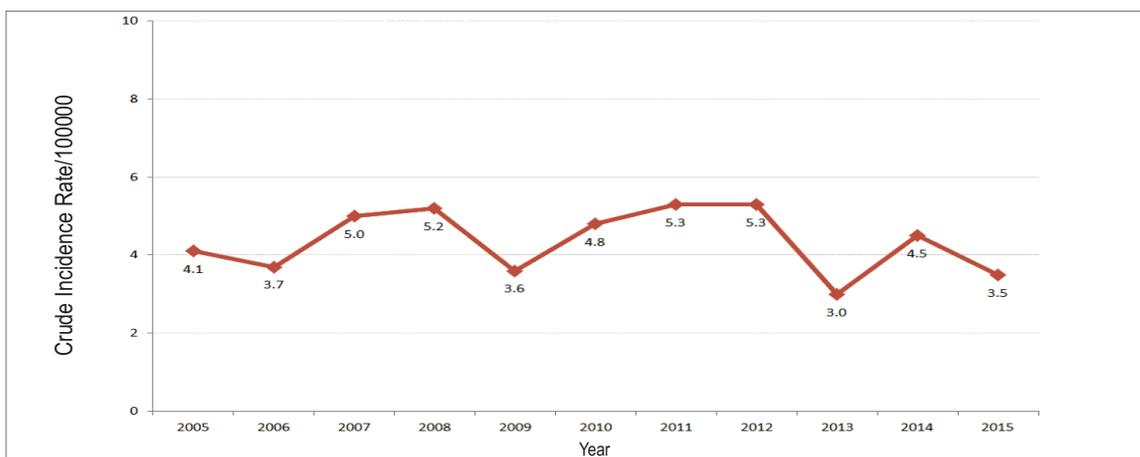
On the 8<sup>th</sup> of December 2019, the first case of COVID-19 infection was identified in Wuhan, China. Rapidly the virus spread worldwide with 9,551,507 cases and 485,423 deaths on June 25 [20].

In Lebanon, until April 20, we registered 677 cases of COVID-19 infected patients and 21 deaths, an incidence considered excessively low compared to other countries [20].

Furthermore, the local prevalence of cancer is particular to each population.

According to the NCR data 2015, the incidence rate of cancers among Lebanese females is 0.23% [21], and over a period of 10 years, the graph showed an increase in the incidence (Figure 4).

In 2015 and among 100000 cancer patients, the distribution varied according to cancer types.



**Figure 5.** Cervical cancer, crude incidence rates/100000, Lebanon, 2005-2015 [21]

**Cervical cancer**

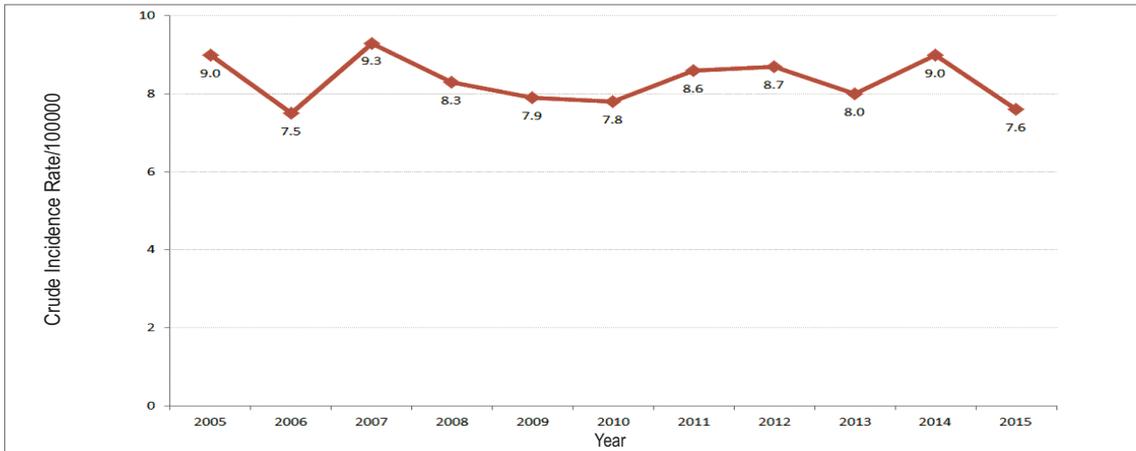
Below we list the numbers between some gynecologic cancers:

- Cervix: 3.5 (Figure 5)
- Ovaries: 7.6 (Figure 6)

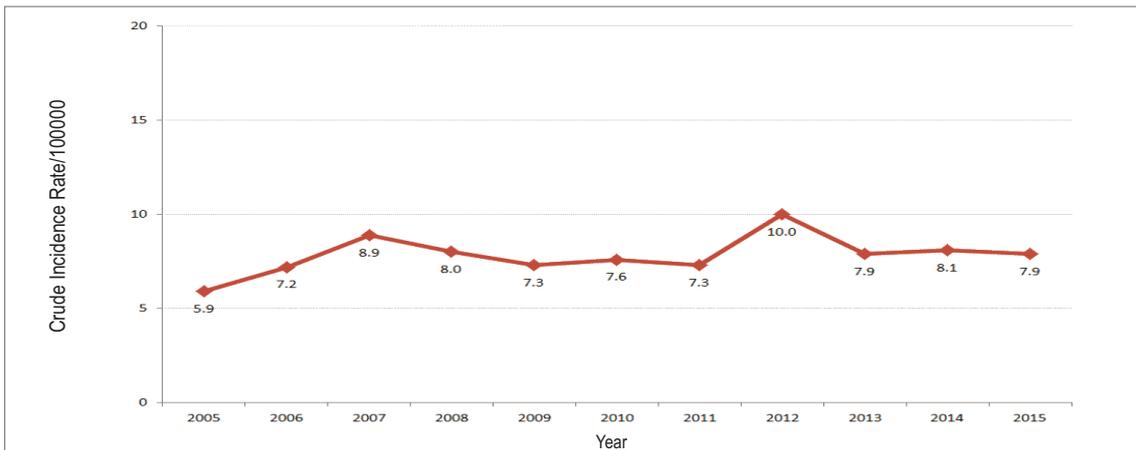
- Endometrium: 7.9 (Figure 7)

- Breast: 84 (Figure 8)

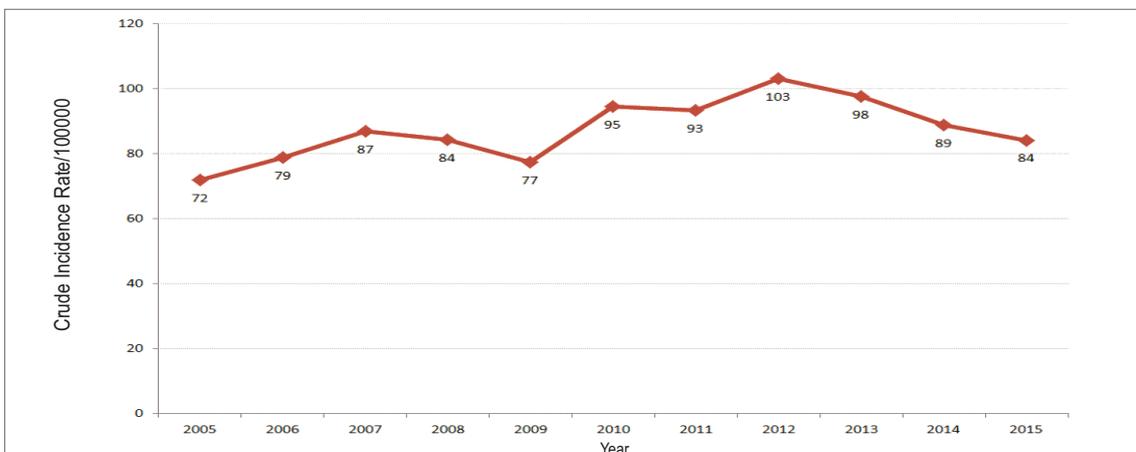
Over a period of eleven years, a recent Lebanese epidemiologic analysis showed that breast cancer account nowadays for 20% of all cancer types, an



**Figure 6.** Ovarian cancer, crude incidence rates/100000, Lebanon, 2005-2015 [21]



**Figure 7.** Endometrial cancer, crude incidence rates/100000, Lebanon, 2005-2015 [21]



**Figure 8.** Breast cancer, crude incidence rates/100000, Lebanon, 2005-2015 [21]

incidence among the highest in the world [22].

Therefore, in Lebanon, the COVID-19 prevalence is low and gynecologic cancers are frequent. For social and political reasons, our health care system is already vulnerable and overstretched, thus we should manage our resources wisely in order to limit the burden of the crisis.

#### CONCLUSION

The COVID-19 infection is a serious disease that causes severe morbidity and mortality especially when it occurs in patients with cancer. 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 needed to prevent delay in the treatment and worsening of the prognosis and to safeguard the health care providers safety. The disease is worldwide but loco-regional circumstances vary, thus practice guidelines must be individualized according to the prevalence of COVID-19 infection, the prevalence of various cancers and the available medical resources.

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