Curr. Treat. Options in Oncol. (2021) 22:117
DOI 10.1007/s11864-021-00905-5

Gynecologic Cancers (LA Cantrell, Section Editor)

COVID-19 and Gynecologic Oncology: What Have We Learned?

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This article is part of the Topical Collection on *Gynecologic Cancer*

Keywords COVID-19 · Gynecologic cancer · Pandemic

Opinion statement

COVID-19 has transformed the care we provide to gynecologic oncology patients. In addition to directly impacting the diagnosis and treatment of women with gynecologic cancer, it has affected our patient's ability to undergo recommended surveillance and has made an impact on every caregiver providing care during this time. Herein we review the current literature on the impact of COVID-19 on gynecologic oncology and highlight new approaches and innovations that have resulted in gynecologic cancer care as a result of the pandemic. The impact of COVID-19 on the field of gynecologic oncology has been profound. In addition to directly impacting the diagnosis and treatment of women with cancer, it has also challenged the very ethics with which we practice medicine. The equitable distribution of resources is paramount to upholding the Hippocratic Oath which we all invoke. The COVID-19 pandemic has stripped this oath down to its very core, forcing all medical practitioners to scrutinize who gets what resources and when. As the pandemic continues to unfold, the question remains — in the setting of a strained and overburdened healthcare system, how do we maximize beneficence to one group of patients, while maintaining non-maleficence to others? As gynecologic oncologists, we are responsible for advocating for our patients to ensure that

Published online: 23 November 2021

the quality of their cancer care is not compromised, while also not overutilizing resources that are sorely needed for the care of COVID-19 victims, and not making them more likely to succumb to COVID-19 by the very nature of the treatment we provide. The effects of the pandemic are far-reaching and broad, and many of these are yet to be determined. Future studies are needed to analyze how the above-utilized strategies in GYN cancer care during the pandemic will impact the long-term outcomes of our patients.

Introduction

More than 12 months into the COVID-19 pandemic, over 100 million cases and 2.3 million COVID-19-related deaths have been confirmed globally [1]. While the pandemic has forced many industries to shut down, the healthcare sector remains open and, in many countries, overwhelmed. The resources that have been diverted to care for victims of the pandemic have left other patients vulnerable. In the case of gynecologic oncology patients, both the diversion of resources and the precautions taken to prevent exposure and spread of the virus have impacted every aspect of their disease course, from diagnosis to treatment, and even supportive care. Early data from New York City, the initial epicenter in the USA, show that over 38% of gynecologic oncology patients experienced a modification to their treatment due to COVID-19 during the peak of New York's pandemic [2]. There are currently limited data on the impact of this delayed treatment and divergence from standard of care in this patient population.

In addition, gynecologic cancer patients are a high-risk group for severe COVID-19 infection due to their immunocompromised status [3]. A study from six NYC-area hospitals showed that of 121 gynecologic cancer patients with COVID-19 infections during the peak of New York's pandemic, 66 patients (54.5%) required hospitalization, and 30.3% were admitted to the intensive care unit (ICU). Seventeen patients, or 14%, died due to COVID-19-related complications, representing a mortality rate that is much higher than that of the general population [4••]. In-depth data regarding the safety of undergoing surgery and cancer-directed therapy in the midst of a pandemic are lacking. The aim of this paper is to review the current literature on the impact of COVID-19 on gynecologic oncology and to highlight new approaches and innovations in gynecologic cancer care.

Impact on screening and diagnosis

COVID-19 has significantly impacted our standard methods for screening and diagnosis of gynecologic cancer. With regard to primary and secondary prevention of cervical cancer, COVID-19 has interrupted HPV vaccination schedules and delayed outpatient screening with cytology/HPV testing and subsequent referrals for colposcopy. HPV vaccination programs in areas with low prevalence of COVID-19 have resumed in the outpatient setting with the use of personal protective equipment (PPE), increased office-cleaning practices, and social distancing measures in accordance with guidelines from local government and healthcare authorities; however, in areas with a high prevalence of COVID-19, outpatient providers may be reassigned to help overwhelmed healthcare systems and vaccination programs may be suspended for patient and provider safety [5].

In March 2020, the American Society for Colposcopy and Cervical Pathology (ASCCP) released interim guidelines with regard to management of abnormal cervical cancer screening results during COVID-19 (Table 1):

Guidelines from ASCCP

Telehealth visits to provide justification and reassurance for delay in treatment should be implemented if time and resources allow. Additionally, from a preventive standpoint, some studies suggest that home-based screening for cervical cancer can be implemented during and even after the pandemic [7]. A study of over 5000 women in the Netherlands showed that women in the general population are receptive to self HPV-screening. Further data are needed to validate this method prior to regular implementation [8].

Although there is no routine screening for vulvar, endometrial, or ovarian cancers, early studies have shown that there have been delays in diagnosis secondary to patients with early symptoms waiting longer than usual to make appointments to see their provider due to fear of acquiring COVID-19. For example, a large retrospective study from the Kaiser Permanente network in Northern California showed that there was a 33% decline in patient calls for abnormal uterine bleeding during the first months of the pandemic compared to pre-pandemic times, and a corresponding 35% decline in endometrial cancer diagnoses [9]. The long-term impact of delays in screening and diagnosis of gynecologic cancers is an area of continued interest and research that has yet to be fully explored.

Impact on surgical approach

Management of gynecologic malignancies hinges on the intent of treatment. Specifically, two general strategies for treatment are employed: curative and palliative [10]. The mainstay of treatment for many gynecologic cancers including early stage cervical, low-risk endometrial, and vulvar cancers, as well as high-risk molar pregnancies, is primary surgery. The decision to perform surgery is typically determined by a number of factors, including extent of disease, patient performance status, and medical comorbidities. In the

Table 1. ASCCP interim guidelines for management of abnormal cervical cancer screening results during the COVID-19 pandemic [6]

Cervical cancer screening results	ASCCP interim recommendations
Low-grade screening tests	Permissible to postpone evaluation up to 6–12 months
High-grade screening tests	Evaluation within 3 months
High-grade cervical disease, low suspicion for invasive disease	Evaluation and procedure scheduled within 3 months
High suspicion for invasive disease	Contact within 2 weeks, evaluation within 2 weeks thereafter

context of the COVID-19 pandemic, factors such as ICU and resuscitative resource utilization as well as attempts to minimize patient and provider exposure to the virus should additionally influence the decision to perform surgery [10].

The Society of Gynecologic Oncology (SGO) has created a set of guidelines for classification of surgical urgency during the pandemic. Gynecologic cancer cases are considered semi-urgent by surgical societies due to the potential for increased morbidity and mortality in these patients if delayed [11••]. The decision to prioritize surgery should be individualized for each patient. Patients should be advised that this decision is based on local resources, disease prevalence, patient characteristics, tumor characteristics, and the potential for adverse outcomes with delayed surgery [11••]. Patients with high-risk or aggressive histologies and those who are at risk of rapid disease progression and metastases should be prioritized. Additionally, those with early-stage disease for whom surgery is considered curative should be prioritized, although well-differentiated endometrial cancer can be treated or temporized hormonally. For those patients with advanced ovarian cancer, interval debulking surgery (IDS) should be prioritized unless the prevalence of COVID-19 is high and hospital resources such as PPE and ventilators are precious. In these cases — especially in those patients who have received neoadjuvant chemotherapy (NACT) and are immunocompromised — additional chemotherapy should be considered. When possible, a minimally invasive approach to surgery should be utilized [11••].

While there appears to be a consensus on most of these guidelines, oncologic societies in countries outside of the USA differ in some of their recommendations. For example, the National College of French Gynecologists and Obstetricians recommends replacing surgery with radiotherapy whenever possible in cervical cancer and completing 6 cycles of NACT prior to considering IDS in advanced ovarian cancer [10]. Despite these recommendations, more recent studies support SGO guidelines of prioritizing surgery when a cure is possible. For example, while a single-institution study by Matsuo et. al showed that an 8-week wait time for surgery in early cervical cancer did not impact short-term disease recurrence, a separate retrospective observational study querying the National Cancer Database suggests that longer wait time up to 16 weeks is associated with increased parametrial involvement and a slightly increased adjusted all-cause mortality risk [12, 13]. While acknowledging the limitations of their retrospective study, the authors suggest that attempts should be made to avoid prolonged delays in hysterectomy for early-stage cervical cancer.

Additional perioperative factors such as COVID testing, PPE, and the safety of exposure to aerosolized particles are also to be considered when discussing surgery during COVID-19. While early publications warned about the risk of exposure to COVID-19 particles in laparoscopic smoke, more recent statements from societies including SGO, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), and the American Association of Gynecologic Laparoscopists (AAGL) have affirmed that current data does not suggest an increased risk of exposure from abdominal procedures, even with a laparoscopic approach [11••, 14]. General safety precautions include preoperative COVID-19 testing, the use of appropriate PPE, limited personnel

during intubation and extubation, and limiting insufflation pressures and electrocautery power levels [11••, 15]. The Society of European Robotic Gynaecological Surgery (SERGS) additionally suggests that robotic procedures are better able to contain body fluids and surgical gases and decrease any theoretical risk to healthcare providers [16]. Furthermore, when resources are available, a COVID-free surgical pathway with complete segregation of the operating rooms, critical care, and inpatient areas was shown to decrease 30-day postoperative pulmonary complications after elective procedures (2.2% vs. 4.9%, aOR 0.62, 95% CI 0.44–0.86) [17•]. The limited data that we have thus far do not suggest an association of recent major surgery with death or severe disease due to COVID-19 [4••].

Impact on cancer-directed treatment

Radiation

Radiation therapy is a critical part of treatment for many gynecologic cancers and can be delivered in definitive, palliative, and adjuvant settings. Radiotherapy differs from surgery and chemotherapy in that it often requires patients to make many trips to and from the hospital for treatment, thus increasing the exposure risk for both patient and provider [18•]. An international consensus panel of radiation oncologists specializing in gynecologic malignancies suggests three categories for prioritizing patients for radiotherapy [18•]:

Priority A: Patients with rapidly progressing tumors, those for whom radiotherapy is potentially curative, or those with intractable bleeding or pain.
Priority B: Those for whom radiotherapy is needed but is not critical; can be delayed up to 8–12 weeks without causing significant harm.
Priority C: Patients with non-life threatening conditions, for whom treatment could be replaced with an alternative therapy or even omitted altogether without causing significant harm.

The authors go on to subdivide patients with different types of gynecologic cancers into each prioritized group. For example, all locally advanced cervical cancer patients are considered priority A as they can progress rapidly and radiotherapy is potentially curative. Patients who have undergone surgery for early cervical cancer and who require adjuvant radiation are considered priority B. Across the disease sites, the panel recommends that the total number of EBRT and brachytherapy fractions be minimized when possible. When brachytherapy is required, locoregional anesthesia is preferred over general to reduce aerosolizing particles. The risk of immunocompromised states from concurrent chemotherapy should be weighed against the benefit of chemosensitization, and case-by-case decisions should be made [18•].

A literature review by Williams et al. reported that in cervical cancer, every 1-day delay of radiotherapy over the median resulted in a 1% loss of pelvic control [19]. Additionally, multiple studies analyzed by the authors showed significant differences in pelvic control and overall survival when comparing

treatment completed in less than 55 days with treatment prolonged past 55 days [19]. Overall, the consensus appears to be that external beam radiation therapy (EBRT) and brachytherapy for gynecologic malignancies should not be delayed when cure can be reached or when there is a high risk for loss of pelvic control. Overall treatment time should be limited to less than 8 weeks and hypofractionation should be considered, while taking into consideration the radiation dose effects on surrounding organs. Hypofractionation may not work in some cases where there is high risk of skin toxicity, such as in vulvar cancers [20].

In the setting of oncologic emergencies due to metastases, the patient's prognosis is an important factor in determining the delivery of palliative radiotherapy. Yeramilli et. al suggest hypofractionated radiation in patients with emergencies such as brain metastases, cord compression, superior vena cava syndrome, or tumor bleeding if treatment will alleviate the symptoms in a patient who has a life expectancy longer than days to weeks [21]. The authors do not propose a "prognosis cut-off" after which palliative radiation should not be offered, but rather stress that patients should have undergone a goals-of-care discussion and be aware of their prognosis prior to being offered this treatment [21].

Chemotherapy, immunotherapy, and clinical trials

The effects of cancer-directed therapy on a patient's immune system are of great concern during a pandemic. Large studies out of Wuhan, China, show that cancer patients have double the risk of infection when compared to the general population (OR 2.31, 95% CI 1.89–3.02) [22••]. Furthermore, cancer patients with COVID-19 were much more likely to have severe outcomes such as ICU admission, mechanical ventilation, and death when compared to non-cancer patients (39% vs. 8%, $p = 0.003$) [23••]. Additionally, early studies from New York show that while immunotherapy does not increase susceptibility to COVID-19, recent use is associated with death due to COVID-19 (RR 3.49, 95% CI 1.08–11.27) [24.4].

In light of these findings, an SGO expert panel was convened to provide consensus guidelines for cancer-directed therapy in the setting of strained resources and increased risk of morbidity and mortality during the pandemic [24•]. While the benefits of chemotherapy are significant, the risks of immunosuppression, acute toxicities requiring hospitalization, and multiple trips to and from treatment must be carefully considered for each patient. Much like the guidelines for surgery and radiotherapy, consensus guidelines for chemotherapy outline general considerations for therapy as well as more specific recommendations for each cancer subtype. General recommendations include avoiding inpatient chemotherapy, utilizing regimens with short infusions and more time between cycles, and regularly testing all patients for COVID-19 if able [24•]. Furthermore, the authors recommend the liberal utilization of granulocyte colony-stimulating factor, local collection of nadir labs, and maximizing the use of telemedicine. If suspicious for neutropenic

fever, patients should be managed at home with oral antibiotics if clinically stable, with daily telemedicine visits.

For those patients enrolled in clinical trials, tier 1 studies that have great potential to benefit patients should be prioritized. While deviations from trial protocols are to be expected given strained resources, trial sponsors and the IRB should be informed of these deviations and the patients' safety should always be prioritized [24•].

Oral medications

Whereas upfront and adjuvant therapy with curative intent should not be delayed, the risks/benefit ratio of maintenance infusions such as bevacizumab should be carefully weighed, and an oral maintenance drug such as a PARP-inhibitor substituted in appropriate cases [24•]. Multiple randomized placebo-controlled trials have shown improved progression-free survival with the use of maintenance poly adenosine diphosphate-ribose polymerase inhibitors (PARP-I) in first-line and platinum-sensitive recurrent ovarian cancers [25]. The SOLO3 trial demonstrates that PARP-I have improved efficacy over nonplatinum IV chemotherapy in patients with platinum-sensitive recurrent ovarian cancer and a germline BRCA 1/2 mutation. Based on these trials, Monk et al. suggest a brief "treatment holiday" or switching from IV therapy to PARP-inhibitors in select patients in order to decrease risk of COVID-19 exposure during the pandemic [25].

PARP-inhibitors have also been investigated as an alternative to surgery in BRCA-mutated ovarian cancers. In one case series, two patients — both with unresectable disease — underwent 6 and 9 cycles of NACT respectively, and ultimately had complete clinical response by CA-125 and imaging findings. Both patients were transitioned to maintenance Olaparib in lieu of IDS, and both remain without evidence of disease [26]. Given that IDS is considered semi-urgent during COVID-19, as well as the known responsiveness of BRCA-mutated patients to PARP inhibition, the authors suggest consideration of PARP-I maintenance in BRCA + patients who have complete clinical response to NACT. While this strategy is only based on two cases, it does provide a viable alternative during this pandemic [26].

Other oral agents such as hormonal agents for endometrial intraepithelial neoplasia or low-grade endometrial cancer should also be considered in patients who are at high risk for surgical morbidity or if elective surgery is currently restricted due to high COVID volume [27••].

Impact on surveillance

Given the increased vulnerability of oncology patients to COVID-19, post-treatment surveillance for gynecologic malignancies, including in-person visits for exams, laboratory testing, and imaging studies, should be tailored to take into account this risk [4••, 23••, 28]. Surveillance algorithms for

cervical, endometrial, and epithelial ovarian cancers were proposed by Mancebo et al. with the suggestion of alternating or integrating telemedicine visits with in-person visits using a shared decision-making model as outlined below (Table 2) [29]:

Imaging was only recommended if there was a high suspicion for disease recurrence, such as new symptom onset, abnormal physical exam findings, or increase in tumor markers.

Impact on providers

The impact of COVID-19 on gynecologic oncology providers' well-being and emotional health is an additional challenge that has been under-recognized during this pandemic. It is important for healthcare organizations and local authorities to appreciate the impact of COVID-19 on physicians, both mentally and physically, in order to keep up with increased demands of healthcare professionals during this time. Numerous studies have shown increased rates of anxiety, depression, and post-traumatic stress disorder in healthcare workers during the COVID-19 pandemic [30]. With regard to oncology providers in particular, a cross-sectional anonymous online survey of oncologists in the USA during the first month of the pandemic showed that approximately 62% of physicians reported anxiety and 23.5% reported depression symptoms, both of which were associated with (1) inadequate access to PPE, (2) concern about contracting COVID-19 or transmitting COVID-19 to a patient or family member, and (3) concern about accessing adequate care for themselves in the case of serious illness [31]. Interestingly, during the initial period of the outbreak, frontline healthcare workers in Wuhan, China, reported lower rates of burnout compared to their colleagues who continued to work in non-COVID-related roles, such as oncology specialists [32]. The authors suggest that this difference is due to the perception of increased control and responsibility by frontline healthcare workers, whereas oncologists who continued to work in their usual practice experienced increased burnout because they feared how COVID-19 would disproportionately impact their vulnerable cancer patients and interrupt treatments with no sense of control over the situation [32].

A viewpoint article published in JAMA in April 2020 conducted eight listening sessions during the first week of the pandemic to ascertain the main concerns of healthcare workers and how those concerns could be alleviated [33]. These concerns included fear that provider expertise would not be appreciated, fear of acquiring COVID-19, lack of appropriate training, lack of support services in response to increased demand, and fear that the individual or their family would not be cared for if they fell ill [33]. The main requests from healthcare professionals in response to these concerns were divided into the following categories: "hear me," "protect me," "prepare me," "support me," and "care for me" [33]. It is the responsibility of healthcare leaders and government representatives to acknowledge these requests and fulfill them to the best of their abilities. Although gynecologic oncologists may not be

Table 2. Gynecologic cancer surveillance modifications during the COVID-19 pandemic [29]

Gynecologic cancer	Stratification	Recommendations
Cervical cancer	-Low risk (FIGO 2009 stage IA-IB1) -High risk (locally advanced disease and beyond)	**Low risk** — Alternate in-person and telemedicine visits every 3 months during the first 2 years of follow-up **High risk** — In-person evaluation by GYN every 3 months and RT or ONC every 6 months for the first 2 years of follow-up
Endometrial cancer	-Low risk -Low-intermediate risk -High-intermediate risk -High risk *Stratified by ESMO-ESGO guidelines	**Low and low-intermediate risk** — Alternate in-person and telemedicine visits every 6 months during the first 2 years of follow-up with RT present for in-person visit if radiotherapy adjuvant therapy received **High-intermediate and high risk** — Alternate in-person and telemedicine visits every 3 months with GYN and RT+/−ONC to assess for side effects of treatment
Epithelial ovarian cancer	No data supporting surveillance stratification based on histologic type	GYN+ONC evaluation in-person every 6 months and ONC alone over telemedicine every 6 months between in-person visits

ESMO-ESGO, European Society for Medical Oncology-European Society of Gynaecological Oncology; *GYN*, gynecologic oncologist; ***RT***, radiation oncologist; *ONC*, medical oncologist

considered "frontline healthcare workers," their continued work throughout the pandemic to care for some of the most vulnerable patients requires recognition of their contributions and attention to the mental health and well-being of these providers.

Innovations as a result of the pandemic

While COVID-19 has profoundly challenged our field, it has also presented opportunities for growth and innovation. The integration of telemedicine has allowed for continued surveillance of asymptomatic and low-risk patients. While it certainly cannot replace clinical exams for diseases such as cervical and endometrial cancers, telemedicine has helped providers and patients safely stay in contact during the pandemic [10]. A survey of 215 breast and gynecologic oncology patients who participated in telemedicine at a large New York City hospital showed that telemedicine was widely accepted, with 92% reporting it saved time, 73% reporting increased access to care, and 82% reporting an improvement in their health due to telemedicine [34]. A similar patient satisfaction survey at a large urban academic center showed that telemedicine can be rapidly implemented while maintaining quality of care, with 82.3% of patients reporting they would use telemedicine again [35]. The use of telemedicine for surveillance purposes during COVID-19 is an important opportunity to evaluate the routine integration of telemedicine in gynecologic oncology practices.

Additionally, the use of technology provides a window of opportunity for flow of information across departments and institutions. Teleconferencing allows for safe and easily coordinated multidisciplinary conferences and tumor boards to discuss patient care. In addition, cross-institutional communication via teleconferencing provides a unique opportunity to learn from and collaborate with practitioners at other institutions [36]. Academically, web-based systems have additionally helped to standardize and maintain high-quality educational programs, such as that offered by ***GYOedu.org*** so that trainees can continue to learn during the pandemic.

From a support system standpoint, many patients were abruptly isolated during the pandemic due to the rapid halt of non-essential clinical encounters. A survey of 129 GYN cancer patients across Europe by the European Society of Gynecologic Oncology (ESGO) showed that patients primarily feared cancer progression or disruption in cancer care (70.9%) rather than fear of contracting COVID-19 from a clinic visit (18.3%) [37]. Interviews with women undergoing treatment revealed the themes of feeling alone during treatment, loss of cancer-specific social support, and varying access to information [38]. The pandemic has certainly left many women feeling isolated and abandoned due to the loss of their usual support systems. At our own institution, the authors worked with the *Women to Women* support group organizers to transition to virtual support group meetings. Our data show that transitioning to a virtual forum more than doubled support group attendance, allowed for diversification of topics, reached a broader group of women with a variety of needs, and increased physician involvement in patient support groups. Thus, teleconferencing and virtual forums are excellent tools to ensure gynecologic cancer patients continue to feel supported during the pandemic.

Author Contribution

All authors contributed to the manuscript conception. Dr Blank had the idea for the manuscript, Dr. Leibold performed the literature search, Dr. Leibold and Dr. Papatla drafted the manuscript, and Dr. Zeligs and Dr. Blank critically revised the work. All authors read and approved the final manuscript.

Declarations

Conflict of Interest

Aurora Leibold declares that there is no conflict of interest. Katyayani Papatla declares that there is no conflict of interest. Kristen P. Zeligs declares that there is no conflict of interest. Stephanie V. Blank declares that there is no conflict of interest.

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