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Clinical Practice Statement

Anti-cancer therapy and clinical trial considerations for gynecologic oncology patients during the COVID-19 pandemic crisis☆

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HIGHLIGHTS

- The world wide COVID-19 pandemic has limited cancer care and clinical trials.
- Strategies should be employed to limit contact points with health care facilities.
- All care should consider the risks of cancer care balanced against the risk of COVID-19 infection.

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ABSTRACT

Objectives. The COVID-19 pandemic has consumed considerable resources and has impacted the delivery of cancer care. Patients with cancer may have factors which place them at high risk for COVID 19 morbidity or mortality. Highly immunosuppressive chemotherapy regimens and possible exposure to COVID-19 during treatment may put patients at additional risk. The Society of Gynecologic Oncology convened an expert panel to address recommendations for best practices during this crisis to minimize risk to patients from deviations in cancer care and from COVID-19 morbidity.

Methods. An expert panel convened to develop initial consensus guidelines regarding anti-neoplastic therapy during the COVID-19 pandemic with respect to gynecologic cancer care and clinical trials.

Results. COVID-19 poses special risks to patients who are older, have medical co-morbidities, and cancer. In addition, this pandemic will likely strain resources, making delivery of cancer care or conduct of clinical trials unpredictable. Recommendations are to limit visits and contact with health care facilities by using telemedicine when appropriate, and choosing regimens which require less frequent visits and which are less immunosuppressive. Deviations will occur in clinical trials as a result of limited resources, and it is important to understand regulatory obligations to trial sponsors as well as to the IRB to ensure that clinical trial and patient safety oversight are maintained.

Conclusions. The ongoing crisis will strain resources needed to deliver cancer care. When alterations to the delivery of care are mandated, efforts should be taken to minimize risks and maximize safety while approximating standard practice.

☆ On behalf of the Society of Gynecologic Oncology. This SGO Clinical Practice Statement has been reviewed and approved by the SGO Clinical Practice Committee, Publication Committee and Board of Directors. This SGO Clinical Practice Statement was not peer-reviewed by Gynecologic Oncology.

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1. Introduction

The COVID-19 pandemic has rapidly and drastically changed the care of gynecologic cancer patients. Regardless of geographic location, COVID-19 will impact all practitioners; however, the degree will vary based on COVID-19 burden and available local resources. Given this variability, decisions regarding cancer care delivery should be individualized, and institutional and government mandates prioritized based on locoregional factors. Special considerations are needed with regard to decisions of systemic cancer-directed therapy and clinical trial enrollment during this unprecedented time. Chemotherapy and other anticancer treatments may result in significant immune compromise in patients, rendering them more susceptible to viral and other infectious illnesses. The recent Wuhan experience of 1524 patients reported in JAMA Oncology noted that the infection rate in cancer patients was double that of general population (OR, 2.31; 95% CI, 1.89–3.02) [1]. In addition, over 41% of COVID-19 infections were contracted in the hospital [2]. Cancer patients admitted were at higher risk of severe events (composite endpoint: percentage of patients admitted to ICU, ventilated, or death) compared with patients without cancer (seven [39%] of 18 patients vs 124 [8%] of 1572 patients; Fisher's exact $p = 0.0003$). Lastly, patients who underwent chemotherapy or surgery within the previous month had a numerically higher risk of severe events [3]. Though these were small series reported in China with differences in cancer care and no gynecologic cancer patients diagnosed with COVID-19 during the study period, the findings are informative in helping us understand the potential risks to our patients with cancer.

Given this information, we must carefully weigh the risk that COVID-19 presents to patients receiving anti-neoplastic therapy and participating on clinical trials. Traveling to treatment centers and interacting with the healthcare team increases patients' risk of COVID-19 exposure and transmission. Cancer treatment causes its own toxicities requiring acute care, and possibly hospitalization, and can increase severe COVID-19 infection risk via immunocompromise. Nonetheless, chemotherapy has a therapeutic benefit, and careful deliberation is required in the decision-making surrounding anti-cancer therapy and clinical trials management during this challenging time (Table 1).

2. Frontline considerations in COVID-19 burdened regions

- *Neoadjuvant chemotherapy for ovarian cancer compared with primary surgical debulking can reduce morbidity and reduce risk of hospitalization over primary surgical debulking especially in high COVID-19 burden areas* [4,5].
- *Delaying interval debulking surgery beyond 3–4 cycles of neoadjuvant chemotherapy can reduce morbidity and hospitalization for patients with ovarian cancer.*
- *Choose regimens that necessitate the fewest infusion visits (*i.e.*, q 3 week paclitaxel/carboplatin)* [6]*. Consider avoiding/limiting the prescription of dose-dense, intraperitoneal, and HIPEC regimens.*
- *Consider oral hormonal mono-therapy in patients with low-grade serous ovarian cancers* [7].
- *For early endometrial cancer, treatment with progesterone therapy or a progesterone containing IUD may decrease bleeding and provide temporizing benefit if primary surgery is delayed for lower grade cancers* [8].
- *For advanced/recurrent endometrial cancer consider the use of megestrol acetate, or megestrol acetate alternating with tamoxifen for endometrial cancer with endometrioid histology, or if estrogen/progesterone receptor status positive* [9,10]*. Oral everolimus/letrozole may have a better response rate compared to hormonal therapy alone but the impact of the increased toxicity and possible immunosuppression should be considered* [11].
- *Avoid radiation if possible unless for curative intent (i.e., locally advanced cervical cancer)*
- *For patients with recurrent cervical cancer who have received prior cisplatin, consider paclitaxel/carboplatin over paclitaxel/cisplatin based regimen due to shorter total time in infusion center and less toxicity* [12].
- *For Stage IV primary high grade endometrial and cervical cancers, consider delaying/deferring non-curative treatment, especially if patients are older or possess significant co-morbidities unless to control symptoms that may necessitate/lead to hospitalization. Goals of care discussion are of paramount importance in this situation.*

Table 1
General considerations for cancer directed therapy.

Prior to start of therapy	- Consider goals of therapy: Frontline curative intent should be prioritized, maintenance therapy should be evaluated in terms of incremental survival benefit, and palliative treatment should be utilized to mitigate uncontrolled cancer symptoms that may lead to inpatient hospitalization - Transfer patients to infusion centers not at main hospital campuses where patients with COVID-19 are being evaluated and treated. - Consider local administration of chemotherapy if a patient lives far from the current infusion site or it requires traveling to a COVID-19 “hotspot”. - Test for COVID-19 prior to cancer directed therapy if testing capabilities allow - Try to limit frequency of infusions; avoid weekly infusions - Consider single agent therapy or holding cancer-directed therapy for patients >65 years old, patients at any age with significant co-morbidity (DM, chronic lung disease and cardiovascular disease) or ECOG status ≥2 [74]. Patients with these co-morbid conditions appear to be at higher risk for severe COVID-19 disease than those without. Fatality was highest in persons ≥85 years old, ranging from 10% to 27%, followed by 3% to 11% among persons aged 65–84 years, 1% to 3% among persons aged 55–64 years, <1% among persons aged 20–54 years, and no fatalities among persons aged ≤19 years [75]. More recent reports note very few fatalities in ≤19 years age group. - Consider oral therapies over infusion-based treatments when appropriate; be mindful that some oral regimens may have more toxicities than infusion-based therapies. - With select exceptions (i.e. high risk GTD), avoid inpatient administration of chemotherapy, when possible. - Screen all patients for symptoms of COVID-19 and ensure temperature <99.5 prior to treatment and consider testing if possible, prior to chemotherapy
During therapy	- Utilize telemedicine to reduce the frequency of in person evaluation and allow for patients to proceed directly to infusion center for treatment. - Obtain local collection of labs whenever possible. - Consider liberal use of granulocyte colony stimulating factor. Prioritize home administration or use of pegfilgrastim on-body injector in lieu of return for pegfilgrastim on day 2. - Consider outpatient management of neutropenic fever when clinically stable with moxifloxacin 400 mg po daily or ciprofloxacin po 500–750 mg BID and Augmentin 875 mg BID po. Maintain close follow-up with daily phone contact for at least 3 days to ensure no clinical deterioration [76,77].
Post-therapy	- Delay imaging during or after completion of treatment to a post-COVID surge timeframe unless critical to patients' immediate care. - Ensure that goals of care discussions with patients (including DNR/DNI status) are prioritized prior to or shortly after admission, even if via telephone or telemedicine. - Increase interval for routine port flushes to 8–12 weeks.

Table 2
Issues to deliberate when starting/continuing anti-cancer therapy in gynecologic oncology patients during COVID-19.

Issue	Consideration
What is the goal of treatment for your patient?	• Are you impacting OS? Cure? • Are you expecting meaningful prolongation of PFS?
What is the health status of your individual patient?	• Can you assess their overall morbidity and mortality due to cancer? Use of Geriatric Screening G8 for older patients (9)
What is the likelihood of toxicity from anti-cancer treatment?	• Utilization of CARG toxicity tool to predict grade 3–5 toxicity • http://www.mycarg.org/Chemo_Toxicity_Calculator
Are there alternatives of similar efficacy which minimize toxicity from anti-cancer therapy and/or risk from exposure to the health care system?	• Oral agents (oral ≠ non-toxic) • Fewer in-person visits • Treatment holidays

The general considerations outlined in Tables 1 and 2 should be utilized when deliberating front-line anti-cancer therapy. For specific treatment options see Tables 3 and 4 in selecting primary treatment for early stage and late stage gynecologic malignancies, respectively.

In advanced ovarian cancer the decision between primary debulking surgery (PDS) and neoadjuvant chemotherapy (NACT) must be made with respect to COVID-19 burden and available resources. Careful decision-making regarding surgery should be utilized in older patients, those with significant medical co-morbidities, poor nutritional status, and those who may require prolonged ICU/hospital stay or require nursing home/facility placement post-surgery. While NACT can avoid many of these challenges, it does require a biopsy for pathologic confirmation, and chemotherapy will still result in an immunocompromised state. Randomized phase 3 trials, including EORTC and CHORUS, demonstrated that NACT is not inferior to primary surgical cytoreduction with respect to overall and progression-free survival, with lower morbidity [4,5]. NACT in patients with advanced stage disease is a viable alternative to PDS when resources for surgical intervention are restricted during the pandemic crisis.

For high-grade serous ovarian cancer, a 3 week taxane/platinum regimen is optimal and dose-dense and intraperitoneal regimens should probably be avoided [6]. With NACT, consider delaying interval debulking surgery beyond 3–4 cycles to reduce surgical morbidity and hospitalization in high COVID burden areas. Hormonal therapy has demonstrated efficacy in low grade serous ovarian cancer; consider transitioning from chemotherapy to hormonal monotherapy [7].

Progesterone therapy with megestrol acetate or levonorgestrel intrauterine device for early stage, grade 1/2 endometrioid endometrial cancer can be utilized in lieu of surgery due to limited capability secondary to resource limitations [8]. In advanced stage endometrioid and/or hormone receptor positive tumors, oral megestrol acetate, or megestrol acetate alternating with tamoxifen can be utilized [9,10]. Increased efficacy of oral everolimus and letrozole must be balanced with greater toxicity and immunosuppression [11].

Radiation therapy should be utilized for curative intent. Chemoradiation offers improved survival in locally advanced cervical cancer and should be prioritized [13–15]. For metastatic cervical cancer, use of q 3-week paclitaxel and carboplatin can reduce total time in infusion center and toxicity [12]. Consider the overall survival benefit with bevacizumab versus risk of fistula and hospitalization in cervical cancer [16].

3. Maintenance therapy considerations

- *If utilizing maintenance therapy, consider the risk/benefit ratio with respect to exposure and infection during infusion* versus *the risk of immunosuppression with PARP inhibitor (PARPi) therapy*
  - *While bevacizumab can delay recurrence in the primary and recurrent settings this treatment does necessitate frequent visits to the cancer center*
  - *Oral PARPi should be considered in patients with high benefit to risk ratio (*i.e. *BRCA1/2 mutations and HRD)*

- *Patients should wait up to 8–12 weeks for recovery of blood counts from front line chemotherapy prior to starting maintenance PARPi; if not recovered, consider not starting PARPi maintenance*
- *Consider deferring/delaying IV maintenance therapy*
  - *The risk benefit ratio should be considered based on resources available and the risk for infection at the time of infusion*
  - *For patients currently on IV maintenance therapy review individualized COVID-19 risk factors and benefit of continued maintenance*

- *For those in prolonged remission, consider holding maintenance therapy during COVID-19 crisis.*

Table 3
Front-line cancer-specific chemotherapy considerations for women with early-stage gynecologic malignancies during the COVID-19 pandemic.

High-grade ovary stage 1/2	Low-grade ovary stage 1/2	Germ cell tumors ovary	Endometrial	Cervix	GTN (low risk WHO score 0–6)
Platinum/taxane chemotherapy every 3 weeks [78]	Oral aromatase inhibitor monotherapy versus observation [7]	Hold bleomycin in dysgerminoma, consider holding bleomycin due to pulmonary toxicity, inability to obtain PFTs [61,62,79]	Platinum/taxane chemotherapy every 3 weeks (high risk histologic subtypes) [80,81]	Chemo-radiation in curative cases [82,83]	D and C prior to treatment if indicated and resources allow [65] MTX IM daily × 5 (0.4 mg/kg q 14 d) [67] MTX (1 mg/kg or 50 mg) IM D 1,3,5,7 with folinic acid rescue q 14 d [66]
					Consider MTX po Daily × 5 0.4 mg/kg, Dose cap = 25 mg/day Repeated in 14 d [68]
		Consider observation for select early-stage patients (enrollment or following the guidance in COG study, AGCT1531, a Phase 3 Study of Active Surveillance for Low Risk and a Randomized Trial of Carboplatin vs. Cisplatin for Standard Risk Pediatric and Adult Patients with Germ Cell Tumors) [60]	Consideration of oral or intrauterine options, when available: levonorgestrel IUD (22) or megestrol acetate (23) for Gr 1/2 endometrioid histology [84,85]		Consider for score 0–1: MTX weekly 50 mg/m2 IM [69] Can also consider dactinomycin for all low risk GTD to reduce number of visits but must weigh against toxicity and need for central access [69]

Table 4
Front-line cancer-specific chemotherapy considerations for women with advanced- stage gynecologic malignancies during the COVID-19 pandemic.

High-grade ovary	Low-grade ovary	Endometrial	Cervix	Vulva	GTN (high risk WHO score ≥ 7)	Leiomyosarcoma
Neoadjuvant chemotherapy preferred over primary debulking in high COVID burden regions [4,5] Platinum/taxane chemotherapy every 3 weeks [6]; consider thoughtful incorporation of bevacizumab (i.e., stage IV, significant ascites) [18,25]	Chemotherapy followed by aromatase inhibitor therapy vs. aromatase inhibitor monotherapy [7,86]	Platinum/taxane Chemotherapy every 3 weeks [87]	Chemoradiation for curative cases [13–15]	Neoadjuvant chemo-radiation [88]	Inpatient EMA-CO for choriocarcinoma [89] EMA-EP for placental site trophoblastic tumor (PSTT) [70]	Single agent doxorubicin q 3 wks [57]
Preferred oral maintenance PARPi vs. bevacizumab use based on assessment of COVID 19 exposure risk vs. benefit or observation only	Low threshold to transition to oral hormonal maintenance	Avoid radiation unless indicated for curative intent	Paclitaxel/carboplatin [12] or taxane/platinum with bevacizumab every 3 weeks (weigh survival benefit versus risk of fistula) [12,16]			Aromatase inhibitors in ER + uLMS [58] Oral pazopanib [52]
		Consideration of oral options: megestrol acetate, or megestrol acetate alternating tamoxifen, oral everolimus/ letrozole, weigh increased toxicity over above hormone regimens [9–11]	Stage IV and high risk for COVID-19 morbidity consider delaying/deferring non-curative intent treatment; goals of care discussion			
		Stage IV (high grade) and high risk for COVID-19 morbidity - consider delaying/deferring non-curative intent treatment; goals of care discussion				

Two main classes of maintenance therapies FDA approved for ovarian cancer include IV anti-angiogenic agent (bevacizumab) and oral PARPi (olaparib, niraparib, rucaparib), [17–27]. While both agents prolong progression-free survival, one must consider incremental benefit and the risk of traveling for infusion as well as the risk of immunosuppression and COVID-19 infection when selecting use. Oral agents are preferred and PARPi can be utilized especially in biomarker positive (i.e. *BRCA* 1/2 mutation and HRD) patients. When utilizing PARPi maintenance adequate time should be allowed for bone marrow recovery and consideration should be given to delaying initiation of PARPi (8–12 weeks). Selection of PARPi should take into consideration the need for laboratory analysis, and ease of modifications for toxicity and dosing via telehealth modalities. Thoughtful incorporation of bevacizumab with chemotherapy in high-risk disease (stage IV, symptomatic pleural effusion/ascites) may decrease symptoms more quickly and keep patients from needing hospitalization or other interventions; the risk of added toxicity must be considered. In the maintenance setting, consider bevacizumab use based on assessment of COVID-19 exposure risk vs. benefit.

4. Considerations for surveillance and recurrent disease

- *Routine surveillance of asymptomatic patients should be postponed as appropriate, or conducted* via *telemedicine.*
- *Consider delaying start of new therapy for patients with asymptomatic recurrence (and/or CA125 only recurrence for ovarian cancer patients)* [28].
- *For patients with symptomatic, recurrent disease, choice of therapy should be predicated on minimizing exposure to other contacts, risk from therapy, and life expectancy/prognosis.*
- *Consider lower dosing intensity and less myelosuppressive regimens to reduce lymphopenia and neutropenia. While the exact role of lymphopenia and neutropenia in COVID-19 infections remains unclear, lymphopenia has been described to be associated with poor outcome or more severe disease for patients with COVID-19 infections* [29–31].
- *In certain patients, oral therapies may be a preferred alternative to minimize visits and exposure to the medical setting. In patients with grade 1/2 endometrioid endometrial cancers, oral hormonal therapy regimens such as megestrol acetate or alternating megestrol acetate/tamoxifen can be considered* [9,10]. *PARPi can be used as treatment for BRCA associated or platinum-sensitive HRD ovarian cancers* [32–34]. *Oral chemotherapies (etoposide or cyclophosphamide) are other options for patients with ovarian cancer* [35,36].
- *One should be cognizant of the risks and benefits of further therapy, considering the risk for potential COVID-19 complications. Best supportive care may provide better outcomes for patients in whom the likelihood of benefit from further therapy is low (*e.g., *platinum-refractory ovarian cancer).*

Principles surrounding surveillance and treatment of recurrent gynecologic malignancies mirror considerations for front-line therapy and center around minimizing the risk of COVID-19 exposure and the risk of toxicity from therapy in these patients (Tables 1 and 2). While prospective data regarding early treatment of asymptomatic recurrence are limited, a randomized trial of 527 patients treated for recurrent ovarian cancer based on CA125 level alone compared to clinical or symptomatic relapse demonstrated no difference in overall survival between these two groups [28]. Additionally, case series have reported that between 41 and 83% of endometrial cancer patients and between 46 and 95% of cervical cancer patients will have symptoms at the time of recurrence, even in the setting of surveillance, suggesting that remote telemedicine visits can identify many patients with potential recurrence [37]. For patients in whom chemotherapy is being considered, emerging data have reported both higher rate of COVID-19 infection in cancer patients as well as increased risk of severe events, especially in patients who have received recent cancer-directed therapy [1,3,38]. As such, when making decisions about proceeding with therapy for recurrent disease and choice of therapy regimen, careful consideration must be made regarding the benefits of therapy in terms of symptomatic relief, survival, and prevention of hospitalization, compared to the risks of

increased exposure to the medical setting for therapy, possible complications of therapy, and potential for increased risk of COVID-19 infection or severity.

5. Considerations for immunotherapy

- *Immunotherapy: COVID-19 infection and early immunotherapy-related pneumonitis have similar presentations. In the case of suspected pneumonitis, test for COVID-19 prior to start of steroids and collaborate with pulmonary consultants.*
- *Access to PFTs and bronchoscopy may be limited and decisions may need to be determined based on clinical findings and severity of symptoms.*
- *Consider utilizing less frequent dosing intervals for immune checkpoint inhibitors*

  Pembrolizumab, 400 mg IV q 6 weeks

  Nivolumab 480 mg IV q 4 weeks

  Atezolizumab 1680 mg IV q 4 weeks

Immunotherapy is increasingly used to treat gynecologic cancers [39–41]. Currently no evidence demonstrates that immunotherapy, in cancer patients, increases COVID-19 susceptibility. Strong overlap between immune-related (IR) pneumonitis and COVID-19 infection exists, including cough, dyspnea, fever and CT findings of ground-glass opacities and interstitial changes [42,43].

Patients on immunotherapy with unexplained fever and pulmonary symptoms or new CT findings (symptomatic or undergoing bronchoscopy and/or corticosteroid intervention) should have COVID-19 testing. While corticosteroids are a mainstay of treatment of IR-related pneumonitis [43], steroids can prolong immunosuppression; increase risk of infections; delay viral clearance; and increase viral pneumonitis mortality [44,45]. Currently, the WHO and CDC recommend that corticosteroids not be used in treatment of COVID-19 viral pneumonia or ARDS unless indicated for another reason (asthma, COPD, septic shock) [46].

Carefully evaluate anticipated benefit before starting immunotherapy. Pre-existing lymphopenia is associated with lower immunotherapy response and predicts more severe COVID-19 infections [31,47]. Immunotherapy administration at higher dose and longer treatment intervals can decrease clinic visit frequency [48].

6. Considerations for older and medically vulnerable patients

- *Consider the goals of care for the patient with respect to relief of symptoms or improvement in overall survival.*
- *Evaluation of the patient's health status with respect to COVID-19 morbidity will help determine treatment*
- *Determine how the toxicity from treatment will put the patient at risk*
- *Decrease the frequency of visits to reduce the risk with less frequent schedules or oral alternatives*

Older patients (≥65) and/or those with medical comorbidities are at significantly increased risk of morbidity and mortality if the contract COVID-19. In addition to general considerations to mitigate COVID-19 infections (Tables 1 and 2), consider assessment of frailty and prediction of toxicity risk in this most vulnerable population. The Geriatric 8 panel (G8) is a concise version of the geriatric assessment tool (18 items) and assesses frailty. The lower the score (< 14), the more frail the patient may be and the higher the risk for chemotherapy related toxicities. The 8-item scale may be completed by phone using the patient's reported weight [49]. The Cancer Aging Research Group (CARG) toxicity calculator (http://www.mycarg.org/Chemo_Toxicity_Calculator) is a simple, complimentary, online tool that provides a percentage of chemotherapy related toxicity (grade 3–5) based on patient information and selected regimens [50,51]. These assessments, combined with candid goals of therapy discussions, can help counsel older patients and assist with treatment decisions.

7. Considerations for uterine leiomyosarcoma

- *There is no proven benefit from adjuvant therapy in early stage uterine leiomyosarcoma*
- *Single agent doxorubicin requires less frequent visits and may represent the best choice to limit visits during treatment*
- *Oral tyrosine-kinase inhibitor, pazopanib is an approved treatment option for sarcoma* [52].

The doxorubicin, ifosfamide, and the combination of gemcitabine and docetaxel represent the mainstays of front-line treatment for those patients with advanced or recurrent uterine leiomyosarcoma (uLMS). There is no proven benefit to adjuvant therapy in stage I or stage II uLMS [53]. For advanced or recurrent uLMS the gemcitabine/docetaxel doublet has demonstrated activity in prior trials, but requires administration on days 1 and 8 of a 21 day cycle and is associated with significant hematologic toxicity, including neutropenia, necessitating use of granulocyte colony stimulating factors [54–56]. Single agent doxorubicin is probably the optimal first-line treatment option during the COVID-19 crisis. In a phase III trial comparing doxorubicin q 21 days to the combination of gemcitabine and docetaxel every three weeks in patients with unresectable or metastatic soft tissue sarcoma, response rates, progression-free survival and overall survival were similar in both arms [57]. Dose delays and dose reductions were frequent in both groups, with the main reason being febrile neutropenia. Single-agent doxorubicin in the front-line setting should be considered, after balancing these risks with gemcitabine/docetaxel and the patient's risk of cardiac dysfunction with doxorubicin during the COVID-19 crisis. Pazopanib is an oral tyrosine-kinase which represents an option with activity in uLMS [52]. Aromatase inhibitors have limited toxicity and can result in stable disease in patients with ER positive uLMS [58]. With all of these non-curative therapies, the toxicity and risk of viral infection during treatment must be weighed against the potential benefit of these therapies.

8. Considerations for malignant germ cell tumors

- *Stage I grade 1 immature teratomas can be followed without treatment* [59]
- *Stage I dysgerminomas can be followed without treatment but tumor markers including LDH, hCG, and AFP should be checked to exclude a mixed tumor* [59]
- *Active surveillance could be considered in patients with complete staging who have a stage IA, grade 2/3 immature teratoma* [60]
- *The risks and benefits of bleomycin should be considered due to the concern for pulmonary toxicity and the risk of respiratory failure with COVID-19* [61]

Malignant germ cell tumors are chemo-sensitive and curable tumors that occur in young healthy patients and should be high priority if resources are limited. Conservative therapy can be considered but complete surgical staging including omentectomy and lymph node assessment is critical if adjuvant therapy is omitted. Active surveillance in grade 2/3 immature teratomas is currently being investigated in pediatric studies. However, there is some indication that pediatric tumors may have a less aggressive biology [62]. Stage IA yolk sac tumors and embryonal carcinoma could possibly be followed without treatment in extremely resource limited settings. In all cases of active surveillance,

tumor markers should be followed to make sure they decline appropriately.

Bleomycin can cause pulmonary toxicity in about 10% of patients and there is concern that this could increase the risk with co-existing COVID-19 infection [61]. Bleomycin can be safely omitted in dysgerminomas with no detriment in survival [63]. Based on the experience with non-seminomatous testicular cancers, the relapse rate increases by about 8% when bleomycin is not included in the chemotherapy regimen [61]. Therefore, the risks and benefits as well as the resources and rate of viral infection should be carefully considered when considering this chemotherapy regimen.

9. Considerations for Gestational Trophoblastic Disease (GTD)

- *Hysterectomy can be considered if fertility is not desired to reduce the need for chemotherapy if resources allow* [64]
- *A second D&C will result in remission in 38% of patients* [65]
- *Standard 5-day or 8-day methotrexate regimens are preferred in low risk GTD (WHO ≤ 6)* [66,67]
- *A 5-day oral regimen has been described in low risk GTD with similar efficacy to IM regimens* [68]
- *Weekly methotrexate at 50 mg/m2 can be considered for very low risk disease (WHO 0–1)*
- *Dactinomycin at 1.25 mg/m2 has been shown to be more efficacious than weekly methotrexate in patients with a WHO score ≤ 6* [69]
- *EMA-CO should be given to patients with a WHO score ≥ 6 even though this regimen requires hospitalization* [70]

GTD is a chemo-sensitive and curable disease that occurs in premenopausal patients. A second D&C would be recommended to avoid chemotherapy in 38% of patients [65]. Either the 8-day or 5-day regimens are acceptable for women with a WHO score of ≤6 but both regimens require frequent visits for the injections which may increase exposure to viral infection [66,67]. A small series of an oral 5-day regimen has been described with outcomes that are similar to those reported with methotrexate injections and could be considered to reduce the risk of exposure or when infusion resources are limited [68]. Dactinomycin at 1.25 mg/m2 has the advantage of every 2 week dosing and has been shown to be superior to weekly methotrexate [69]. However, the success rate for this regimen was only 44% in women with a WHO score of 5–6 and generally should be given through a central line to reduce the risk of extravasation injury. All regimens should be continued until 3 treatments past a normal hCG defined as (<5 mIU/ml) [64]. The inpatient EMA-CO regimen is recommended for patients with high risk disease (WHO > 6).

10. Clinical trial considerations

- *Prioritize Tier 1 studies where there is high potential benefit (i.e., trial that offers drug where alternative treatments are limited) in resource-stratified environments.*
- *Identify and inform sponsors when there will be deviations for visits/labs/physical exam/radiology tests that are not essential such as pharmacokinetics tests*
- *Be aware of your institutional regulatory guidelines regarding how COVID-19-related deviations should be tracked and reported.*
- *Prioritize shipping oral drugs to patients to minimize in-person visits.*
- *Consider COVID-19 burden and ability to enroll new patients on trial (safety, staffing resources including clinical trial nurses, data mangers, and regulatory staff)*

Conducting clinical trials during the COVID-19 crisis is challenging and will vary based on geographic location and institutional resources.

Table 5
Prioritization criteria for clinical trials during the COVID-19 pandemic.

Clinical research studies		
Essential studies		Non-essential Studies
Tier 1	Tier 2	Tier 3
High potential direct benefit to research participants[a]	Moderate potential direct benefit to research participants[b]	
All COVID-19 clinical research protocols		
Clinical research protocols with high potential benefit for an individual's survival or when alternative treatments are severely limited and there is a potential serious or immediate harm for an individual without protocol participation	Clinical research protocols that provide moderate potential benefit for an individual's health or well-being over time which, if unavailable, may pose a long-term risk to the research participant	Studies are observational or behavioral studies, surveys, focus groups, retrospective studies, archival data/sample-based research studies, or non-critical interventional studies, phase IV or biosimilar equivalency studies

[a] Clinical research protocols (1) involving treatments for acute, life threatening health conditions (i.e., some cancer trials) or (2) where stopping the intervention could be harmful (i.e., some investigational drugs, or vaccines or preventative drug).
[b] Clinical research protocols (1) evaluating treatments for chronic conditions or (2) involving assessment of the safety or efficacy of an intervention in which, if stopped, the potential societal benefit of the science would be significantly and adversely impacted, for example where a research assessment (blood collection or imaging study) is only valuable if at a very specific time.

Clinical trial guidelines are available from the FDA, National Cancer Institute, NRG Oncology, and local institutions [71–73]. Develop COVID-19 guidelines for investigator-initiated trials internally and distribute to participating sites. Clinical trials should be prioritized based on the study type and benefit potential (Table 5). Tier 2 and non-essential Tier 3 (tissue and non-therapeutic studies) are not enrolling at many centers. Before enrolling new patients consider COVID-19 burden and trial conduct capability including staffing, imaging, procedures, and research labs acquisition. Minimize non-critical visits and patient interactions between physicians and research coordinators using telemedicine to conduct visits and assessment of toxicity, symptoms, and concomitant medications. Arrange for delivery of investigative oral drugs directly to patients if possible and obtain labs and imaging locally. Inform and follow sponsor and IRB guidelines regarding deviations and patients diagnosed with COVID-19 while on study.

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Shannon N. Westin writing: Conceptualization, Writing - original draft, Writing - review & editing.

R. Wendel Naumann: Conceptualization, Methodology, Writing - original draft, Writing - review & editing.

Declaration of competing interest

Dr. Huh has nothing to disclose.

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