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Radiation therapy for gynecologic malignancies during the COVID-19 pandemic: International expert consensus recommendations

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Abstract

Objective. To develop expert consensus recommendations regarding radiation therapy for gynecologic malignancies during the COVID-19 pandemic.

Methods. An international committee of ten experts in gynecologic radiation oncology convened to provide consensus recommendations for patients with gynecologic malignancies referred for radiation therapy. Treatment priority groups were established. A review of the relevant literature was performed and different clinical scenarios were categorized into three priority groups. For each stage and clinical scenario in cervical, endometrial, vulvar, vaginal and ovarian cancer, specific recommendations regarding dose, technique, and timing were provided by the panel.

Results. Expert review and discussion generated consensus recommendations to guide radiation oncologists treating gynecologic malignancies during the COVID-19 pandemic. Priority scales for cervical, endometrial, vulvar, vaginal, and ovarian cancers are presented. Both radical and palliative treatments are discussed. Management of COVID-19 positive patients is considered. Hypofractionated radiation therapy should be used when feasible and recommendations regarding radiation dose, timing, and technique have been provided for external beam and brachytherapy treatments. Concurrent chemotherapy may be limited in some countries, and consideration of radiation alone is recommended.

Conclusions. The expert consensus recommendations provide guidance for delivering radiation therapy during the COVID-19 pandemic. Specific recommendations have been provided for common clinical scenarios encountered in gynecologic radiation oncology with a focus on strategies to reduce patient and staff exposure to COVID-19.

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HIGHLIGHTS

• An international panel of gynecologic radiation oncologists offer recommendations for RT during the COVID-19 pandemic.
• Recommendations for cervical cancer, uterine cancer, vulvar cancer, vaginal cancer and ovarian cancer have been provided.
• Recommendations for RT timing, fractionation, and dose have been provided for external beam radiation and brachytherapy.
• The panel emphasizes strategies to reduce risk of transmission of the novel SARS-CoV-2 to patients and healthcare workers.
• These recommendations may be used any time an event occurs which limits healthcare resources, including natural disasters.
1. Introduction

On March 11, 2020, the World Health Organization (WHO) declared the 2019 coronavirus disease (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) a pandemic [1]. Currently, there is neither a vaccine nor confirmed effective medical treatments against SARS-CoV-2 [2]. Public health officials from the U.S. Centers for Disease Control and Prevention (CDC) and WHO have issued recommendations for increased hygiene vigilance, use of masks to reduce spread of respiratory droplets, and social distancing for all persons, as well as screening, testing, and contact tracing to be organized by governments. Around the world, local and federal governments have enacted mandatory quarantines, banned mass gatherings, closed non-essential businesses and schools, and significantly reduced or eliminated travel across regional and international borders in an effort to slow the spread of the virus and avoid overwhelming the capacity of the healthcare system [1,3,4].

Many hospitals have implemented strategies to prevent the spread of the virus among patients and staff including converting in-person appointments to telemedicine visits, reducing or rescheduling routine follow up appointments, limiting hospital visitors, restricting or eliminating medical student and resident interactions with patients, and postponing elective procedures and surgeries [5–7]. However, the treatment of patients with cancer is time-sensitive and delayed treatment has been associated with inferior local control and survival [8–17]. As such, several radiation oncology departments around the world have come up with contingency plans for the treatment of cancer patients during the COVID-19 pandemic. Radiation oncology department-specific [5,18–23], disease site-specific [24–30], and patient population-specific guidelines [31,32] have been published in an effort to reduce patient visits to the clinic, prioritize patient treatments, consider testing for asymptomatic patients and provide guidance on how to best protect patients and staff when treating patients with confirmed or suspected infection with SARS-CoV-2.

For patients with gynecologic malignancies, radiation therapy (RT) is often an integral component of multi-modality management and can be delivered in the definitive, adjuvant, and palliative setting. However, RT requires repeated visits to radiation oncology clinics and may place patients at increased risk of exposure to SARS-CoV-2. Additionally, cancer patients may have an increased risk of contracting the virus or difficulty clearing the virus once infected due to their immunocompromised state [19]. Two independent studies have reported a greater risk of severe events (ICU admission, mechanical ventilation, and death) secondary to COVID-19 in cancer patients compared to patients without cancer in China [33,34]. Radiation oncologists must carefully consider the risks and benefits of RT against the risk of contracting SARS-CoV-2 for each individual patient. Furthermore, the risks to healthcare staff and the use of limited healthcare resources, such as personal protective equipment (PPE) and ventilators, must be considered as well.

An international panel of experts in gynecologic radiation oncology convened to review relevant literature and discuss recommendations regarding the timing and delivery of RT for patients with gynecologic malignancies. This report is meant to provide a framework for clinical decision making. However, when evaluating a patient for consideration for RT during the COVID-19 pandemic, the radiation oncologist should take into consideration the following: the anticipated peak and length of the pandemic in a certain geographic area, the capacity of the healthcare system (including the availability of PPE and highly-trained staff), the age and medical comorbidities of each patient, the magnitude of benefit derived from delivery of RT, and the potential risk of delay, modification, or omission of RT.

The impact of the pandemic on radiology, surgical oncology, and medical oncology may influence RT recommendations. In some locations, cancer screening examinations such as mammography and colonoscopy are not being offered which may result in more advanced disease presentations. In many countries, elective surgical procedures have been delayed in order to limit patients from entering the health care system, provide adequate intensive care facilities for COVID positive patients, and to preserve crucial supplies of PPE. Though most cancer operations are not considered elective, the lack of available ventilators, recovery spaces, and PPE may result in delays for surgical procedures. Finally, use of chemotherapy may be limited or unavailable in some countries due to manufacturing and supply chain disruptions or deferred to avoid risks of patients becoming immunocompromised.

2. Methods

An international panel of ten gynecologic radiation oncologists convened to develop consensus guidelines regarding the timing and delivery of RT for patients with gynecologic malignancies. Based on different clinical scenarios, the panel was asked to place patients in three priority risk groups (A, B, or C) adapted from the Pandemic Planning Clinical Guideline for Patients with Cancer published by Cancer Care Ontario [35]. For the purposes of our panel recommendations, priority A patients are defined as patients who are deemed critical and may require treatment during the pandemic, even if the patient has known or suspected infection with COVID-19. Priority A also includes patients with rapidly progressive tumors that are potentially curable with prompt initiation of treatment. Priority B patients are those who require treatment but whose situation is non-critical. If staff or PPE shortages occur to the extent that clinics are only able to provide care for priority A patients, priority B patients could be delayed up to 8–12 weeks without significant risk of harm. Priority C patients include patients with non-life-threatening conditions whose treatment may be delayed without anticipated change in outcome for an indeterminate period of time. In this group, we have also included patients for whom observation or alternative therapies could be considered instead of RT with minimal or no detriment in outcome. Table 1 summarizes the working definitions of the priority groups.

For patients with metastatic disease, we have compiled recommendations on treatment of symptomatic abdominopelvic disease. However, recommendations for palliative RT to other distant metastatic sites (e.g. brain metastases, spine metastases, etc.) from gynecologic primary sites have not been considered for the purpose of this paper. Recommendations regarding palliative RT during the COVID-19 pandemic have been previously published [31].

Consensus on treatment recommendations was reached through extensive discussion via videoconference call. All authors had access to a shared electronic document and they were able to provide recommendations for treatment management as well as references to published literature to support their recommendations. Recommendations were compiled by author C.E. and forwarded to all members of the expert consensus panel. Any disagreements among members of the panel were discussed by e-mail until a consensus was reached. All authors have reviewed and given support to the final recommendations.

3. Results

3.1. Cervical cancer

The recommendations from the consensus panel for patients with cervical cancer are provided in Table 2.

Table 1

| Priority A | Priority B | Priority C |
|------------|------------|------------|
| Critical patients due to severe pain or bleeding or patients who require treatment during a pandemic due to potentially curable, rapidly dividing tumors | Patients who can safely be delayed (up to 8–12 weeks if necessary) | Patients with non-life-threatening conditions. Radiation therapy can be reasonably delayed throughout the duration of the pandemic or omitted |
A summary of recommendations from the consensus panel includes:

General

- Given the nature of cervical cancer as a rapidly dividing tumor with a high potential for cure, the panel did not feel any clinical scenario was appropriate to be categorized as priority C.

Patients with locally-advanced disease

- For patients with cervical cancer who require treatment breaks, treatment with additional RT dose, while respecting tolerance doses to nearby critical structures, should be considered to account for tumor repopulation. Gay et al. have provided suggestions regarding dose escalation for patients who require treatment breaks [38].

- For patients requiring brachytherapy, inpatient treatment with one insertion rather than outpatient treatment with multiple insertions is preferable to reduce aerosolizing procedures that may occur during anesthesia and to minimize close contact with the patient required for procedures. An attempt should be made to maximize the number of fractions of RT delivered for each applicator insertion.

- The number of delivered RT fractions should be reduced to the fewest number when possible while respecting tolerance doses of nearby OARs. For instance, HDR brachytherapy delivered as 24 Gy in three fractions or 28 Gy in four fractions should be prioritized over longer fractionation schedules. For external beam RT, any boosts should be performed using a simultaneous integrated boost (SIB) technique rather than a sequential cone-down boost to reduce the number of RT fractions [37–39].

### Table 2

Consensus panel recommendations for patients with cervical cancer.

| Priority A | Technique and Dose | Priority B | Technique and Dose |
|------------|-------------------|------------|-------------------|
| Locally advanced, inoperable disease (Stage IB3-IVA) or Stage IB1-IIA who are medically inoperable or refuse surgical intervention | Definitive CRT WP/EF; EBRT to 45 Gy; SIB boost to gross disease to 55–60 Gy followed by BT | Stage IA1, IA2 who are medically inoperable or refuse surgical intervention | Definitive RT alone: |
| | Suggested HDR dose: 7 Gy × 4 f. or 8 Gy × 3 f. [42–44] | | Medically inoperable patients with Stage 1A1 disease may receive BT alone |
| | If chemotherapy not available: RT alone to 40–50 Gy in 2 Gy/fraction (depending on stage and disease burden) with SIB boost to gross disease followed by BT | | EBRT + BT is indicated in all patients with stage ≥IA2 [41] |
| Regardless of tumor stage, any patient with severe bleeding secondary to cervical cancer | Non-metastatic radical treatment: definitive CRT with WP/EF to 45 Gy, SIB nodal boost to 55–60 Gy or RT alone 40–50 Gy followed by a BT boost | Post-operative Stage IA1-IIB2 with risk-factors meeting criteria for adjuvant EBRT based on GOG 92 [53] | EBRT 40–50.4 Gy in 1.8–2 Gy fractions [53] |
| | Suggested HDR dose: 7 Gy × 4 fx, or 8 Gy × 3 f. [42–44] | | Can be delayed up to 12 weeks based on consensus panel opinion |
| | Metastatic or non-metastatic palliative treatment: tumor-directed RT alone as palliation based on extent of disease and performance status | | No consensus on hypofractionation dose or duration for pelvic RT |
| | Palliative RT: 10 Gy × 1 f. (can be repeated monthly up to 2 more times) [45–48] | | |
| | “Quad Shot” of 3.7 Gy BID x 4 f. (can be repeated monthly up to 2 more times) [49,50] | | |
| | 4 Gy × 5 f. [51,52] | | |
| | Post-operative patients with positive pelvic (or PA nodes), surgical margins, or parametria who require CRT based on GOG 109 [54] | | CRT to 45–50 Gy [54] |
| | Patients with metastatic disease with discomfort controlled with oral pain medications or minimal bleeding who require palliative RT | | Can be delayed up to 8 weeks [55] if necessary based on consensus panel opinion |
| | “Quad Shot” of 3.7 Gy BID x 4 f. (can be repeated monthly up to 2 more times) [49,50] | | 10 Gy × 1 f. (can be repeated monthly up to 2 more times) [45–48] |
| | 4 Gy × 5 f. [51,52] | | 4 Gy × 5 f. [51,52] |

**BID**: twice daily; **BT**: brachytherapy; **CRT**: chemoradiotherapy; **EBRT**: external beam radiation therapy; **EF**: extended field; **Fx**: fraction; **GOG**: Gynecologic Oncology Group; **Gy**: Gray; **IC**: intracavitary; **IS**: interstitial; **HDR**: high-dose rate; **LDR**: low-dose rate; **PA**: paraaortic; **PDR**: pulsed-dose rate; **RT**: radiation therapy; **SIB**: simultaneous integrated boost; **WP**: whole pelvis.

* Boost clinically positive nodes with SIB technique to reduce total number of fractions.

* HDR, PDR, or LDR brachytherapy may be used based on resource availability.

* Combined intracavitary/interstitial applicators.

* To reduce risk of exposure to COVID-19, a single application with the delivery of multiple fx is preferred.

* The decision to delay therapy and the interval of delay should be determined based on (1) individual risk of the patient to have an adverse outcome due to COVID-19 based on age and medical comorbidity, (2) individual risk of disease progression given treatment delay, and (3) epidemiologic data based on the projected peak of the pandemic in a specific geographic area.
• For patients who cannot receive systemic therapy and require external beam RT, the panel recommends a dose of 50 Gy in 25 fractions to the pelvis when possible. In addition, accelerated radiation therapy delivered six days per week may also be used [40].
• All treatment should be completed within 8 weeks when feasible, and delays are not recommended given the potential impact on survival [41].

Post-operative patients
• Patients receiving post-operative RT may be delayed up to 8–12 weeks if necessary depending on the clinical scenario.

3.2. Endometrial cancer

The recommendations from the consensus panel for patients with endometrial cancer are provided in Table 3.
A summary of recommendations from the consensus panel includes:
General
• For patients with symptomatic, inoperable disease receiving radiation therapy with or without chemotherapy should be treated expeditiously.
• For patients with endometrioid histology, hormonal therapy may be used to delay RT start.
• SBRT delivered to a dose of 20–30 Gy in 4–5 fractions may be used as a boost in patients who cannot tolerate or refuse brachytherapy [58,59]. However, the consensus panel recommends that brachytherapy boosts remain the standard of care and should always be preferred over SBRT boosts. The potential risks of increased toxicity and inferior local control associated with SBRT boosts should be discussed with the patient prior to treatment [59].

Patients with inoperable disease
• Patients with symptomatic, inoperable disease receiving radiation therapy with or without chemotherapy should be treated expeditiously.
• For patients with endometrioid histology, hormonal therapy may be used to delay RT start.
•SBRT delivered to a dose of 20–30 Gy in 4–5 fractions may be used as a boost in patients who cannot tolerate or refuse brachytherapy [58,59]. However, the consensus panel recommends that brachytherapy boosts remain the standard of care and should always be preferred over SBRT boosts. The potential risks of increased toxicity and inferior local control associated with SBRT boosts should be discussed with the patient prior to treatment [59].

Post-operative patients
• Many patients receiving adjuvant radiation therapy may safely be delayed between 6 and 8 weeks after surgery depending on the clinical scenario.
• Brachytherapy fractionation regimens with fewer total fractions should be preferentially used, while respecting tolerance doses to nearby OARs. For instance, patients receiving post-operative vaginal cuff brachytherapy may be treated with a shorter fractionation regimen such as 21 Gy in 3 fractions instead of longer fractionation regimens such as 24 Gy in 6 fractions.
• The panel recommends patients with stage IA grade 3, Stage IB grade 1–2, and patients with low-risk stage II disease [60] may be preferentially treated with adjuvant vaginal cuff brachytherapy instead of external beam radiation therapy to minimize the number of treatment visits required.

3.3. Vulvar cancer

The recommendations from the consensus panel for patients with vulvar cancer are provided in Table 4.
A summary of recommendations from the consensus panel includes:
General
• Patients with intact de novo or recurrent disease receiving definitive radiation therapy with or without chemotherapy should be treated expeditiously.
• For external beam RT, any boosts should be performed using a simultaneous integrated boost (SIB) technique rather than a sequential cone-down boost to reduce the number of RT fractions [39,74].

Post-operative patients
• Patients receiving adjuvant radiation therapy may be safely delayed between 6 and 8 weeks after surgery depending on the clinical scenario.
• Post-operative patients found to have positive nodes at the time of surgery should have RT promptly initiated.

3.4. Vaginal cancer

The recommendations from the consensus panel for patients with vaginal cancer are provided in Table 5.
A summary of recommendations from the consensus panel includes:
General
• There were no clinical scenarios reviewed that were categorized as priority C.
• Patients with intact disease receiving definitive radiation therapy with or without chemotherapy should be treated expeditiously.
• For external beam RT, any boosts should be performed using a simultaneous integrated boost (SIB) technique rather than a sequential cone-down boost to reduce the number of RT fractions [39].

Post-operative patients
• Post-operative patients with close or positive margins or pathologically involved nodes with no gross residual disease, may be delayed up to 6–8 weeks from the time of surgery depending on the clinical scenario.

3.5. Ovarian Cancer

The recommendations from the consensus panel for patients with ovarian cancer are provided in Table 6.
A summary of recommendations from the consensus panel includes:
General
• There were no clinical scenarios reviewed that were categorized as priority C.
• Patients previously treated with surgery and chemotherapy with an isolated locoregional relapse may be treated with involved-field radiation therapy.

3.6. All disease sites

Across disease sites, the panel has recommendations regarding external beam and brachytherapy fractionation, treatment breaks, and systemic therapy.

3.6.1. External beam radiation therapy

When different fractionation regimens are available for external beam radiation therapy, the panel recommends the total number of fractions be minimized while respecting the tolerance doses of organs at risk. For instance, when possible, the use of a simultaneous integrated boost (SIB) should be used instead of a sequential cone-down boost to limit the number of fractions [37,39]. This will help to minimize patient visits to the clinic as well as risks of infection to patients and healthcare personnel. Finally, if a patient contracts the SARS-CoV-2 virus or is a person under investigation (PUI), a treatment break may be required. For patients requiring a treatment break, consider adding additional radiation dose to account for tumor repopulation during the treatment break. The potential benefits of additional radiation dose must be carefully weighed against the potential risks of additional dose to organs at risk. Gay et al. have outlined specific guidelines regarding treatment breaks for patients with cervical cancer [36]. For patients who cannot be safely put on a break throughout the duration of infection with
Table 3
Consensus panel recommendations for patients with endometrial cancer.

| Priority A | Technique and Dose | Priority B | Technique and Dose | Priority C | Technique and Dose |
|------------|--------------------|------------|--------------------|------------|--------------------|
| Regardless of stage, patients with severe vaginal bleeding | | | | | |
| | Definitive RT for inoperable cases: | Post-operative stage IA, grade 3 or stage IB, grade 1–2, and low-risk stage II endometrioid carcinoma [60] | Post-operative stage IA, grade 1–2 endometrioid carcinoma with higher risk features (age > 60, LVSI) | | |
| | EBRT to WP to 45 Gy followed by HDR IC boost: 8.5 Gy × 2 fx, or 6.3–6.5 Gy × 3 fx [42,61] or SBRT boost if BT is not tolerated [58] | HDR VCBT 7 Gy × 3 fx [63,64] (preferred)* | Consider observation (preferred) [65] | | |
| | EBRT to WP to 50.4 Gy followed by HDR IC boost: 6 Gy × 2 fx [42,61] or SBRT boost if BT is not tolerated [58] | | If patient prefers VCBT, treatment can be deferred up to 12 weeks based on consensus panel opinion | | |
| | HDR IC monotherapy (Stage I) [42,61,62]: 8.5 Gy × 4 fx, or 8–10 Gy × 3 fx | | | | |
| | Palliative RT: 10 Gy × 1 fx. (can be repeated monthly up to 2 more times) [45–48] | | | | |
| | “Quad Shot” of 3.7 Gy BID x 4 fx. (can be repeated monthly up to 2 more times) [49,50] | | | | |
| Medically or surgically inoperable patients with non-endometrioid histology who are not candidates for systemic therapy | | | | | |
| | 4 Gy × 5 fx [51,52] Definitive RT: | Post-operative stage IB, grade 3 and Stage II endometrioid carcinoma | EBRT to 45 Gy [66] | Medically or surgically inoperable endometrioid carcinoma patients who are candidates for hormone therapy and can begin immediately | |
| | EBRT to WP to 45 Gy followed by HDR IC boost: 8.5 Gy × 2 fx, or 6.3–6.5 Gy × 3 fx [42,61] or SBRT boost if BT not tolerated [58] | | EBRT should begin within 6–8 weeks of surgery | | |
| | EBRT to WP to 50.4 Gy followed by HDR IC boost: 6 Gy × 2 fx [42,61] or SBRT boost if BT not tolerated [58] | | | | |
| | HDR IC monotherapy (Stage I) [42,61,62]: 8.5 Gy × 4 fx, or 8–10 Gy × 3 fx | | | | |
| Recurrent vaginal cuff disease | | | | | |
| | Definitive (chemo) RT with EBRT to 45–50.4 Gy followed by IC/ISd HDR Boost: 7–8 Gy × 3 fx or 6 Gy × 4 fx, twice daily [67,68] or SBRT boost if BT not tolerated | Post-operative patients with grade 1-histology with positive nodes (Stage III) | Consider EBRT* to 45–50.4 Gy without chemo [60,70] | Post-operative stage III-IV patients who meet criteria for GOG 258 [71] can be considered for chemotherapy alone (+/− EBRT after chemotherapy) | |
| | | | | | |
| | Post-operative Stage IA-IV non-endometrioid histology who have completed systemic therapy* | Stage IA: HDR VCBT* 7 Gy × 3 fx | | | |
| | | Stage IB-IV: EBRT* 45–50.4 Gy; consider HDR VCBT boost of 5–6 Gy × 2 fx [42,63] for adverse risk factors | | | |
| | | Or | | | |
Table 3 (continued)

| Priority A | Technique and Dose | Priority B | Technique and Dose | Priority C | Technique and Dose |
|------------|--------------------|------------|--------------------|------------|--------------------|
|            | If patient meets criteria for GOG 99 [72], can avoid brachytherapy boost and deliver EBRT to 50.4 Gy |

ABS: American Brachytherapy Society; BID: twice daily; Chemo: chemotherapy; EBRT: external beam radiation therapy; fx: fraction; GOG: Gynecologic Oncology Group; Gy: Gray; HDR: high dose rate; IC: intracavitary; IS: interstitial; LVSI: lymphovascular space invasion; RT: radiation therapy; SBRT: stereotactic body radiation therapy; VCBT: vaginal cuff brachytherapy; WP: whole pelvis.

a VCBT can be delayed but should start no later than 9 weeks post hysterectomy [73]; if already started on treatment and the patient becomes COVID-19 positive or a person under investigation (PUI), then up to 14 days between fractions is acceptable.
b VCBT can be completed after the completion of chemotherapy instead of prior to chemotherapy or between chemotherapy cycles.
c EBRT can be delayed but should not start no later than 8 weeks post chemotherapy; consider if BT alone is a reasonable substitute for these patients after weighing risks and benefit.
d Patients with bulky disease (≥0.5 cm thick) should be considered for IS brachytherapy.
e EBRT should be started within 6–8 weeks post-operatively.

Table 4
Consensus panel recommendation for patients with vulvar cancer.

| Priority A | Technique and Dose | Priority B | Technique and Dose | Priority C | Technique and Dose |
|------------|--------------------|------------|--------------------|------------|--------------------|
|            | Palliative RT: 10 Gy × 1 f. (can be repeated monthly up to 2 more times) [45–48] | Post-operative stage IB-II patients with positive margins who are not candidates for margin re-excision | EBRTa,b to the vulva 45–50.4 but higher doses up to 60 Gy may be required depending on the margin or presence of LVSI [75–78] | Post-operative stage IB-II patients with close margins who are not candidates for margin re-excision (or possibly for patients with +LVSI, DOI >5 mm, tumor size ≥4 cm, diffuse or spray histology) | Consider observation for close margins [79] |
|            | 4 Gy × 5 fx |                                                                 |                                                                 |                                                                 | If treatment is clinically indicated, EBRTa,c to the vulva 45–50.4 but higher doses up to 60 Gy may be required depending on the margin or presence of LVSI [75–77,80] |
|            | Post-operative patients with ≥1 positive lymph nodes | Adjunctive EBRTa,d to 45–50 Gy to the WP, bilateral inguinal nodes +/+ vulva [81,82] | Preoperative CRT to 45 Gy to regional nodes with a booste to the primary site and any other site of gross disease to 57.6–60 Gy [83] |                                                                 |                                                                 |
|            | Intact stage III/IVA disease | Definitive/preoperative CRT | Preoperative CRT to 45 Gy to regional nodes with a booste to the primary site and any other site of gross disease to 57.6–60 Gy [83] |                                                                 |                                                                 |
|            | Recurrent vulvar disease in patients who are not candidates for further surgery and were previously not treated with RT | Definitive (chemo)RT to the pelvis and inguinal nodes to 45 Gy–50.4 Gy with a booste to the vulva to 60–70 Gy [84–86] |                                                                 |                                                                 |                                                                 |
|            | Intact recurrent inguinal or pelvic disease in patients who are not candidates for further surgery | Definitive (chemo)RT to the pelvis and inguinal nodes to 45 Gy–50.4 Gy with a booste to gross disease to 60–70 Gy [87,88] |                                                                 |                                                                 |                                                                 |

BID: twice per day; chemo: chemotherapy; CRT: chemoradiotherapy; DOI: depth of invasion; ECE: extracapsular extension; EBRT: external beam radiation therapy; fx: fraction; LVSI: lymphovascular space invasion; RT: radiation therapy; SIB: simultaneous integrated boost; WP: whole pelvis.

a The decision to delay therapy and the interval of delay should be determined based on (1) individual risk of the patient to have an adverse outcome due to COVID-19 based on age and medical comorbidity, (2) individual risk of disease progression given treatment delay, and (3) epidemiologic data based on the projected peak of the pandemic in a specific geographic area.
b Can be delayed up to 6 weeks based on consensus panel opinion.
c Can be delayed up to 8 weeks based on consensus panel opinion.
d If margins are negative and there is no ECE, EBRT can be delayed up to 6 weeks.
e Any EBRT boosts should be delivered with SIB technique, if possible, to reduce the total number of fractions.
SARS-CoV-2, we recommend these patients be treated at the end of the day to minimize risks of infection to other patients.

3.6.2. Brachytherapy

When planning brachytherapy, consider the use of locoregional anesthesia or conscious sedation over the use of general anesthesia to minimize aerosolizing procedures such as general endotracheal intubation or use of laryngeal mask airways (LMA). There is an increased risk of aerosol generation associated with these procedures that may lead to airborne transmission of the virus to healthcare personnel [93,94]. Intubation has a high risk of aerosol production during the procedure; but once the tube is in place, the cuff provides a seal within the airway preventing further aerosolization [95]. While empirical data is currently lacking, expert opinion suggests that LMA use may carry greater risk of adverse outcomes than general anesthesia or conscious sedation over the use of general anesthesia to minimize aerosol transmission to healthcare personnel [96-98].

Precautions should be taken to limit the number of individuals in the room to anesthesia personnel only during intubations and extubations and all individuals present must have airborne PPE.

To further mitigate risk, some institutions have initiated universal COVID-19 testing for all patients undergoing procedures, particularly those requiring endotracheal intubation [99]. When available, testing for COVID-19 prior to the procedure will help determine if a patient is COVID-19 positive and will inform providers of appropriate PPE requirements. This information may also be used to decide if a patient should be delayed or treated with an alternative method such as SBRT. At a minimum, for all patients with negative COVID-19 testing or

ABS: American Brachytherapy Society; BID: twice per day; BT: brachytherapy; CRT: chemoradiotherapy; EBRT: external beam radiation therapy; EQD2: Equivalent dose in 2 Gray fractions; fx: fraction; Gy: Gray; IC: intracavitary; IS: interstitial; RT: radiation therapy; SIB: simultaneous integrated boost; WP: whole pelvis

Table 5
Consensus panel recommendation for patients with vaginal cancer.

| Priority A | Technique and Dose | Priority B | Technique and Dose |
|------------|--------------------|------------|--------------------|
| Bleeding or severely painful lesions in patients with metastatic disease | 10 Gy × 1 f. (can be repeated monthly up to 2 more times) [45–48] | Post-operative patients with close/positive margins or pathologically involved nodes with no gross residual disease. | Close/positive marginsa,b; IC/IS BT +/− EBRT [67,69] or CRT [96] |
| Medically or surgically inoperable patients with stage I disease | “Quad Shot” of 3.7 Gy BID x 4 f. (can be repeated monthly up to 2 more times) [49,50] | 4 Gy × 5 f. [51,52] | Pathologically involved nodes: CRT to 45–50.4 Gy with consideration of SIB boost to 55–60 Gy to any areas of gross disease [91] |
| Intact stage II-IVA disease | 4 Gy × 5 f. [51,52] | Definitive RT | 4 Gy × 5 f. [51,52] |

ABS: American Brachytherapy Society; BID: twice per day; BT: brachytherapy; CRT: chemoradiotherapy; EBRT: external beam radiation therapy; EQD2: Equivalent dose in 2 Gray fractions; fx: fraction; Gy: Gray; IC: intracavitary; IS: interstitial; RT: radiation therapy; SIB: simultaneous integrated boost; WP: whole pelvis

a The decision to delay therapy and the interval of delay should be determined based on (1) individual risk of the patient to have an adverse outcome due to COVID-19 based on age and medical comorbidity, (2) individual risk of disease progression given treatment delay, and (3) epidemiologic data based on the project peak of the pandemic in a specific geographic area.

b EBRT can be delayed up to 6 weeks for patients with positive margins and up to 8 weeks for patients with close margins.

c Any EBRT boosts should be delivered with SIB technique, if possible, to reduce the total number of fractions.

Table 6
Consensus panel recommendation for patients with ovarian cancer.

| Priority A | Technique and Dose | Priority B | Technique and Dose |
|------------|--------------------|------------|--------------------|
| Bleeding or severely painful disease in patients with metastatic disease who are not candidates for surgical or systemic therapies | Palliative RT: 10 Gy × 1 f. (can be repeated monthly up to 2 more times) [45–48] | Isolated locoregional relapse in patients with prior surgery and chemotherapy | Definitive IFRT to 45–68.2 Gy [92] |
| | “Quad Shot” of 3.7 Gy BID x 4 f. (can be repeated monthly up to 2 more times) [49,50] | | |
| | 4 Gy × 5 f. [51,52] | | |

BID: twice per day; Fx: fraction; Gy: Gray; IFRT: involved-field radiation therapy; RT: radiation therapy.
those presumed to be negative when pre-operative testing is not available, the panel recommends the use of a surgical mask and eye protection. In addition, appropriate PPE should be used even with procedures being performed with conscious sedation as there is a risk of coughing associated with sedative agents [100] and some patients may ultimately require intubation during the course of the procedure if complications arise.

The number of fractions delivered for each applicator insertion should be monitored and brachytherapy fractionation regimens that minimize the total number of fractions delivered should be considered, when normal tissue tolerance permits, to reduce the number of required procedures and treatments during an RT course. For inpatient tandem and ovoid or interstitial procedures, this includes the use of twice daily treatments delivered a minimum of 6 h apart with immobilization and imaging, if available, each day to ensure accurate treatment of the target and avoidance of organs at risk.

3.6.3. Chemotherapy

The decision to proceed with concurrent, sensitizing chemotherapy should be made after a careful assessment of patient risk factors, expected magnitude of benefit from systemic therapy, and resource availability. If chemotherapy is omitted in patients with cervical cancer, dose escalation with external beam RT or brachytherapy may be used but tolerance doses to nearby organs at risk should be respected. Alternatively, accelerated RT delivered in six daily fractions per week may be used to compensate for omission of chemotherapy in patients who cannot or refuse to receive chemotherapy [40]. These decisions should be made using a shared decision making approach with patient and caregiver knowledge and involvement.

4. Discussion

An international expert consensus panel comprised of ten experts in gynecologic radiation oncology have reviewed the relevant literature and developed clinical practice recommendations to assist radiation oncologists treating gynecologic malignancies during the COVID-19 pandemic. Dissenting opinions were discussed openly and completely. Consensus was reached via the communications methods described above.

Similar to other disease sites, a priority scale was developed to triage patients with gynecologic malignancies [101]. Priority A patients should be treated expeditiously due to the severity of patient symptoms or because these patients have potentially curative, rapidly growing tumors and the opportunity for cure may be lost if treatment is delayed. While resources are not constrained, many priority B patients should be treated expeditiously, but radiation oncologists should consider if a potential delay in therapy may allow patient treatment after the regional peak of COVID-19 cases. If the capacity of the healthcare system is overwhelmed and resources are limited, priority B patients may be safely delayed in order to conserve resources for priority A patients. Priority C patients may delay RT for a longer interval or omit radiation in favor of observation or other therapeutic options. In the event that the pandemic continues for an extended period of time, patients who were initially placed into priority B may ultimately choose to omit RT. These patients should be closely monitored and should receive early salvage therapy at the time of recurrence. This approach is supported from prospective phase II data by Chopra et al. that established 5-year local control, disease free, and overall survival rates of 84%, 73%, and 74.5%, respectively, with the use of RT as early salvage therapy for vaginal recurrences of cervical cancer [102].

These guidelines are meant to help clinicians prioritize treatments but are not meant to serve as a replacement for clinician judgement. For each patient, the radiation oncologist must carefully consider the patient’s risk of contracting SARS-CoV-2 (based on age, comorbidities, immunocompetence), the risks of modifying, delaying or omitting radiation therapy, epidemiologic characteristics of the geographic region (anticipated peak, anticipated duration of peak), and availability of healthcare resources (highly-trained personnel, PPE). For patients with a diagnosis of COVID-19, there must be a careful balancing of the risks of immunosuppression from RT and chemotherapy with the risks of cancer progression that may arise from delay or omission of therapy. Additionally, the risks of exposure to SARS-CoV-2 among other patients and healthcare workers should be considered.

Clinicians may use these guidelines, along with their clinical judgement, when determining if or how RT should be modified during the COVID-19 pandemic. All decisions regarding modification, delay, or omission of RT should be clearly communicated to the patient along with the rationale, risks, benefits, and alternatives. If a decision to delay RT is made, the clinician and patient should have a thorough understanding of a follow up plan to minimize the risk of patients being lost to follow-up. Patients who choose to omit radiation therapy should be provided with a plan for cancer surveillance.

These recommendations are not intended to be static and they will continue to evolve based on local epidemiology of the SARS-CoV-2 virus, resource availability, and the development of effective medical therapies or a vaccine for SARS-CoV-2. However, these recommendations are meant to provide clinicians with a framework for triaging patients with gynecologic malignancies when there is any kind of resource limitation. As such, in the future, these guidelines may also be used for patient triage in the aftermath of other resource-limiting events such as natural disasters.

Declaration of Competing Interest

Christen Elledge, Supriya Chopra, Beth Erikson, David Gaffney, Anuja Jhingran, Ann Klopp, and Catherine Yashar have nothing to disclose. Akila Viswanathan is the principal investigator of NIH R01 CA237005. Sushil Berival is a consultant for Varian and Medical Director of Via Oncology, outside the submitted work. Cyrus Chargari receives grant funding from Roche, personal fees from Merck Sharp & Dohme Corp, Elekta, and GlaxoSmithKline, as well as non-financial support from TherAguiX and GlaxoSmithKline, all outside the submitted work. William Small is the co-chair of the NRG Gyn Committee, has served on an advisory board for Merck, and has received honoraria for invited talks from Carl Zeiss Meditec, outside the submitted work.

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