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COVID-19

# COVID-19 impact on timing of brachytherapy treatment and strategies for risk mitigation

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## ABSTRACT

**PURPOSE:** The purpose of this study was to highlight the importance of timely brachytherapy treatment for patients with gynecologic, breast, and prostate malignancies, and provide a framework for brachytherapy clinical practice and management in response to the COVID-19 pandemic.

**METHODS AND MATERIALS:** We review amassing evidence to help guide the management and timing of brachytherapy for gynecologic, breast, and prostate cancers. Where concrete data could not be found, peer-reviewed expert opinion is provided.

**RESULTS:** There may be a significant negative impact on oncologic outcomes for patients with gynecologic malignancies who have a delay in the timely completion of therapy. Delay of prostate or breast cancer treatment may also impact oncologic outcomes. If a treatment delay is expected, endocrine therapy may be an appropriate temporizing measure before delivery of radiation therapy. The use of shorter brachytherapy fractionation schedules will help minimize patient exposure and conserve resources.

**CONCLUSIONS:** Brachytherapy remains a critical treatment for patients and may shorten treatment time and exposure for some. Reduced patient exposure and resource utilization is important during COVID-19. Every effort should be made to ensure timely brachytherapy delivery for patients with gynecologic malignancies, and endocrine therapy may help temporize treatment delays for breast and prostate cancer patients. Physicians should continue to follow developing institutional, state, and federal guidelines/recommendations as challenges in delivering care during COVID-19 will continue to evolve. © 2020 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

## Keywords:

Coronavirus; COVID19; COVID-19; Cervical cancer; Uterine cancer; Breast cancer; Prostate cancer; Brachytherapy; Radiotherapy; Radiation oncology

Received 3 April 2020; received in revised form 10 April 2020; accepted 10 April 2020.

Disclosures: The authors declare no conflict of interest. There are no funding sources to disclose. There were no grants, monies, or other financial incentives or coercions used or offered in the preparation of this article. This article has not been presented or published, in part or in full, before this submission.

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## Introduction

The novel SARS-CoV-2 (severe acute respiratory syndrome corona virus 2) causing CORonaVirus Disease-19 (COVID-19) has resulted in a global pandemic with unprecedented impact on medical resources and personnel, and patient care access issues. Given the ease of host–host transmission and impact on medical resources, much of the world has implemented physical distancing and restrictions on when it is appropriate to leave home to further reduce transmission and subsequent strain on medical

resources. There is some suggestion that patients with cancer and COVID-19 may have worse respiratory outcomes than patients without cancer (1); however, these data are preliminary (2).

Given the constantly evolving challenges surrounding COVID-19 and the potential impact on health care, we reviewed amassing evidence to help guide the management and timing of brachytherapy for gynecologic, breast, and prostate cancers. Where concrete data could not be found, peer-reviewed expert opinion is provided. Importantly, these recommendations apply only to patients not known to be infected with SARS-CoV-2. For patients with symptoms concerning for COVID-19, or who have already tested positive, we recommend following the local clinic and/or hospital treatment policies and procedures given the unique resources of each institution. Delay of treatment until a negative COVID-19 test may be indicated to protect the patient and the treating team, and to maintain access to care for all other patients treated at that facility. Given this, the purpose of the following commentary is to highlight the importance of timely brachytherapy (BT) treatment for patients with breast, prostate, and gynecologic malignancies and provide a framework for clinical practice and management in response to the COVID-19 pandemic.

## The impact of time on treatment outcomes

### *Cervix*

During the COVID-19 pandemic, it is important to recognize that prolongation of the treatment duration has been shown to negatively impact tumor control outcomes through tumor repopulation (3). Fyles *et al.* retrospectively assessed the impact of overall treatment time (external beam RT, EBRT, and BT) on pelvic control in patients with FIGO Stage I-IV cervical cancer. Over 800 women were included and the median treatment time (weekends excluded) was 36 days. The authors found that every delay in treatment of 1 day over the median was associated with a 1% loss of pelvic control (4). In a similar retrospective study by Petereit *et al.*, in 209 patients with FIGO Stage IB-IIIIB cervical cancer who received EBRT and BT, the median duration of treatment was 55 days (duration included planned weekend breaks). They found that pelvic control (87% vs 72%,  $p = 0.006$ ) and 5 year survival (65% vs 54%,  $p = 0.03$ ) varied between treatment duration < 55 days and duration  $\geq 55$  days, respectively (5). This study also identified time between EBRT and initiation of BT as the most common cause of treatment prolongation (combined with holidays). Several other studies confirmed that treatment prolongation over 55 days ( $\geq 8$  weeks) adversely affected pelvic control in cervical cancer, and each additional day over this threshold was associated with  $\sim 1\%$  decrement in both pelvic control and overall survival (OS) (6,7). The effect on tumor control and survival was examined by Song *et al.* in the era of concurrent

chemotherapy. In a retrospective review of 113 women with FIGO Stage IB2-IIIIB cervical cancer, the authors found that time to completion of therapy (EBRT plus BT)  $> 56$  vs  $\leq 56$  days was associated with pelvic failure rate of 26% vs 9% ( $p = 0.04$ ). Therefore, even with concurrent chemotherapy, prolongation of the total treatment interval remains an essential factor impacting pelvic control (8,9). Finally, recent data from retroEMBRACE published by Tanderup *et al.* (9) in 488 women with locally advanced cervical cancer treated with chemotherapy and EBRT plus image-guided BT showed that overall treatment times (OTT)  $\leq 7$  weeks resulted in 3-year local control (LC) rates of  $> 86\text{--}94\%$ . OTT was found to be significantly associated with LC and an additional 5 Gy was required to compensate for loss of LC due to an increase of OTT beyond 7 weeks.

### *Uterus*

Timing of adjuvant therapy for uterine malignancies is important to patient treatment outcomes. Ahmed *et al.* (10) reviewed the records of 195 patients after total abdominal hysterectomy with or without lymph node sampling and found that delay in the interval from surgery to the start of radiation  $> 6$  weeks decreased disease-specific survival ( $p < 0.005$ ). Likewise, Fabrini *et al.* (11) investigated the impact of the interval between surgery and initiation of radiation in 177 patients with endometrial cancer. They found a significantly increased rate of local recurrence associated with a  $> 9$  week interval between surgery and radiation (11% vs 0%,  $p = 0.046$ ). Cattaneo *et al.* (12) found that delay in the time to initiation of radiation after hysterectomy with or without lymph node dissection in women with uterine carcinomas  $\geq 9$  weeks was associated with worse recurrence free survival (39% vs. 90%,  $p < 0.001$ ). Finally, a large, retrospective NCDB analysis reviewed the records of 16,520 patients with endometrial cancer for the impact of treatment interval on OS. They found that an interval between surgery and radiation  $\leq 8$  weeks was associated with improved 10-year OS ( $p = 0.014$ ) (13).

### *Special cases: vaginal cuff brachytherapy and medically inoperable endometrial cancer*

Vaginal BT is often considered as adjuvant therapy for patients with early-stage uterine carcinoma at intermediate or high risk of recurrence given that the vagina is the primary site of failure (14–16). There is limited data on the timing of vaginal BT relative to surgery.

Timing of vaginal BT can be individualized based on risk of recurrence. Patients should be counseled that salvage of a vaginal cuff recurrence is about 60–70% at skilled centers (ranges 50–90%) with intensification of treatment required for salvage (17). The risk of recurrence and the ability to deliver salvage therapy are considerations when jointly deciding the delivery and timing of vaginal BT.

In low-grade, early-stage cases (FIGO Stage I), medically operable endometrial cancer patients may be surgically delayed with an intrauterine device (IUD) delivering hormonal therapy. Medically inoperable patients are those who are deemed inoperable after assessment by their gynecologic oncologist or other qualified health professional involved in their care based on medical comorbidities. Although no data exist for patients with high-grade uterine malignancies, after surgery, these patients can be treated with BT alone or a combination of EBRT and BT (LDR or HDR) (18). Although it may be possible to delay surgery in patients with high-grade malignancies using an IUD delivering hormonal therapy during COVID-19, caution should be exercised as the long-term oncologic outcome in this situation is unknown.

### *Vaginal cancers*

Given the location of the vagina in close proximity to the bladder, rectum, and urethra, organ preservation with radiation or chemoradiation is often the best definitive treatment option (19). After EBRT, for tumors  $>0.5$  cm, interstitial BT is required to ensure adequate dosing to achieve a cure (20,21). Extrapolating from cervical cancer, and given the aggressive nature of vaginal tumors, treatment should be initiated as soon as is feasible and completed within  $\leq 8$  weeks.

### *Breast cancer*

In women with mammographically detected ductal carcinoma in situ (DCIS)  $< 2.5$  cm of low- or intermediate-grade and surgical margins  $\geq 2$  mm (22), or  $> 70$  years with invasive estrogen-receptor positive, node-negative tumors  $\leq 3$  cm, and negative surgical margins who are eligible to receive endocrine therapy (23), omission of RT is appropriate. The use of BT as adjuvant therapy is an alternative for select patients with an early-stage breast cancer. Consensus statements and guidelines have been published by ASTRO (24), the American Brachytherapy Society (25), and the American Society of Breast Surgeons (26). Accelerated partial breast irradiation (APBI) is an accepted standard of care for patients who fall into appropriate categories per guidelines. In the setting of single-entry intracavitary devices, timing is predicated by technical factors, primarily the presence of a seroma cavity in which to place the device. In general, it is the best practice to place the catheter and begin treatment within 4 weeks of breast-conserving surgery (BCS). With a multicatheter interstitial approach, the timing of BT is less dependent on the presence of a seroma cavity, and therefore falls in line with timing of external beam. For patients with DCIS radiation can be safely delayed up to 12 weeks after BCS (27). For patients with invasive disease, there are mixed data regarding timing of adjuvant treatment. Some studies show that RT treatment delay of 8–12 weeks after BCS

was associated with inferior local control (28), and a large systematic review of 46 studies showed local recurrence rates to be significantly higher in patients receiving adjuvant RT more than 8 weeks after surgery compared with those treated within 8 weeks (OR 1.62, 95% CI 1.21–2.16) (29). Other studies have shown that intervals up to 20 weeks may be safe and have no detriment to local control or OS for some patients without adverse tumor control or survival outcomes (30–34).

### *Prostate cancer*

There are conflicting data regarding whether postponement of treatment after diagnosis leads to worse outcomes in prostate cancer (35), for both surgery (36–38) and RT (39,40). It is likely that the retrospective nature of these studies and heterogeneous patient groups play a large role in the variability of findings. The largest of these studies involving surgery examined 3969 prostatectomy patients who underwent surgery within 1 year of diagnosis (36). It found no impact by time from biopsy to surgery on biochemical recurrence after a mean followup of 5.4 years; this remained true even when they examined the subset of higher risk patients. Similarly, the largest study on RT examined 1322 patients who underwent EBRT alone (39). They found no difference in OS, cause-specific survival, distant metastasis, or freedom from biochemical failure based on time to treatment ( $<3$ , 3–6, 6–9, or  $> 9$  months after diagnosis). They also found no difference in freedom from biochemical failure or distant metastasis in high-risk patients. Based on these studies, and others (41), the safe interval of postponement until definitive treatment may be 6–12 months. Even if there is a true detriment in cancer outcomes with postponement of therapy that is not fully captured by these studies. The conflicting data suggest a small magnitude that must be weighed against the risks posed to patients and society during the COVID-19 pandemic.

Overall, it is unlikely that postponement of a few months is unlikely to significantly impact disease outcomes. This is likely true for most grade Group 1 and 2 cancers because of their more indolent rate of growth, and for most higher-grade cancers because of the efficacy of androgen deprivation therapy (ADT). Traditionally, 2 months of neoadjuvant ADT is given before RT, although recent evidence suggests this is not necessary (42). However, in the setting of COVID-19 and to attempt to reduce patient exposure, neoadjuvant ADT may be given for as many as 6 months (and possibly longer) before definitive therapy given the excellent and equivalent results seen in studies using this approach.

The use of BT in the treatment of prostate cancer is typically as definitive treatment alone in low-risk and favorable intermediate-risk patients, and in combination with EBRT in unfavorable intermediate-risk and high-risk patients. In lower-risk patients, most evidence indicates the equivalence of BT alone compared with surgery or EBRT, and it has the

advantage over EBRT of a much shorter time commitment for the patient to be in a health care setting. Similarly, combining BT with EBRT decreases the total time a patient would need to be away from home, and some data show improved biochemical progression-free survival in select patients (43,44).

## Treatment recommendations

### Timing of therapy

#### Cervix

- For definitive therapy, the chemotherapy and external beam radiation plus BT total treatment package time should be  $\leq 8$  weeks.
- For adjuvant external beam radiation therapy (with or without BT) after surgery in patients meeting GOG 92 criteria (45), external beam radiation should ideally begin 4–6 weeks after surgery, but not longer than 12 weeks, and treatment interruption should be kept to a minimum. For adjuvant chemotherapy and external beam radiation (with or without BT) after surgery in patients meeting GOG 109 criteria (46), chemotherapy and external beam radiation should ideally begin 4–6 weeks after surgery, but not longer than 8 weeks, and treatment interruption should be kept to a minimum.

#### Uterus

- For adjuvant vaginal cuff BT after surgery, BT should ideally begin  $\leq 8$  weeks after surgery, but no more than 12 weeks.

#### Breast

- Physicians should consider department resources, patient COVID-19 infection risk (age, comorbidities), and technical factors when deciding if EBRT or breast BT is the most appropriate treatment modality.
- For patients with early-stage, favorable disease neoadjuvant endocrine therapy may be advised during the COVID-19 crisis as surgeries are being delayed. For patients requiring adjuvant treatment after BCS, breast BT is considered an equivalent option to EBRT. However, physicians should carefully consider the effect of neoadjuvant endocrine therapy on pathologic findings that are used to determine eligibility for APBI particularly in cases where endocrine therapy has extended beyond 3–6 months.
- APBI with a single-entry intracavitary, or multicatheter interstitial technique, can be initiated immediately after surgery. Once the seroma cavity has resolved, a multicatheter interstitial technique may be preferred.
- For patients with DCIS who proceed with breast BT after BCS, treatment should start within 12 weeks after surgery.

- For patients with invasive breast disease who proceed with breast BT after BCS, treatment should start within 12 weeks after surgery, and not more than 20 weeks.

#### Prostate

- For definitive treatment of localized low- and intermediate-risk prostate cancer, BT alone is adequate treatment (47,48). In the setting of COVID-19, treatment can be postponed for at least 3–6 months. For patients anxious about delaying treatment during COVID-19, BT alone would minimize treatment time and health care exposure compared with other modalities.
- For patients with high-risk factors, having the patient on ADT for 3–8 months is recommended until definitive BT can be delivered. For patients receiving a prostate BT boost, BT should begin within 2–4 weeks after completion of EBRT (49). If significant delays are anticipated, ADT should continue before initiating EBRT.

#### Fractionation options

##### Cervix

The ABS lists several recommended fractionation schemes for cervical cancer (50). Delivery of 28 Gy during four fractions (2 or 4 separate implantations) is appropriate, and shorter fractionation regimens may be considered to decrease treatment time, if appropriate (51–53), Table 1. Recent results from a prospective randomized trial carried out in India demonstrate that three fraction regimens may not increase toxicity greatly while providing equivalent tumor outcomes (54). However, caution should be used when deciding what fractionation schedule to use as there are data to suggest that two fractions may result in decreased tumor control (55).

For interstitial cervical HDR BT, the ABS recommend a single implantation with five treatments delivered twice daily with a minimum of 6 h separation between fractions (50). Alternatively, if delivery of five or more fractions during a single hospitalization is not feasible, delivery of 7 Gy twice per day separated by a 6 h interval performed twice during two separate implantations on consecutive weeks has also been found effective. Various fractionation options are shown in Table 1. For tumors with distal vaginal extension or involvement, smaller fraction sizes and additional fractions may be necessary that may minimize risk of high-grade toxicity and dose to organs at risk (OARs).

##### Uterus

For early-stage uterine cancer, adjuvant vaginal cuff monotherapy using HDR BT in three to six fractions is common. In the setting of COVID-19, minimizing patient exposure risk is imperative. The use of 7 Gy  $\times$  3 fractions

Table 1  
Potential fractionation options for gynecologic, breast, and prostate brachytherapy

Disease site	Dose per fraction, Gy	Fx, #	EQD2 (+45 Gy EBRT, $\alpha/\beta = 10$ )	Author/Reference
<b>Cervical Cancer</b>				
Point A based	8	3	80.3	Souhami <i>et al.</i> (51)
	7	4	83.9	Phan <i>et al.</i> (62)
	6	5	84.3	Rao <i>et al.</i> (54)
	5.5	5	79.8	ABS Consensus (63)
	5	6	81.8	ABS Task Group Report (50)
	5–6	5 (BID)	75–84	
HDR interstitial (1 insertion)	5–6	5 (BID)	75–84	
HDR interstitial (2 or 4 insertions)	7	4	83.9	
<b>Uterine Cancer</b>				
Vaginal cuff HDR monotherapy	7 Gy at 0.5 cm	3	57.8 (surface dose)	ABS Task Group Report (57)
	5.5 Gy at 0.5 cm	4	54.2 (surface dose)	PORTEC-2 (16)
	5 Gy at 0.5 cm	5	58.9 (surface dose)	ABS Task Group Report (50)
	8.5 Gy at surface	4	52.4 (surface dose)	Jolly <i>et al.</i> (64)
	6 Gy at surface	5	40 (surface dose)	ABS Task Group Report (57)
	4 Gy at surface	6	28 (surface dose)	MacLeod <i>et al.</i> (65)
	6 Gy at surface	2	60.3	ABS Task Group Report (50)
Vaginal cuff HDR boost	6 Gy at surface	2	60.3	Townamchai <i>et al.</i> (66)
	6 Gy at surface	3	68.3	RTOG 0921 (67)
	6 Gy at surface	3	68.3	RTOG 0418 (68)
Inoperable Stage I HDR monotherapy	8.5 Gy	4	52.4 (no EBRT)	ABS Task Group Report (57)
	7.3	5	52.6 (no EBRT)	ABS Task Group Report (57)
Inoperable Stage I HDR boost + EBRT	8.5	2	70.5	
	6.5	3	71.1	
Inoperable Sstage I HDR boost + EBRT	6	2	65.6	
	6	2	65.6	
<b>Breast Cancer</b>				
HDR accelerated partial breast irradiation	3.4–4.0	8–10 (BID)	42–45 ( $\alpha/\beta = 4–5$ )	RTOG 9517 (58)
	7.5	3		Strnad <i>et al.</i> (59)
<b>Prostate Cancer</b>				
HDR monotherapy	13.5	2	104.6 ( $\alpha/\beta = 2$ )	Khan <i>et al.</i> (69)
	13.5	1		Morton <i>et al.</i> (60)
LDR monotherapy		1		NCCN Prostate CPG (61)
I-125	145			
Pd-103	125			
Cs-131	115			
HDR boost (EBRT 37.5 Gy/15 fx)	15	1	105.9 ( $\alpha/\beta = 2$ )	Martell <i>et al.</i> (70)
HDR boost (EBRT 45–50.4 Gy)	10.75	2	~113 ( $\alpha/\beta = 2$ )	NCCN Prostate CPG (61)
LDR boost		1		NCCN Prostate CPG (61)
I-125	110–115			
Pd-103	90–100			
Cs-131	85			

ABS = the American Brachytherapy Society; LDR = low-dose-rate; EBRT = external beam radiation therapy; HDR = high-dose-rate.

Fractionation options are in alignment with ABS recommendations, and from published studies/series. Although multiple fractionation options exist, in the setting of COVID-19, priority should be given to shorter treatment courses (where appropriate) to minimize patient and health care worker exposure and resource utilization.

to a depth dose of 0.5 cm is common and safe (56,57). However, in selected patients, such as those with anatomy requiring a cylinder size <20 mm, consideration of a four to five fraction regimen may help prevent excessive vaginal dose and late toxicity (57). A vaginal cuff boost may be delivered after EBRT in women with high-risk factors

and should result in a vaginal surface LDR equivalent (EBRT and BT) of 65–70 Gy (50). A vaginal cuff boost after EBRT is of limited additional benefit, and in the setting of COVID-19, should be restricted to the highest-risk patients (i.e., cervical invasion or positive surgical margins). Various fractionation options are shown in Table 1.

### Breast

For women with breast cancer treated with BCS, APBI is an option, [Table 1](#). Single-entry intracavitary devices will be easier to place at the time of surgery or within 4 weeks thereafter while the surgical cavity/seroma can be identified. Multicatheter interstitial implantations do not strictly rely on implantation into the surgical cavity and can therefore be performed immediately after surgery, or later. The TRIUMPH-T trial of 7.5 Gy  $\times$  3 fraction APBI in women treated with BCS and tumors <3 cm showed low toxicity with excellent cosmetic outcomes and good local control. Other fractionation options include 34 Gy delivered in 10 fractions given twice per day as on RTOG 9517 ([58](#)), or 32 Gy delivered in 8 fractions given twice per day ([59](#)).

### Prostate

For prostate cancer, definitive treatment or boost can be delivered using either LDR or HDR BT approaches. A BT boost can shorten overall treatment times and may improve biochemical disease control. These shorter fractionation regimens have been recommended in instances where compliance and other logistic issues (i.e., COVID-19) make shorter treatment attractive, [Table 1](#). For HDR monotherapy treatment of low- and intermediate-risk prostate cancer, 13.5 Gy  $\times$  2 fractions is preferred, and 19 Gy  $\times$  1 fraction is inferior ([60](#)). Although BT (definitive or boost) offers a shorter overall treatment course than conventional or moderately hypofractionated EBRT, BT practitioners should consider any resource limitations (access to personal protective equipment, limited personnel, limited physical space, etc.) that may prevent or delay BT delivery. Given these considerations it should be noted that stereotactic ablative radiation (SABR) is a safe and effective treatment for all patient risk categories and can be delivered in five or seven fractions ([61](#)).

### Anesthesia for brachytherapy

A cornerstone of safe and effective BT is adequate patient analgesia. In the setting of COVID-19, many BT practitioners may have limited access to BT implantation in the operating room because of reductions in personnel and allocation of hospital resources elsewhere. To overcome these issues, a variety of effective alternative analgesia options exist to allow for the timely completion of BT ([71](#)).

As with patients receiving general analgesia, an individualized anesthesia plan should be developed, and a preprocedural evaluation is required to better understand and minimize patient risks. The ongoing involvement of anesthesiology is strongly encouraged, and their input will be valuable for physicians without moderate sedation experience. Open communication with all team members is necessary to minimize the risk of aerosolizing particles during the BT procedure. For gynecologic, breast, and prostate implantations, procedural analgesia is possible with a combination of: neuraxial analgesia (epidural, spinal, or combined spinal-epidural anesthesia; CSE), pudendal nerve

block, moderate sedation (midazolam and fentanyl) dosed per institutional policy, and local analgesia with topical/mucosal lidocaine and/or tissue infiltration with tumescent technique using buffered lidocaine with or without epinephrine. Buffered lidocaine is preferred as unbuffered lidocaine is acidic and painful when injected ([72–75](#)).

If, after review of patient- and case-specific factors, it is felt that intubation and ventilation is necessary, strong consideration should be given to having only anesthesia staff in the room during intubation and extubation. Awareness of the ventilator filter system is important— $\oplus$  particularly the viral filtration efficiency and use of a breathing system filter ([76](#)). Strong consideration should be given to high-efficiency particulate air filter system between the ventilator system and the patient ([77](#)), and disconnection of the system which the patient is being ventilated should be avoided. Furthermore, similar to patients with tuberculosis, consider implementing a wait period before staff re-entry into the room after extubation; however, this has not been studied for coronavirus to our knowledge.

Finally, early reports show that patients with COVID-19 may experience endothelial damage with severe coagulopathy and/or thromboembolism ([78,79](#)). In such patients who also require BT implantation with planned overnight hospitalization and immobilization, strong consideration should be given to the need for therapeutic anticoagulation and/or augmentation of the implantation technique as necessary.

### BT analgesia treatment recommendations by disease site

#### Gynecologic

It is possible to successfully implant very large gynecologic tumors without the use of general anesthesia using a combination of moderate sedation, topical and local tumescent anesthesia tissue infiltration, and pudendal nerve block ([71](#)). Epidural anesthesia with or without spinal anesthesia using a hyperbaric block may significantly improve patient comfort for longer procedures, or implantations requiring overnight hospitalization in conjunction with patient-controlled analgesia ([71](#)). For centers with in-room imaging capabilities (CT or MRI), general anesthesia may be feasible; however, for most centers without an in-room imaging solution, general anesthesia should be avoided. This results from the need for patient extubation and/or transportation under anesthesia, and to avoid repeated disconnection of the respiratory circuit and potential staff exposure to patient respiratory secretions during imaging.

- For intracavitary (T&R, T&O) implantation, preference for moderate sedation with or without mucosal/injection lidocaine. Supplemental oxygen should be delivered with nasal cannula with surgical mask in place on patient, or with facemask oxygen. All involved staff should wear appropriate surgical PPE.

- For hybrid implantation, preference for moderate sedation with mucosal/injection lidocaine, and with or without pudendal nerve block. Supplemental oxygen should be delivered with nasal cannula with surgical mask in place on patient, or with facemask oxygen. All involved staff should wear appropriate surgical PPE.
- For full interstitial implantation, preference for epidural or CSE with moderate sedation with mucosal/injection lidocaine. Supplemental oxygen should be delivered with nasal cannula with surgical mask in place on patient, or with facemask oxygen. All involved staff should wear appropriate surgical PPE. Ideally, the patient can be kept overnight and all treatments care be delivered in a single episode of care to minimize the need for recurrent patient exposure to the health care system. Limit general anesthesia approaches to centers with in-room imaging capabilities where the ventilatory system can remain in place during periprocedural imaging. For patients requiring general anesthesia, avoid tracheal intubation in favor of laryngeal mask airway to decrease interaction with deep respiratory secretions. HIPA filter system between the patient and ventilator system is preferred. Avoid mask ventilation of the patient. At the very end of the implantation keep the ventilator system intact, then remove the laryngeal mask airway and place surgical mask on the patient.

#### Breast

- For intracavitary cases requiring device exchange before BT, preference for oral pain, and anxiolysis medication (oxycodone, lorazepam) as necessary. All involved staff should wear appropriate surgical PPE.
- For interstitial cases, preference for combined topical analgesia using EMLA cream, local tumescent infiltration of buffered lidocaine with epinephrine, and oral pain medication as aforementioned, or moderate sedation as necessary. Supplemental oxygen should be delivered with nasal cannula with surgical mask in place on patient, or with facemask oxygen. All involved staff should wear appropriate surgical PPE. Alternatively, for patients requiring general anesthesia, recommendations as aforementioned for full interstitial gynecologic implantation.

#### Prostate

For patients undergoing prostate BT, preference for local and/or spinal or CSE anesthesia, supplemental oxygen should be delivered with nasal cannula with surgical mask in place on patient, or with facemask oxygen. All involved staff should wear appropriate surgical PPE.

#### Recommendations for image-guided brachytherapy for gynecologic malignancies

In the era of COVID-19, it is imperative to be mindful of the exposure risks of our patients with every encounter, including diagnostic imaging. MRI improves soft tissue

delineation and greater accuracy in creation of an HR-CTV for cervical BT (80,81). It would be reasonable to perform CT-based planning for patients with cervix-confined local disease and those with limited vaginal involvement (T1b-2a) and reserve MRI-based planning for patients with extracervical spread of disease where delineation of gray zones would be most impacted as with parametrial, uterine body, mid/distal vagina, bladder, or rectal invasion (T2b-T4a).

For those patients where MRI is felt to improve their treatment delivery relative to risk of COVID, responsible utilization of MRI is necessary. MRI with applicator *in situ* for each fraction or application is ideal but may not be possible within the construct of each institution's workflow and access to resources, and this is especially the case in the era of COVID-19. There are experiences with performing MRI-based BT with the applicator *in situ* while keeping the patient as an inpatient and delivering treatment in two applications (82,83). This strategy can be amended to perform all BT in a single well-placed application to avoid multiple admissions. For outpatient scenarios, a pre-BT MRI can be performed and incorporated with CT performed at the time of implant. With this utilization, the MRI resulted in significant alterations in the HR-CTV in about 50% of cases compared with CT alone in patients with parametrial invasion (T2b & T3b) (84).

Pre-BT MRI has been fused to a CT at the time of implant using deformable image registration as well. The GTV can be contoured on the MRI and HR-CTV on the MRI-CT fusion after deformable image registration (85); however, limitations exist with this approach and should be recognized with clinical implementation (86). Another strategy utilized a Smit sleeve placed at the time of first implant with CT-based planning. An MRI was then obtained with Smit sleeve in place with fusion of MRI to subsequent CT-based BT implant coregistered to the Smit sleeve (87). A third strategy, "cognitive fusion," where the treating physician contours on a CT with applicator in place while directly referring to a pre-BT MRI, may also aid in defining an HRCTV in a time and resource efficient manner.

While integration of MRI is optimal and encouraged in the manners noted previously, when logistical barriers exist to prevent this (which may potentially worsen with COVID-19), CT-based volumetric BT planning remains a highly accessible method of both reducing toxicity and improving disease control, when compared with film-based (Point A) planning (88).

#### Strategies to preserve the quality of cancer care while minimizing risk

Temporizing options, such as endocrine therapy, exist for patients who wish to avoid traditional treatment paradigms to decrease the risk of COVID-19. As endometrioid precancerous lesions arise from the prolonged exposure of the endometrium to estrogen, progestins can act to inhibit



endometrial proliferation and are used in the management of low risk or surgically inoperable women with endometrial cancer (89). These agents can be used continuously for 3–6 months with reassessment for response every 6 months. If by 12 months there is not a complete response, definitive surgery should be pursued. A systematic review by Gunderson in 2012 indicated that 53% of women experience a durable response to treatment with recurrence occurring in almost after response occurring in 35.4% of women with invasive disease (90). A recent meta-analysis compared mechanism of progestin administration, either via levonorgestrel IUD or oral cyclic medroxyprogesterone acetate and found that the levonorgestrel IUD had a higher response rate than the oral formulation in nonobese women (91). Finally, a small Japanese prospective trial published in 2007 including 28 women with Stage 1A endometrial cancer demonstrated a similar response rate of 55% to that demonstrated in retrospective studies in women with Stage 1A disease (92).

For breast and/or prostate cancer, delay of definitive or adjuvant therapy may also be possible using endocrine therapy temporizing measures.

**Discussion**

Patients who have gynecologic, breast, and prostate cancers where temporizing therapy is not available/appropriate and BT treatment is indicated should be considered “priority 1”—deemed critical for therapy and require services/treatment because of a clinical situation where delay or omission of therapy will result in severe negative impact on the oncologic outcome or life expectancy. If a delay is anticipated, the treating physician should make alternative plans as early as possible and consider referral, if necessary, to another facility equipped and staffed to deliver treatment with minimal to no disruption in the treatment timeline. There are many potential reasons for treatment delay beyond physician-centric issues, Table 2. Impact of staff shortage, lack of social workers and ancillary support (housing, transportation), socioeconomic factors (loss of job, housing, insurance) may all play a role.

Table 2  
Factors affecting the timely delivery of treatment

Factors affecting timely delivery of treatment	
1	Coordination of care among different sites
2	Multidisciplinary coordination of care
3	Poor patient navigation of system
4	Patient factors, that is—illness, socioeconomic challenges, transportation
5	Institution factors, that is—staffing shortage, equipment shortage, medication shortage

Factors four and five will likely be of most concern during the COVID-19 pandemic.

Table 3  
Strategies to mitigate risk and treatment delay during the COVID-19 pandemic

Strategies to preserve cancer care and minimize risk	
1	Use of altered fractionation schedules
2	Endocrine therapy as a temporizing measure for breast, prostate, and uterine cancer (as appropriate)
3	Eliminate or consolidate nonessential OR procedures
4	Modify general anesthesia protocols or switch to neuraxial sedation and/or moderate sedation with local analgesia
5	Streamline staffing to minimize personnel exposure
6	Incorporate telemedicine where feasible

While all hospital services and personnel are impacted by COVID-19, it is important to recognize strategies that may mitigate or lessen the impact, or delay treatment, Table 3.

In line with these strategies, the ABS (93) and ASTRO (94) recently issued recommendations in the setting of COVID-19, which are outlined in the previous sections. While reduced patient exposure and resource utilization is important during COVID-19, it is critical to maintain BT services for patients. Furthermore, the use of BT may shorten treatment time and exposure for some patients.

The goal and scope of this work is to provide guidance and a framework of how to continue delivering high-quality BT given the current, significant health care resource and personnel restrictions in the setting of the COVID-19 global pandemic. The recommendations made previously are based on data (where available) and expert opinion. However, these are not formal policies, as data in this setting are limited. Given the unique and varied patient populations and resources available, beyond the aforementioned, we recommend that physicians keep open communication with patients and multidisciplinary care teams to optimize treatment at this challenging time, and continue to follow developing institutional, state, and federal guidelines/recommendations as challenges in delivering care during COVID-19 will continue to evolve.

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