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Scientific Article

Prostate Cancer Radiation Therapy Recommendations in Response to COVID-19



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Received 22 March 2020; revised 24 March 2020; accepted 24 March 2020

Abstract

Purpose: During a global pandemic, the benefit of routine visits and treatment of patients with cancer must be weighed against the risks to patients, staff, and society. Prostate cancer is one of the most common cancers radiation oncology departments treat, and efficient resource utilization is essential in the setting of a pandemic. Herein, we aim to establish recommendations and a framework by which to evaluate prostate radiation therapy management decisions.

Methods and Materials: Radiation oncologists from the United States and the United Kingdom rapidly conducted a systematic review and agreed upon recommendations to safely manage patients with prostate cancer during the COVID-19 pandemic. A RADS framework was created: remote visits, and avoidance, deferment, and shortening of radiation therapy was applied to determine appropriate approaches.

Results: Recommendations were provided by the National Comprehensive Cancer Network risk group regarding clinical node-positive, postprostatectomy, oligometastatic, and low-volume M1 disease. Across all prostate cancer stages, telemedicine consultations and return visits were recommended when resources/staff available. Delays in consultations and return visits of between 1 and 6 months were deemed safe based on stage of disease. Treatment can be avoided or delayed until safe for very low, low, and favorable intermediate-risk disease. Unfavorable intermediate-risk, high-risk, clinical node-positive, recurrence postsurgery, oligometastatic, and low-volume M1 disease can receive neoadjuvant hormone therapy for 4 to 6 months as necessary. Ultrahypofractionation is preferred for localized,

Sources of support: This work had no specific funding.

Disclosures: A. Choudhury is supported by the Manchester Biomedical Research Centre.

This article was originally published in the July–August 2020 issue of *Advances in Radiation Oncology*.

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oligometastatic, and low-volume M1, and moderate hypofractionation is preferred for postprostatectomy and clinical node positive disease. Salvage is preferred to adjuvant radiation.

Conclusions: Resources can be reduced for all identified stages of prostate cancer. The RADS (remote visits, and avoidance, deferment, and shortening of radiation therapy) framework can be applied to other disease sites to help with decision making in a global pandemic. © 2020 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Cancer treatment in the era of COVID-19 requires consideration of risks and benefits for patients and staff.¹ Recent data suggest patients who have cancer are at increased risk of infection and serious complications from COVID-19.¹ Although the American Society of Clinical Oncology has provided resources for patients receiving systemic therapy (<https://www.asco.org/asco-coronavirus-information>), there remains minimal granular guidance on the delivery of outpatient radiation therapy. Radiation therapy is delivered to nearly 50% of patients with cancer, a particularly vulnerable group given their older age, frequent comorbidities, and underlying cancer diagnosis.²

Prostate cancer is frequently treated with radiation. It is the most common solid tumor in men; it is a heterogeneous disease for which timely therapy is indicated for some cases and watchful waiting, active surveillance, or deferral of treatment could be acceptable for others.^{3,4} Given the current epidemic crisis, delaying radiation therapy treatment (which requires multiple visits to health care facilities) for patients with prostate cancer may potentially reduce the risk of iatrogenic exposure to COVID-19.

At the health care system level, when clinically appropriate, reducing visits conserves limited hospital resources (eg, personal protective equipment [PPE]) for use by health care workers who will have to care for the potentially vast number of hospitalized patients with COVID-19. The decision to delay life-saving cancer treatment in a time of a resource-intensive pandemic represents a clinical conundrum without modern precedent. In these exigent circumstances, guidelines for managing patients who present with prostate cancer would be valuable for the practicing clinician. This article attempts to provide guidance based on rapid expert opinion regarding how to manage patients with prostate cancer requiring radiation therapy during the COVID-19 pandemic.

Methods and Materials

Given the swiftly evolving clinical knowledge surrounding COVID-19 and the potential impact on radiation oncology departments worldwide, we performed a rapid review of evidence assessing the management of localized prostate cancer with radiation therapy. The goal of this rapid review was to synthesize knowledge to provide a

framework for clinical practice and management of prostate cancer during the COVID-19 pandemic, but this framework could similarly be applied in any resource-constrained setting or other disease type.

Within this framework we sought to answer these key questions:

1. Which patients can have in-person clinic visits safely delayed or converted to telehealth visits?
2. Which patients can safely avoid treatment or have treatment deferred, and for how long?
3. Which patients can have radiation therapy safely deferred with the initiation of androgen deprivation therapy, and for how long?
4. For patients undergoing treatment, what are the preferred treatment modalities and fractionation schedules by disease risk?

To answer these questions, we assessed systematic reviews, national guidelines, results from randomized clinical trials, and treatment arms in ongoing randomized trials assessing radiation therapy for prostate cancer. Studies were required to be published in English between January 1990 and March 2020. Results published only in abstract form were limited to the period between January 1, 2015 and March 15, 2020. This literature search was performed using MEDLINE via PubMed only. Dual screening of the literature for inclusion was performed by W.C.J. and D.E.S. to minimize the risk of selection bias and was performed over the course of 3 hours.

Importantly, these recommendations apply only to patients not infected with COVID-19. For patients who have symptoms concerning for COVID-19, or who have tested positive, please follow local hospital plans and procedures.

In generating these recommendations, the following assumptions were made: (1) the pandemic will last for multiple months, often occurring in multiple waves with variable peaks of severity; (2) during the pandemic, a significant proportion of staff will not be available to work (eg, because of illness, quarantine, family responsibilities from school closures); (3) capacity of hospital services will be exceeded and stress the hospital system; and (4) available staff will be deployed to essential services. Ultimately, the combined effect is that resources will be stressed and normal workflow will not be possible.

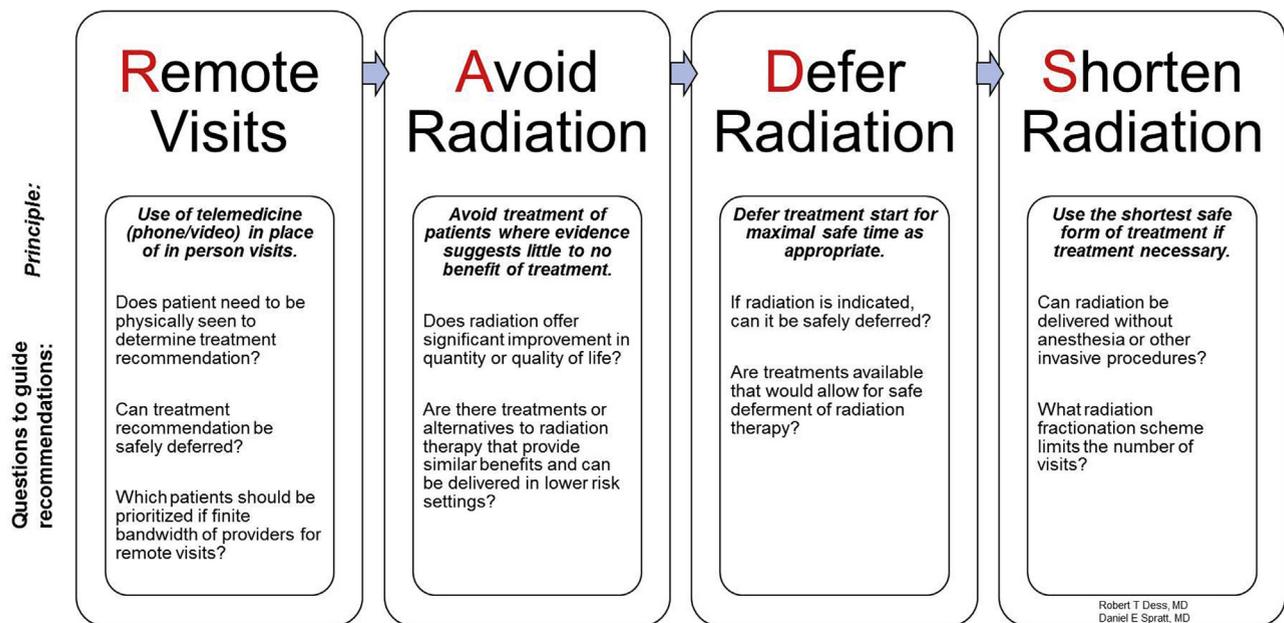


Figure 1 The remote visits, and avoidance, deferment, and shortening of radiation therapy (RADS) framework.

Recommendations

The RADS (remote visits, and avoidance, deferment, and shortening of radiation therapy) framework was developed and applied for all prostate cancer disease states commonly treated with radiation therapy (Fig 1). Table 1 summarizes the group's recommendations for each disease stage and according to visit type, simulation, fiducial marker and rectal spacer placement, and treatment itself. In all scenarios, the visits, procedures, and treatment can safely be delayed by variable durations based on stage of disease.

Remote visits

All visits should be transitioned to telehealth visits. Although video visits are preferred, these telehealth visits can include simple phone calls if video visits are not possible given the limitations of technological infrastructure at select centers. Very few patients with prostate cancer require an in-person visit during a pandemic, and the minimal value of a digital rectal examination is less important than the risk of COVID-19 exposure to patients and staff. Based on your institutional resources and legal requirements, on-treatment visits can also be performed using telehealth technology to further reduce exposure risk. For patients who must be seen in clinic, consideration should be given to having patients wait in their cars or outside the facility before their appointment to promote social distancing, given high surface stability of COVID-19.⁵ Additionally, the number of people accompanying patients should be reduced to a minimum. Laboratory testing (eg, prostate-

specific antigen [PSA] testing) should be performed in settings with minimal contact with staff or other patients, preferably outside of a busy hospital setting if possible. Routine PSA testing posttreatment can safely be deferred by ≥ 3 months in most instances.

Avoidance of radiation therapy

Generally, for very low-, low-, and favorable intermediate-risk disease, treatment deferral until after pandemic-related restrictions have been lifted was thought to be safe. This advice is based on multiple clinical trials demonstrating that these patients have very favorable outcomes with watchful waiting, active monitoring, or active surveillance.^{6,7} This is reflected in national guidelines that recommend broad use of active surveillance for very low- and low-risk prostate cancer and selective use in favorable intermediate-risk disease.⁴ The safety of avoidance presumes that the pandemic will wane over the next 12 months.

Deferral of radiation therapy

Patients with unfavorable intermediate-risk, high-risk, very high-risk, postprostatectomy, clinical node-positive, oligometastatic, and low-volume M1 can variably delay in-person new patient consultations and return visits, but these should be converted to timely remote telehealth visits. After these patients have initiated treatment, androgen deprivation therapy (ADT) can allow for further deferral of radiation therapy as necessary based on the nature of the ongoing epidemic.^{8,9} If ADT cannot be delivered (eg, absolute patient refusal, supply exhausted,

Table 1 Recommendations

Disease state	Visits		Simulation/preparation			If treatment is warranted during pandemic			
	New consults*	RVs*	Fiducials [†]	Rectal spacers [‡]	Simulation scans	Preferred treatment during pandemic	Brachytherapy [‡]	EBRT type	ADT
Localized/locally advanced									
Very low/low	Delay until safe	Delay until safe	Delay until safe	Delay until safe	Delay until safe	AS	Do not use	Do not use	Do not use
FIR	Delay 3 mo	Delay until safe	Delay until safe	Delay until safe	Delay until safe	AS	Delay until safe	Delay until safe	Do not use
UIR	Delay 1-3 mo	Delay 4 mo	Consider if performing SBRT	Consider if performing SBRT	Delay up to 4-6 mo if ADT given	RT + ADT	Delay until safe	5 fx (preferred) or 20 fx	Can use ADT to delay RT 4-6 mo Consider 6-mo depot
High/very high	Delay up to 1 mo	Delay 3 mo	Consider if performing SBRT	If experienced to place, consider only if performing SBRT	Delay 4-6 mo if ADT given	RT + ADT	Delay until safe	5 fx (preferred) Or 20 fx	Can use ADT to delay RT 4-6 mo Consider 6-mo depot
N+	Delay 2-4 wk	Delay 3 mo	Consider if performing SBRT	Not recommended	Delay 4-6 mo if ADT given	RT + ADT	Not recommended	5 fx or 20 fx	Can use ADT to delay RT 4-6 mo Consider 6-mo depot
Postprostatectomy									
Adjuvant	Strongly consider use of early salvage RT	Delay 4 mo	-	-	Delay allowing treatment up to 120 d after surgery	RT ± ADT	-	20 fx	Can use ADT to delay RT 4-6 mo Consider 6-mo depot
Salvage	Delay up to 1 mo	Delay 3 mo	-	-	Delay depending on PSA level and doubling time	RT ± ADT	-	20 fx	Can use ADT to delay RT 4-6 mo Consider 6-mo depot
Metastatic									
Oligometastatic	If newly diagnosed, asymptomatic, and on ADT, can delay 2-3 mo	Delay 3 mo	-	-	If symptomatic do not delay	RT ± ADT	-	1 fx or 3 fx	Can use ADT to delay RT 4-6 mo
Low-volume M1	If newly diagnosed, asymptomatic, and starting ADT, can delay 4-6 mo	Should follow with medical oncology as needed	-	-	Can delay 4-6 mo if ADT given	Prostate directed therapy + ADT	-	5 fx or 6 fx	Patient should be on ADT as part of standard of care

Abbreviations: ADT = androgen deprivation therapy; AS = Active surveillance; EBRT = external beam radiation therapy; FIR = favorable intermediate risk; fx = fractions; N+ = regional lymph node involvement; PSA = prostate-specific antigen; RT = radiation therapy; RV = return visit; SBRT = stereotactic body radiation therapy; UIR = unfavorable intermediate risk.

* New consults and return visits can be delayed as necessary based on resource availability. If staff is able to conduct these visits without affecting pandemic response resources, these should continue on a regular schedule using remote visits. PSA and other laboratory testing should be deferred as deemed safe. Return visit delay listed is an additional delay beyond the current return visit interval.

[†] Placement of fiducial markers and rectal spacers requires extra personal protective equipment use. The benefit of these procedures should be based on resource and staff availability.

[‡] Brachytherapy should cautiously be used during the pandemic given high personal protective equipment requirements and resource utilization. Avoidance of general anesthesia is preferred if possible.

toxicity of ADT too high for potential benefit), for patients with rapid PSA doubling times (≤ 3 months) the benefits of immediate treatment during a window of potential cure must be weighed against the risk of COVID-19 exposure and subsequent morbidity and mortality (eg, age, comorbidities, immunosuppression).

ADT should not be used in disease states that have not been shown to derive survival benefits (very low-, low-, and favorable intermediate-risk disease). Significant prolongation of ADT beyond standard of care should be avoided given the potential for increased morbidity and other-cause mortality.¹⁰⁻¹²

It was agreed, based on recently presented evidence from Radiotherapy—Adjuvant Versus Early Salvage

trial¹³ and Radiation Therapy and Androgen Deprivation Therapy in Treating Patients Who Have Undergone Surgery for Prostate Cancer (NCT00541047) in 2019, that early salvage radiation therapy is preferred over adjuvant radiation therapy in all scenarios during a pandemic.

Shortening of radiation therapy

If treatment is deemed necessary and safe, the shortest fractionation schedule that has evidence of safety and efficacy should be adopted. For localized prostate cancer, 5- to 7-fraction stereotactic body radiation therapy (SBRT)/ultrahypofractionation should be used, which is

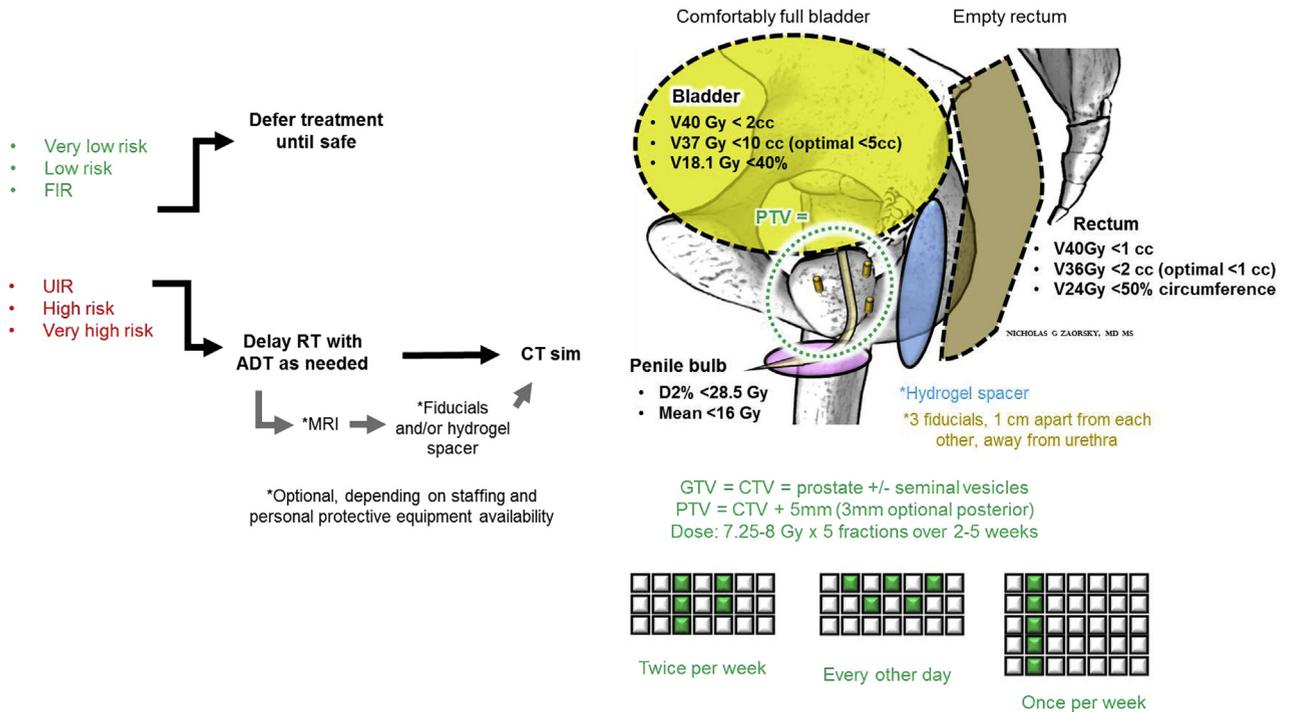


Figure 2 Workflow of prostate stereotactic body radiation therapy (SBRT). Please see [Appendix E1](#) for more details on dose constraints.

in accordance with the 2020 National Comprehensive Cancer Network guidelines as an acceptable regimen for intermediate- and high-risk prostate cancer. A simplified schema to help providers perform SBRT is shown in [Figure 2](#). For centers without the ability to perform image guidance (cone beam computed tomography with or without fiducial markers), a 20-fraction regimen can be used to 60 to 62 Gy.^{14,15} For patients who are post-prostatectomy, a moderate hypofractionated regimen of 20 fractions to 52.5 Gy is preferred (NCT00541047).¹⁶ For low-volume M1 disease, either SBRT or 6 Gy × 6 fractions as used in the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy arm H is safe and acceptable.¹⁷ Dose constraints are provided in [Appendix E1](#) for the aforementioned regimens.

Nonessential procedures that do not have evidence to support their impact on overall survival rates, such as a prostate magnetic resonance imaging (MRI), fiducial markers, and/or rectal spacers, should be used very selectively given they require either prolonged or extra patient visits. These can variably be considered if deemed necessary to perform prostate SBRT to expedite treatment; however, prostate SBRT can safely be performed without all of these additional procedures if necessary (eg, HYPOfractionated RadioTherapy of intermediate risk localised Prostate Cancer trial used 3-dimensional conformal radiation therapy with large 7 mm clinical target volume to planning target volume margins, did not

use rectal spacers, and did not mandate MRI, but did use fiducial markers).¹⁸ Although rectal spacers have been shown to reduce rectal toxicity, recent results from the Prostate Advances in Comparative Evidence, arm B trial demonstrated very low rates of rectal toxicity without the use of a rectal spacer.¹⁴ Thus, the net benefit of a rectal spacer is not justified during a pandemic unless simultaneously placing fiducial markers with the patient under local anesthesia.

There was unanimous consensus that if treatment needs to be performed during the peak of the pandemic, brachytherapy is not recommended given its reliance on anesthesia staff and PPE. However, if brachytherapy can be performed with use of local anesthesia, this may be a suitable option for those experienced with this method and if resources are available.

There was also unanimous consensus that once restrictions have been removed, radiation therapy of any form can be delivered. However, it is important to remain cognizant that additional waves of the pandemic may occur and restrictions may be reinstated. Thus, using shorter courses of radiation therapy may still be necessary.

Palliative care

This review does not discuss the use of palliative radiation therapy because often this is not necessarily tumor-type specific (eg, bone metastases, spinal cord

compression, bleeding). The same principles of the RADS framework apply, and the variable efficacy of palliative radiation therapy should be weighed against the risks of bringing patients in for radiation therapy, alternative treatment options (oral analgesics), use of radiation therapy to avoid treatments that may cause even greater exposure (surgery), or immunosuppression (systemic therapy).

Discussion

Prostate cancer is the most common cancer in men worldwide and one of the most common cancers treated within radiation oncology departments.³ The proportion of patients with prostate cancer receiving radiation therapy continues to expand; it is now used commonly for definitive treatment of localized and locally advanced disease, adjuvant and salvage treatment postsurgery, oligometastatic-directed radiation therapy, and treatment of the primary in low-volume metastatic disease.⁴ Furthermore, the complexity of treatment of prostate cancer has increased with more frequent use of advanced imaging, including MRI and molecular positron emission tomography imaging, image guidance with fiducial markers, and rectal spacers, most of which require extra procedures or visits and some of which require extra use of PPE. Thus, patients with prostate cancer represent an important population that radiation oncology departments need to efficiently manage in times when resources are limited.

Patients with prostate cancer are somewhat unique (other than patients with breast cancer); not only is prognosis generally favorable, but for patients with more aggressive disease, the use of ADT can safely delay the need to start radiation therapy for multiple months. For this reason, delaying radiation therapy is almost always safe.

Prostate cancer is also unique in that it is one of the few cancers we treat with curative intent where radiation therapy has a survival advantage.¹⁹ Very few cancers have randomized evidence from a single trial that demonstrates radiation therapy improves survival. In other cancers with worse prognosis, such as pancreatic cancer, radiation therapy has questionable survival impact. Thus, excessive delay of radiation therapy in patients with aggressive prostate cancer should be avoided.

Additionally, although ADT has been safely used for extended periods neoadjuvantly, it must be recognized that prolonged courses of neoadjuvant ADT do not provide oncologic benefit⁸ and can contribute to excessive morbidity and even mortality.¹⁰⁻¹² Thus, the benefit from receiving radiation therapy (large) must be balanced with the impact of delays in treatment start (small), excessive use of ADT (variable), and risk of infection and morbidity/mortality from COVID-19.

The group agreed that there are variable levels of evidence to support ultra- and moderate hypofractionation in localized and recurrent disease and that no randomized trial has demonstrated that altering field size or fractionation or using extreme dose escalation has affected overall survival. Thus, in the setting of a pandemic where mortality from COVID-19 is possible, the shortest safe regimen should be used and is unlikely to affect long-term survival.

These recommendations are not formal rules or policies; we do not believe this is possible when data are so limited. Rather, the goal was to provide guidance and a framework of thinking in the way numerous programs are approaching the care of patients with prostate cancer at their own clinics, all of which are experiencing various stages of impact and restrictions due to the COVID-19 global pandemic. We recommend that you follow your institutional, state, and federal recommendations when available to best manage your patients in your own practice.

Supplementary materials

Supplementary material for this article can be found at <https://doi.org/10.1016/j.adro.2020.03.010>.

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