

Critical Review

ACR Appropriateness Criteria[®] external beam radiation therapy treatment planning for clinically localized prostate cancer, part I of II

Expert Panel on Radiation Oncology-Prostate:

Nicholas G. Zaorsky MD^a, Timothy N. Showalter MD MPH^{b,*}, Gary A. Ezzell PhD^c, Paul L. Nguyen MD^d, Dean G. Assimos MD^e, Anthony V. D'Amico MD PhD^f, Alexander R. Gottschalk MD PhD^g, Gary S. Gustafson MD^h, Sameer R. Keole MDⁱ, Stanley L. Liauw MD^j, Shane Lloyd MD^k, Patrick W. McLaughlin MD^l, Benjamin Movsas MD^m, Bradley R. Prestidge MD MSⁿ, Al V. Taira MD^o, Neha Vapiwala MD^p, Brian J. Davis MD PhD^q

^a Fox Chase Cancer Center, Philadelphia, Pennsylvania (research author)

^b University of Virginia, Charlottesville, Virginia (principal author)

^c Mayo Clinic, Phoenix, Arizona (research author, contributing)

^d Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, Massachusetts (panel vice-chair)

^e University of Alabama School of Medicine, Birmingham, Alabama (American Urological Association)

^f Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, Massachusetts (American Society of Clinical Oncology)

^g University of California San Francisco, San Francisco, California

^h William Beaumont Hospital, Troy, Michigan

ⁱ Mayo Clinic, Scottsdale, Arizona

^j The University of Chicago Medical Center, Chicago, Illinois

^k Huntsman Cancer Hospital, Salt Lake City, Utah

^l University of Michigan, Novi, Michigan

^m Henry Ford Health System, Detroit, Michigan

ⁿ Bon Secours Cancer Institute, Norfolk, Virginia

^o Mills Peninsula Hospital, San Mateo, California

^p University of Pennsylvania, Philadelphia, Pennsylvania

^q Mayo Clinic, Rochester, Minnesota (panel chair)

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* Corresponding author. 1891 Preston White Drive, Reston, VA 20191
E-mail address: tshowalter@gmail.com (T.N. Showalter)

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Summary of literature review

Introduction/background

Prostate cancer is the most common cancer among men in the United States, with an estimated 220,800 new diagnoses in 2015.¹ External beam radiation therapy (EBRT) is the treatment of choice for many men with localized prostate cancer.² It is generally accepted that EBRT is a first-line treatment option for localized prostate cancer, as are radical prostatectomy and brachytherapy.³⁻⁶ Advances in image-based EBRT treatment planning and localization have contributed to better targeting of the prostate and greater sparing of normal tissues, permitting dose escalation while maintaining safe doses to adjacent normal tissues. As shown in [Appendix 1](#), the available published evidence suggests that advances in EBRT technologies have translated to improved clinical outcomes. This review complements other American College of Radiology Appropriateness Criteria[®] on localized prostate cancer^{7,8} by focusing on the practical and technical elements of EBRT. This document provides guidance for EBRT treatment planning for localized, organ-confined prostate cancer; locally advanced node-negative disease; and postprostatectomy radiation therapy (RT). The first part of the review covers treatment planning: target volume definitions, patient setup, and dose constraints. The second part of the review covers treatment delivery: organ motion, target localization, image guidance, and RT delivery techniques; additionally, clinical variants are presented (see [Variants 1-7](#)).

Prostate cancer risk definitions

This document provides guidance for EBRT treatment planning for definitive primary therapy for localized prostate cancer, including low-risk, intermediate-risk, and high-risk organ-confined disease as well as for postprostatectomy RT. Risk groups for localized prostate cancer are defined in this document per D'Amico et al⁹ and the National Comprehensive Cancer Network.⁶ The D'Amico criteria classify patients as follows: low risk, for clinical stage T1c-T2a tumor, Gleason score ≤ 6 , and prostate-specific antigen (PSA) ≤ 10 ng/mL; intermediate risk, for clinical stage T2b tumor, PSA 10 to 20 ng/mL, or Gleason score 7; and high risk, for clinical stage T2c tumor, PSA >20 ng/mL, or Gleason score ≥ 8 .⁹ The National Comprehensive Cancer Network risk-grouping system is similar to the D'Amico guidelines, with the exceptions of including T2c tumors in the intermediate-risk group and T3a tumors in the high-risk group.⁶

RT fractionation definitions

This article relates mostly to men treated with dose-escalated conventionally fractionated EBRT (a single 1.8-

to 2.0-Gy fraction, delivered in approximately 15 minutes per day, 5 days per week, for 8 to 9 weeks, to a total dose of 76 to 80 Gy), which is an established treatment modality for men in all disease risk groups. Notably, other fractionation techniques to treat prostate cancer patients exist. For example, moderately hypofractionated RT (HFRT, 2.1-3.5 Gy/fraction, for approximately 15 minutes per day, 5 days per week, for about 4 weeks, to a total dose of ~ 52 to 72 Gy) has been tested in phase 1-3 trials since the 1990s.¹⁰ Extremely fractionated RT, also termed stereotactic body RT (SBRT, the delivery of 3.5-15 Gy per fraction, in 5 fractions or less), is an emerging form of EBRT that to date has mostly been reserved for low-risk prostate cancer patients.¹¹ HFRT and SBRT deliver a higher dose per fraction to the prostate; thus, these methods also require diligence in treatment planning. We outline special considerations for HFRT and SBRT in this article.

Definitions for target volumes and organs at risk

The outcomes and toxicities with different EBRT technologies and fractionation techniques are shown in [Appendix 1](#).¹²⁻²³ The definitions of target volumes and planning target volume margins for EBRT in published clinical protocols are shown in [Appendix 2](#).^{14,24-30} Target volumes are described in this document according to the standard terms recommended in Report 83³¹ of the International Commission on Radiation Units and Measurements for specifying dose prescription and are summarized as follows.

Gross tumor volume

The gross tumor volume (GTV) is the gross demonstrable extent and location of the malignant growth; it consists of the primary tumor, which for prostate cancer has historically been defined as the entire gland as well as any visualized extension into surrounding normal tissues, the regional lymph nodes (LNs), or distant metastases based on clinical data (eg, physical examination, anatomic imaging with computed tomography [CT] and magnetic resonance imaging [MRI], and functional and molecular imaging). The GTV is delineated during the RT-planning process before the start of EBRT.

Clinical target volume

The clinical target volume (CTV) encompasses the GTV as well as areas at risk for subclinical cancer involvement. The CTV may include a margin around the prostate GTV, and it may include adjacent regions at risk of having subclinical disease. For example, this may

include the seminal vesicles (SVs), an expansion for extraprostatic extension (EPE), or pelvic LNs.

In cases in which the disease is confined to the gland (clinical stages T1-2) but the risk of SV invasion exceeds 15%, 2 CTVs can be defined. The first should encompass the prostate and the SVs (ie, CTV1), and the second boost CTV is the prostate alone (ie, CTV2, which equals the GTV). In these cases, a radiation dose that controls sub-clinical disease is prescribed to the first target volume, and a higher dose is intended for the prostate itself. When there is evidence of EPE on physical examination or imaging modalities such as MRI (radiographic stage T3), the SVs could be included for the total radiation dose prescription.

As a general rule, the CTV should be influenced by potential EPE, as described in the following section regarding disease extension. With this in mind, the Genitourinary Section of the Radiation Oncology Group of the European Organisation for Research and Treatment of Cancer (EORTC) guidelines include recommendations for CTV definition according to risk group for prostate EBRT.³² The EORTC guidelines recommend that the CTV include a 5-mm expansion of the prostate to address EPE for patients with intermediate- and high-risk tumors and that the proximal 1 cm or 2 cm of the SVs be included for patients with intermediate- and high-risk tumors, respectively.³² The most recent Radiation Therapy Oncology Group (RTOG) protocol for high-risk prostate cancer (0924) recommends that the proximal 1 cm of the SVs be included in the boost CTV, but does not require a specific expansion to account for EPE.³³ It is recognized that there may be some variation in clinical practice on this point, and CTV-to-planning target volume (PTV) expansion margins may also provide some coverage of potential EPE.

Planning target volume

The PTV encompasses the CTV plus an additional margin to account for patient movement, setup error, and organ movement.³⁴ Each CTV should have a corresponding PTV design based upon consideration of the extent of immobilization and use of image guided RT (IGRT). For prostate cancer, the PTV is typically the CTV plus a 0.5- to 1.0-cm margin; the margin may be reduced posteriorly to minimize the volume of rectum exposed to higher radiation doses. Guidance for CTV-to-PTV expansion margins is provided in the following section.

Contouring organs at risk

RTOG provides recommendations for contouring normal tissue structures in the form of a contouring atlas on the RTOG Web site and published consensus guidelines.³⁵ Adherence to these guidelines is recommended to ensure that published evidence and trial protocol recommendations may be readily extrapolated to clinical

decisions regarding EBRT treatment planning. Normal tissue structures for prostate EBRT treatment planning include the rectum, bladder, penile bulb, bowel bag, and proximal femurs. The rectum should be contoured from the lowest level of the ischial tuberosities up to the rectosigmoid junction, where the rectum loses its round shape on axial imaging. The entire rectum (as a cylinder), not just the anorectal wall, should be contoured. The penile bulb contour should encompass the portion of the bulbous spongiosum that is adjacent to the genitourinary diaphragm without extending the contour anteriorly into the penile shaft. The penile bulb may be visualized on CT and T2-weighted MRI scans. Proximal femurs should be contoured from the top of the femoral head inferiorly to the lowest level of the ischial tuberosities. The bowel bag may be defined by contouring the abdominal contents, excluding muscle and bones, and then subtracting any overlapping nongastrointestinal normal structures using the treatment-planning software.

Determining CTVs for prostate EBRT

EBRT planning is performed with volumetric imaging to visualize the target volumes and relevant pelvic anatomy and perform dose calculations in treatment planning. CT imaging is the most common modality for EBRT planning, but complementary imaging modalities may enhance delineation of CTVs.

Imaging modalities for prostate cancer

CT

CT simulation can help localize the urogenital diaphragm, which abuts the prostatic apex. Typically, the location of the apex can be resolved to 2 or 3 CT slices obtained at 3- to 5-mm intervals, and with an experienced radiation oncologist, the use of CT simulation alone may be adequate based upon this consideration.³⁶ Furthermore, interobserver variations can be reduced by learning to define the prostate on CT after studying the common sites of target definition errors using MRI prostate volumes defined by an expert radiologist.

MRI

Advantages. It has long been recognized that there is substantial interobserver variability in the definition of prostate EBRT target volumes on CT imaging.³⁷ Target definition remains 1 of the largest sources of uncertainty and error in prostate EBRT, particularly in the era of highly conformal EBRT planning and delivery.³⁸ Incorporating MRI in the planning process for prostate target volume delineation offers an advantage because it

has been shown to decrease contouring variability when compared with the use of CT imaging.^{39,40}

MRI-defined prostate volumes are typically smaller than CT-defined volumes, particularly near the base and apex, and result in reduced EBRT doses to the rectum.⁴¹ Similarly, prostate volumes are approximately 30% larger on CT imaging than ultrasound (US) imaging.⁴² MRI- and US-based prostate contours show less variation than CT-based contouring, and these 2 modalities have the closest correspondence, suggesting that MRI and US may be preferred over CT for prostate EBRT target delineation,⁴³ especially at the prostatic apex.

MRI may also allow better identification of structures adjacent to the prostate that are associated with erectile function.⁴⁴ McLaughlin et al⁴⁵ were able to spare the critical erectile structures more often with a T2-weighted MRI and MRI angiogram-based treatment plan than with a plan using conventional CT-based contouring. In a similar analysis, Steenbakkers et al⁴⁶ reported improved sparing of the rectum and penile bulb with the use of MRI-based delineation of the prostate on 3-dimensional conformal RT (3D-CRT) treatment plans. At this time, it is unclear whether sparing erectile tissues leads to better sexual outcome or quality of life. It is also not established whether sparing of these tissues will compromise long-term tumor control.

Coregistration of MRI with CT may be more accurate in delineating the prostate and SVs than use of CT alone.⁴⁷ CT overestimates the size of the gland approximately by 30% to 50%; additionally, there is a systematic discrepancy in the posterior apical prostate border, which observers define as being ~3.6 mm more posterior on MRI than on CT.⁴⁸

Disadvantages. The disadvantages of MRI-based prostate localization are its limited availability, CT/MRI fusion inaccuracies, treatment-planning spatial warping, and a lack of radiographic density information for calculating radiation doses and reconstructing digital radiographs for treatment verification. CT scans permit standard dose calculations during RT planning, so the combination of CT and MRI may be advantageous in this regard. Several centers are exploring methods to reduce the dosimetric and positional uncertainties associated with MRI simulation.^{49,50} At this time, it is reasonable to use MRI to facilitate the definition of target volumes, especially if CT/MRI fusion capabilities or an MRI simulator are available. Some investigators have explored EBRT treatment planning using MRI alone, suggesting that it is feasible.⁵¹

Technical aspects. Traditionally, MRI for prostate cancer has been performed with a 1.5T scanner and endorectal coil, which has a greater accuracy than 0.3T or 0.5T scanners. With the introduction of higher field strength, such as 3.0T,

and thus higher spatial resolution, endorectal coils may not be essential to achieve high-quality magnetic resonance-based imaging.⁵² Consequently, MRI may become more readily used⁵³; however, the field strength of MRI is only 1 factor that may influence prostate cancer imaging.⁵⁴ Although a 3.0T MRI scan shows a high accuracy for the staging of clinically localized prostate cancer, it is currently unknown whether the improved spatial resolution and signal-to-noise ratio of 3.0T scanners improve diagnostic performance over 1.5T scanners.⁵⁵

Magnetic resonance spectroscopy, dynamic contrast-enhanced MRI, and diffusion weighted imaging MRI are novel magnetic resonance-based imaging techniques under investigation. Radionuclide-based techniques with small molecules (eg, 18F-FDG, 11C-choline, 18F-choline, 11C-acetate, 18F-acetate, 18F-NaF, 18F-DHT), amino acids (eg, 11C-methionine), and protein-specific molecules are other forms of imaging that are also largely experimental. These techniques may prove useful for target delineation in the future. Currently, they are not widely available in routine clinical practice; thus, we have not included them in this manuscript.

Uncertainty regarding disease extension

Extraprostatic extension

The radial distance of EPE (EPEr) is the perpendicular distance away from the edge of a prostate where cancer may be present. An additional volumetric expansion around the prostate may be necessary to account for EPEr. Chao et al⁵⁶ performed a detailed pathologic analysis of 371 prostatectomy specimens to determine CTV margins. EPE was present in one-third of patients. The median EPE distance was 2.4 mm (range, 0.05-7.0 mm). The 90th percentile distance was 5.0 mm. Of the 121 cases with EPE, 55% had a distance ≥ 2 mm, 19% ≥ 4 mm, and 6% ≥ 6 mm. EPE occurred posterolaterally along the neurovascular bundle in all cases. The pretreatment PSA, biopsy Gleason, pathologic Gleason, clinical stage, bilateral involvement, positive margins, percentage of gland involved, and maximal tumor dimension were associated with presence of EPE.

Similarly, Zlotta et al⁵⁷ concluded that PSA ≥ 10 ng/mL and biopsy Gleason score ≥ 7 , or $>50\%$ of prostate biopsy cores being positive, argued in favor of removing the SVs with surgery. On the other hand, a review of other studies found that the distance of EPEr for the vast majority of patients ranges from 0.5 to 2.4 mm⁵⁸; thus, EPEr should be readily contained within a 5-mm prostate GTV-to-CTV expansion for most patients; for high-risk patients, a posterolateral CTV expansion of up to 7 mm may be considered.

SV coverage

In selected patients, it is necessary to include the SVs in the CTV, which are typically well-visualized on a cross-section CT scan of the pelvis. Nomograms may be used to determine the probability of EPE, SV, or pelvic LN involvement using clinical stage, pretreatment PSA, and Gleason score,⁵⁹ and SV coverage can be based upon predicted probability of SV involvement.

Kestin et al⁶⁰ published an analysis of 344 radical prostatectomy specimens in which they measured the length of SVs, length of involvement by carcinoma, and percentage of SV involved. Of the 81 patients with SV involvement, the median length of tumor presence was 1 cm. In the entire population, only 7% of patients had SV involvement beyond 1 cm. The authors recommend that the proximal 2.0 to 2.5 cm (approximately 60%) of the SVs be included in the CTV for intermediate- and high-risk patients (ie, PSA ≥ 10 , Gleason ≥ 7 , $\geq T2b$). Zlotta et al⁵⁷ concluded that PSA ≥ 10 ng/mL and biopsy Gleason score ≥ 7 , or $>50\%$ of prostate biopsy cores being positive, argued in favor of removing the SVs with surgery.

LN_s. Lawton et al⁶¹ conducted a study of CTV definition of pelvic LN_s by radiation oncologists with expertise in prostate cancer and observed significant variation among physicians in the CTV structures contoured. To provide guidance for the safe and effective use of intensity modulated RT (IMRT) for pelvic LN irradiation, RTOG developed a contouring atlas for pelvic LN irradiation for prostate cancer.⁶² When irradiating the pelvic LN_s for prostate cancer, the RTOG consensus guidelines recommend including the distal common iliac, presacral, external iliac, internal iliac, and obturator LN_s. Pelvic LN CTVs include the vessels with a 7-mm radial margin, anatomically constrained to exclude bowel, bladder, bone, and muscle. Pelvic LN CTVs begin superiorly at the L5-S1 interspace and end inferiorly at the superior border of the pubic bone.⁶² These RTOG guidelines are recommended for prostate EBRT treatment planning when pelvic LN irradiation will be delivered as part of definitive therapy.

Postoperative prostate bed EBRT. Several sets of consensus guidelines have been developed to guide prostate bed target volume delineation for adjuvant and salvage RT,⁶³⁻⁶⁶ relying primarily upon evidence regarding locations of clinical recurrences, anatomy, and expert opinion. The vesicourethral anastomosis, bladder neck, retrovesical region, and SV stumps have been shown in imaging and biopsy series to be at highest risk of clinical recurrence following prostatectomy,^{66,67} and the consensus guidelines aim to encompass these regions. The RTOG guidelines⁶⁶ provide detailed guidance on CTV definition, including variation based upon pathological information, and are supplemented by

an atlas available on the RTOG Web site (<http://www.rtog.org/>). The RTOG-recommended prostate fossa CTV (PF-CTV) spans a cranial border at the caudal vas deferens remnant cranially down to a caudal border that is 8 to 12 mm inferior to the vesicourethral anastomosis. The PF-CTV extends anteriorly to the posterior aspect of the pubis below the cranial border of the pubic symphysis and encompasses the posterior 1 to 2 cm of the bladder wall above the pubic symphysis. The lateral border of the PF-CTV is at the sacrorectogenitopubic fascia superiorly and the levator ani muscles inferiorly. The posterior border of the PF-CTV extends to the mesorectal fascia superiorly and the rectum inferiorly. If SV involvement is evident, the SV remnants should also be included in the PF-CTV.⁶⁶ Although there is some evidence that pelvic nodal irradiation may improve disease control for patients with high-risk prostate cancer after prostatectomy,^{68,69} the addition of pelvic nodal irradiation may increase the risk of treatment-related toxicities compared with treating the prostate bed alone.⁷⁰ Whether to include pelvic LN_s in postprostatectomy RT is an unresolved question and is being evaluated by the RTOG cooperative group in a phase 3 randomized controlled trial (RTOG 0534).⁷¹

Some limitations in PF-CTV delineation should be noted. A comparative study of the 4 consensus guidelines demonstrated significant variations among prostate bed target volumes defined according to these criteria,⁷² suggesting a lack of consistency among the guidelines. Similarly, Ost et al⁷³ have shown significant interobserver variability for application of EORTC contouring guidelines for defining the prostate bed target volume using CT alone. Alternative imaging with MRI has been suggested to help refine PF-CTV contouring. The use of postoperative MRI for prostate bed CTV delineation may reduce the size of the CTV and allow for more precise determination of the CTV.⁷⁴ Interestingly, a recent study by Croke et al⁷⁵ compared the prostate on preoperative MRI with prostate bed CTVs as defined according to consensus guidelines and demonstrated that postoperative CTV guidelines do not adequately cover the at-risk areas identified by preoperative MRI scans. These studies together suggest that guidelines for PF-CTV delineation might be improved by incorporating MRI, a topic worthy of additional study but beyond the scope of the current document.

Techniques of patient immobilization and setup

Before delivering EBRT for clinically localized prostate cancer, a patient must first be optimally positioned and immobilized to maximize accuracy and minimize the movement of the target organ (ie, the prostate). Proper

positioning and immobilization allow target volumes to be treated with smaller margins for setup error.

Patient positioning: prone versus supine

Patient position during simulation treatment has been extensively studied.⁷⁶⁻⁸⁰ Published reports have not demonstrated a clear benefit to using the prone position compared with the supine position.^{78,79} In the prone position, there may be greater rectal sparing, particularly in patients with large SVs. However, a larger percentage of the bladder may be included, which may increase the probability of urinary complications. There may also be greater setup error resulting from patient discomfort.⁷⁹ Furthermore, the prone position is more likely to be influenced by normal respiration,^{81,82} perhaps because of the increased intra-abdominal pressure associated with breathing in a prone position. When treatment is delivered in the prone position, the use of rigid cast immobilization may improve the accuracy of treatment delivery.⁸³ On the other hand, rigid immobilization and abdominal compression do not appear to reduce prostate motion in the supine position.⁸⁴

Bayley et al⁸⁵ conducted a prospective randomized trial of the supine versus prone position in patients undergoing CRT. Twenty-eight patients were randomized to commence RT in the prone or supine position and then change to the alternate position midway through their treatment course. After placement of fiducial markers in the prostate for daily prostate localization, the patients underwent CT simulation and treatment planning in both positions. Observed motion was less in the supine position than the prone position. Moreover, pretreatment positioning corrections were required more often for the prone position. A dose-volume histogram analysis revealed more bladder wall, rectal wall, and small bowel in the high dose volumes when patients were in the prone position than in the supine position. Finally, patients were more comfortable in the supine position than the prone position; 7 patients who started in the supine position refused to be treated in the prone position because of discomfort.

Shah et al⁸⁶ evaluated the differences in target motion during prostate EBRT in the prone and supine positions using electromagnetic transponders. Twenty patients received EBRT in the supine position; for each patient, 10 treatment fractions were followed by a session where the patient was repositioned prone. In the prone position, respiratory motion caused the prostate to be displaced >3 and >5 mm for 38% and 10% of the total tracking time, respectively. In the supine position, the prostate was displaced >3 and >5 mm for 13% and 3%, respectively; therefore, the supine position was associated with less movement. These findings are consistent with those of Wilder et al,⁷⁹ who observed a similar magnitude of

intrafraction prostate motion in the prone and supine positions and improved comfort in the supine position in their prospective evaluation of patients treated with electronic portal images obtained before and after EBRT. In summary, based upon the current evidence, the prone position has not been demonstrated to improve treatment accuracy beyond that achieved with the supine position.

Patient instructions and preparation

Regardless of the type of immobilization device used or the treatment position chosen, it is important that institutional policies are clear and consistent for patient setup for prostate EBRT and that the patient receive clear instructions regarding treatment preparation. In addition, the importance of patient education about bladder filling, rectal emptying, and adherence to recommended diet has been recognized.⁸⁷⁻⁸⁹ Bladder filling instructions, such as drinking a prescribed volume of water at a specific time interval before EBRT, do not result in consistent bladder volumes.⁹⁰ It is not clear that variations in bladder filling status influence target position⁹¹ or delivered doses⁹² in a significant way during prostate EBRT. On the other hand, variations in rectal filling can result in interfraction prostate motion that affects both dosimetric and clinical outcomes.^{89,93} An antifatulent diet and milk of magnesia laxative have been shown to reduce setup error between EBRT fractions,⁹³⁻⁹⁵ but it has not been shown to reduce intrafraction prostate motion.⁹⁵ Although institutional guidelines may vary, it is reasonable to instruct patients to strive for consistency with a comfortably full bladder, an empty rectum, and an antifatulent diet for both simulation and treatment. Given the availability of online daily image guidance strategies for prostate EBRT, which minimize geographic misses of the prostate target volume,⁹⁶ preparation guidelines should not create excessive discomfort or inconvenience for patients.⁹⁷ Finally, the use of contrast (intravenous, intravesicular/ureteral, rectal) is generally not necessary for routine care.

External immobilization methods

Immobilization devices are widely used to allow the use of smaller margins, thus reducing the dose to the surrounding normal tissues. Various forms of immobilization devices exist, including rigid casts⁸³ and vacuum-lock systems.⁸⁴ The average deviation of the isocenter position from the time of simulation to treatment has been shown to be smaller when patients are immobilized as compared with a nonimmobilized control group. Kneebone et al⁸³ reported results of a prospective randomized study that demonstrated that the average simulation-to-treatment deviation of the isocenter position was 8.5 mm in the control group versus 6.2 mm in the immobilized group ($P < .001$). The use of a cast immobilization

device reduced the incidence of major isocenter deviations (>10 mm). The average deviations in the anteroposterior, right-left, and superoinferior directions were reduced to 2.9 mm, 2.1 mm, and 3.9 mm, respectively, among patients treated with immobilization.⁸³

A simple device that allows a comfortable and reproducible setup can reduce large errors. The commonly used immobilization devices are constructed of a melted plastic mold material, a solidified foam mold, or a reusable inflatable mold device. In the era of image guidance, the choice of which immobilization device to use should take into consideration other relevant technical considerations, including the anticipated total dose and dose-fractionation schedule, treatment time required per fraction, and use of image guidance to target interfraction and/or intrafraction target volume motion. For example, alternative options such as leg and ankle supports that may be more comfortable to the patient have been suggested as reasonable immobilization strategies when positioning is later confirmed by image guidance. A range of immobilization options may be reasonable for use in prostate EBRT, and the specific choices may vary based upon other clinical factors.

Internal organ immobilization

Endorectal balloons can reduce prostate motion by stabilizing the rectum, act as an internal immobilization device, and displace the posterior rectal wall away from the high-dose region.⁹⁸⁻¹⁰² When used for prostate EBRT, endorectal balloons are inserted into the rectum for treatment planning and each day before treatment delivery and typically filled with 40 mL or more of air (for photon-based therapy) or water (for proton beam therapy).⁹⁹ The introduction of an air cavity into an endorectal balloon during prostate EBRT may reduce dose to the anterior rectal wall through electronic disequilibrium at the tissue-air interface.⁹⁹ Endorectal balloons are generally well-tolerated by patients and have been shown to reduce radiation doses delivered to the anorectal wall during prostate EBRT.⁹⁹ However, endorectal balloons also have disadvantages: (1) the prostate is deformed by introduction of the balloon; (2) the anterior rectal wall is pushed closer to the prostate; and (3) patient compliance poses barriers to widespread use of balloons.¹⁰³

Dosimetric comparisons have demonstrated that endorectal balloons reduce the volume of rectum exposed to high RT doses, but data regarding impact upon clinical outcomes are relatively scarce.⁹⁹ Wachter et al¹⁰⁴ demonstrated in 10 patients that the dose to the posterior wall of the rectum could be significantly reduced with the use of an endorectal balloon during the prostate boost. The advantage of a rectal balloon was lost if the SVs were treated. Patel et al¹⁰⁵ demonstrated significant dosimetric sparing of the rectum with 3D-CRT or IMRT when a

rectal balloon was used during an entire course of RT in 5 patients. Patients tolerated daily insertion of the balloon exceptionally well.

Bastasch et al¹⁰³ evaluated the tolerance of endorectal balloons in a cohort of 396 patients who received prostate IMRT. The majority of patients (99.2%) tolerated endorectal balloon immobilization with 100 mL of air. Topical anal medications were prescribed for 11.6% of patients during the treatment course. Van Lin et al¹⁰¹ compared endoscopic examinations of patients treated with and without endorectal balloons and found that using endorectal balloons was associated with fewer observed telangiectasias, which is indicative of reduced rectal mucosal wall injury with endorectal balloons. More clinical data are needed to evaluate whether endorectal balloons lead to better clinical outcomes for patients who receive prostate EBRT.

Finally, endorectal balloons may be useful when delivering high doses per fraction. Timmerman et al required endorectal balloons in their phase 1 and 2 trials of prostate SBRT.^{106,107}

Spacers

The injection of foreign material into the plane between the rectum and prostate has been investigated as a strategy to reduce rectal toxicity from prostate EBRT by reducing the radiation exposure of the rectum, with pre-clinical evidence suggesting that prostate-rectum spacers can provide for reduced rectal toxicity and potential for EBRT dose intensification.¹⁰⁸ Clinical studies of injectable hyaluronic acid,¹⁰⁹ a polyethylene glycol-based hydrogel,¹¹⁰⁻¹¹² human collagen,¹¹³ and an implantable, biodegradable balloon^{114,115} to separate the prostate from the rectum during prostate EBRT have been reported. Injection of these spacer materials between the rectum and prostate gland has been shown to be safe and to reduce exposure of the rectum to conventionally fractionated IMRT,^{111-113,115,116} hypofractionated IMRT,¹⁰⁹ and SBRT.¹¹⁷ Although some early evidence suggests lower-than-expected rates of acute gastrointestinal side effects with the use of spacer materials during prostate EBRT,¹¹⁰ further research is needed before this technique can be recommended as a standard component of prostate EBRT, particularly considering potential risks of the implantation. This is a promising area for research, and future clinical trials are encouraged. Notably, however, the use of spacers in prostate cancer EBRT is not routine.

Special considerations for radiation planning

Large prostate size

Special situations may arise in clinical practice, which presents special challenges to the radiation oncologist.

Very large prostate gland size may be a challenge for EBRT planning, because larger PTVs make it more challenging to meet planning objectives for bladder and rectum.¹¹⁸ Short-term androgen deprivation therapy (ADT) may downsize large prostate glands before brachytherapy to mitigate concerns regarding pubic arch interference and toxicity.^{119,120} Likewise, Zelefsky et al¹²¹ reported on the benefit of neoadjuvant ADT in reducing dose to the rectum and bladder in their early experience with 3D-CRT. However, neoadjuvant ADT is usually not necessary or recommended for downsizing in routine clinical practice in the present era of IMRT and IGRT, and it may be appropriate only in highly selected situations.¹²² If neoadjuvant ADT is used, special attention should be given to timing of simulation for treatment planning because the prostate gland volume changes significantly during the first 2 months after starting ADT.¹²³

Hip prostheses

Hip prostheses present a well-recognized challenge for prostate EBRT because these create CT imaging artifacts that can obscure pelvic anatomy and impair the ability of the treatment-planning system to determine the electron densities for dose modeling.¹²⁴⁻¹²⁶ Although challenging, IMRT planning is feasible in a patient with bilateral hip prostheses,¹²⁷ and class solutions have been proposed.^{128,129} Megavoltage CT imaging, if available, may provide better imaging of pelvic anatomy and may be useful as a tool for electron density calibration during EBRT planning.^{130,131} There is some limited evidence that MRI scanning may also be helpful for target delineation for patients with bilateral hip prostheses.^{132,133} EBRT planning requires careful collaboration among radiation oncologists, physicists, and dosimetrists and should include recognition of the uncertainty in target volume definition and dose calculations. Hip implants have minimal effect on most IGRT with US¹³⁴ or radio-frequency transponders.¹³⁵ Recommendations, including those from a 2003 American Association of Physicists in Medicine task group report,¹³⁶ are that beam arrangements avoid the prosthesis,^{124,128,129} use more arcs,¹³⁷ that inhomogeneity corrections be turned off during treatment planning, that dose perturbations be estimated, and that exit doses be measured during EBRT delivery. Additionally, there are special considerations for helical tomotherapy¹³⁸ and proton therapy.¹³⁹⁻¹⁴¹

Obesity

Obese patients may present a challenge for highly conformal EBRT because there may be day-to-day variations in external body contour dependent upon movement of a pannus. Obese patients tend to have larger interfractional shifts because of setup errors,^{142,143} and anatomic

variations in obese patients may lead to significant variations in delivered dose.¹⁴⁴ Obese patients also have been reported to have higher rates of prostate cancer recurrence after EBRT.^{145,146} There is no direct evidence regarding the effectiveness of specific immobilization or IGRT techniques in obese patients. Special attention should be given to the accuracy of patient positioning and daily target localization. Volumetric images obtained during treatment for image guidance, if available, should be reviewed for anatomical variation during the course of EBRT.

When anticoagulation needs present a challenge for fiducial marker insertion, it may be reasonable to forgo the implantation of markers when online volumetric imaging is available. Moseley et al¹⁴⁷ compared cone beam CT (CBCT) with and without implanted gold fiducial markers and found that cone beam CT without fiducial markers provides a reasonably precise method of IGRT for prostate EBRT.

Dose constraints for target volumes and organs at risk

Target volumes

Evaluation of target volume coverage in prostate EBRT planning focuses on percentage of the target volume covered by the prescription dose, as well as maximum and minimum doses. As an example, the RTOG 0924³⁰ trial specifies that 3D-CRT or IMRT doses be normalized so that exactly 98% of the PTV receive the prescription; the maximum allowable dose to 0.03 mL or more of the PTV is 107%, and the minimum allowable dose to 0.03 mL or more is 95%.¹⁸ Similarly, for SBRT and HFRT, the dose is typically prescribed to cover at least 95% of the PTV.¹⁰⁷ Martin et al¹⁴⁸ have published a clinician's guide to prostate IMRT plan assessment, which provides an overview of EBRT treatment planning and additional recommendations for plan review, including the objective of a conformity index of 1.1 and 99% coverage of the CTV by the 100% isodose line. Target volume constraints from selected recent or ongoing RTOG trials (including 0924,³⁰ 0534,⁷¹ 0415,¹⁴⁹ 0938,¹⁵⁰ 9406,³² 0126²⁹) are displayed in [Appendix 3](#).

PTV evaluation generally applies to whole-gland volumes, without specific parameters regarding GTV dose. Although there have been a number of studies boosting dominant prostate tumor nodules, there is no clear evidence or consensus around such an approach and it remains investigational at this time.¹⁵¹

Organs at risk

Safe delivery of EBRT requires care and attention to doses received by adjacent organs at risk, and this is particularly important for dose-escalated prostate EBRT.

Emami et al¹⁵² provided the first comprehensive set of dose-volume constraints for organs at risk in 1991. An updated set of dose-volume parameters was provided in 2010 through the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) program.¹⁵³ The QUANTEC review of rectal dose-volume effects suggested the following constraints: V50Gy <50%, V60Gy <35%, V65Gy <25%, V70Gy <20%, and V75Gy <15%.¹⁵⁴ Additionally, a V70Gy <10%-15% should be considered as a strict cutoff.^{155,156} The QUANTEC report for bladder¹⁵⁷ recommended the dose limits used for the conventional-fractionation arm of RTOG 0415¹⁴⁹ (shown in Appendix 3). For the penile bulb, the QUANTEC report recommends keeping the mean dose to 95% of the penile bulb <50 Gy as well as limiting the D70 and D90 to 70 Gy and 50 Gy, respectively.¹⁵⁸

QUANTEC recommendations apply primarily to conventionally fractionated EBRT, and different dose-volume objectives must be considered for hypofractionated treatments, with an effort toward considering the biological equivalent dose for late normal tissue toxicity for the hypofractionation schedule. Dose-volume constraints from the moderate-hypofractionation (70 Gy in 28 fractions) arm of RTOG 0415,¹⁴⁹ similar to the schedule reported by Kupelian et al,¹⁵⁹ are shown in Appendix 3. For the randomized trial of 70.2 Gy in 26 fractions versus 76 Gy in 38 fractions reported by Pollack et al,¹⁸ the dose constraints used for the hypofractionated arm include rectum, V50 Gy ≤17% and V31 Gy ≤35%; and bladder, V50 Gy ≤25% and V31 Gy ≤50%.¹⁸ Dose-volume constraints for prostate SBRT are shown in Appendix 3, taken from RTOG 0938.¹⁵⁰

Although dose-volume considerations are necessary, it is important to remember that clinical factors are also associated with risk of RT-related complications, including comorbidities such as congestive heart failure or history of myocardial infarction,¹⁶⁰ diabetes mellitus, use of anticoagulation, prior smoking, prior transurethral resection of the prostate, inflammatory bowel disease,^{161,162} and hemorrhoids, as well as tumor size and advanced age.¹⁵⁴ Clinical judgment should be used for patients with significant medical comorbidities, for whom consideration of more stringent dose-volume constraints may be prudent.

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Appendix 1 Outcomes and toxicities with different external-beam radiation therapy technologies and methods for prostate cancer treatment

Study/author	Year accrued/era	Comparison/ clinical question	Arms	N	Risk groups	Med FU (mo)	Outcomes	Toxicities	Conclusion(s)
Perez ¹²	1992-1999	Clinical retrospective comparison of 120 rotational arcs vs 3D-CRT	Standard RT, with 120° bilateral arcs, using portals with 2-cm margins: 68-70 Gy (no ADT)	155	L, I	56	ASTRO FFBFs: T1b/c: 61% vs 75% (SS) T2: 65% vs 79% (SS)	Moderate dysuria: 2%-5% vs 6%-9% (SS) Late GI grade 2 morbidity: 7% vs 1% (SS)	3D-CRT has improved FFBF and toxicity profile for T1-2 cancers
			3D-CRT: 68-74 Gy (no ADT)	312		38			
MD Anderson/ Kuban ^{13,14}	1993-1998	RCT of dose escalation of 3D-CRT	3D-CRT: 78 Gy 3D-CRT: 70 Gy	151 150	L, I, H	108	Phoenix FFBF: 78% vs 59% L: 92% vs 73% I: 78% vs 76% H: 67% vs 33%	Late RTOG grade 3-4 toxicities: GI 7% vs 1% (SS) GU 4% vs 1% (NS)	Dose escalation to 78 Gy improves FFBF, CSS for I, H patients
RTOG 9406/ Michalski ^{15,16}	1994-2000	Phase 1/2 RCT of dose escalation of 3D-CRT	Levels I-V (respective): 68.4, 73.8, 79.2 Gy, all at 1.8-Gy fractions; or 74 Gy and 78 Gy at 2-Gy fractions (±ADT)	1,084	L, I, H	110-140	Phoenix FFBFs (for levels I-V, respectively) L: 68%, 73%, 67%, 84%, 80%; I: 70%, 62%, 70%, 74%, 69% H: 42%, 62%, 68%, 54%, 67%.	Increased GU/GI Grade ≥2 toxicity using 78 Gy vs 68.4 Gy to 79.2 Gy or 74 Gy (hazard ratios 1.6-2.6)	Improved outcomes with 78-79.2 Gy vs lower doses Increased toxicity with higher doses of 3D-CRT
Zelevsky ¹⁷	1992-1998	Clinical retrospective comparison of 3D-CRT vs IMRT	3D-CRT: 72 Gy + 9-Gy boost IMRT: 81 Gy	61 171	L, I, H	12	N/A N/A	Combined rates of acute G1-2 GI toxicities and GI bleeding improved with IMRT (2% vs 10%, SS)	Improved dosimetry, toxicity, safe deliverable dose to target with IMRT vs 3D-CRT
Fox Chase/ Pollack ¹⁸	2002-2006	RCT of HFRT with IMRT vs CFRT with IMRT to improve FFBF	CFRT: 76 Gy in 2-Gy fractions (±ADT) HFRT: 70.2 Gy in 2.7-Gy fractions (±ADT)	152 151	L, I, H	68	5-y Phoenix FFBF similar between the 2 arms (78% vs 77%)	Acute Grade ≥2 GI toxicities similar; Acute GU toxicities statistically higher with HFRT (18.3% vs 8.3%, SS); late toxicities similar	HFRT did not result in improved FFBF but was delivered in shorter time. Men with poor GU function before HFRT may not be ideal candidates for the approach.

Sheets 2012 ¹⁹	2000-2008	SEER analysis of any late toxicity of protons vs IMRT, 3D-CRT	Proton IMRT	684 684	L, I, H	46-50	N/A N/A	Absolute risk per 100 person-years: GU: 26 vs 25 (NS) GI: 25 vs 13 (SS)	IMRT patients had a lower rate of GI morbidity (vs protons).
			3D-CRT IMRT	6,310 6,666	L, I, H		N/A N/A	Absolute risk per 100 person-years: GI diagnoses: 13.4 vs 14.7 (SS) Hip fracture: 0.8 vs 1.0 (SS)	IMRT patients had lower rate of diagnosis of GI morbidity and hip fracture (vs 3D-CRT).
Zelevsky ²⁰	2006-2009	Retrospective cohort study of IMRT vs IMRT with IGRT	IMRT to 86.4 Gy + IGRT kV imaging of implanted prostatic fiducial markers	190 186	L, I, H	34	No differences in 3-y FFBF (88% to 94%) for L or I patients FFBF improved for H patients (97% vs 78%, SS) with IGRT	3-y Grade ≥ 2 GU toxicity: 20% vs 10.4%, respectively (SS) 3-y Grade ≥ 2 GI toxicity similar: 1.0 vs 1.6%, respectively (NS)	IGRT, with fiducial markers, is associated with improved FFBF among high-risk patients and a lower rate of late GU toxicity compared with high-dose IMRT.
Katz ²¹⁻²³	2006-2009	Phase 1/2 dose-escalation study of robotic-arm SBRT	Robotic-arm SBRT: 35-36.25 Gy in 5 fractions	515 186	L, I > H	40	5-y Phoenix FFBFs: L: 98%, I: 93%, H: 75%	RTOG late grade 3-4 toxicity: 0%	SBRT has promising rates of toxicity and efficacy.

ADT, androgen deprivation therapy; ASTRO, American Society for Radiation Oncology; 3D-CRT, 3-dimensional conformal radiation therapy; CFRT, conventionally fractionated radiation therapy (ie, 1.8-2.0 Gy/fraction); CSS, cancer-specific survival; FFBF, freedom from biochemical failure; FU, follow-up; GI, gastrointestinal; GU, genitourinary; H, high risk; HFRT, hypofractionated radiation therapy (ie, 2.1-3.5 Gy/fraction); I, intermediate risk; IGRT, image guided radiation therapy; IMRT, intensity modulated radiation therapy; L, low risk; N/A, not applicable; NR, not reported; NS, not significant; OS, overall survival; RCT, randomized controlled trial; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiation therapy (ie, >3.5 Gy/fraction in 5 fractions or less); SEER, Surveillance, Epidemiology, and End Results; SS, statistically significant.

Note: ASTRO: 3 consecutive PSA (prostate-specific antigen) rises; Phoenix: PSA nadir + 2 ng/mL.

Appendix 2 Definition of target volumes and planning target volume margins for EBRT in published clinical protocols

Protocol/reference(s)	GTV and CTV	PTV
MD Anderson: RCT of 70 Gy vs 78 Gy Kuban, 2008 ¹⁴	<ul style="list-style-type: none"> • CTV = prostate and SVs 	<ul style="list-style-type: none"> • Conventional 4-field box, 11 × 11 cm for AP/PA fields, 11 × 9 cm for lateral fields, then reduce all fields to 9 × 9 cm • On 70-Gy arm, CT performed to confirm that margins from CTV to block edge were 1.25 to 1.5 in anterior and in dimensions and 0.75 × 1.0 cm in posterior and superior dimensions • CTV + 7-10 mm
PROG 9509 RCT of 70.2 Gy vs 79.2 Gy Zietman, 2010 ²⁴	<ul style="list-style-type: none"> • CTV = prostate + 5-mm margin 	<ul style="list-style-type: none"> • CTV + 7-10 mm
GETUG: RCT of 70 vs 80 Gy Beckendorf, 2004 ²⁵	<ul style="list-style-type: none"> • CTV = prostate ± SVs 	<ul style="list-style-type: none"> • Phase 1: prostate and SVs + 10-mm margin, reduced posteriorly to 5 mm • Phase 2: prostate alone with same margins • CTV + 10 mm during first 68 Gy • CTV + 5 mm (except 0 mm toward the rectum) for last 10 Gy in high-dose arm
Dutch CKVO96-10: RCT of 68 Gy vs 78 Gy Al-Mamgami, 2008 ²⁶	<ul style="list-style-type: none"> • CTV = GTV <ul style="list-style-type: none"> ◦ Group 1: prostate only ◦ Group 2-3: prostate and SVs (for first 50-68 Gy), then prostate only for remainder ◦ Group 4: prostate and SVs 	<ul style="list-style-type: none"> • CTV + 10 mm during first 68 Gy • CTV + 5 mm (except 0 mm toward the rectum) for last 10 Gy in high-dose arm
UK MRC RT01: RCT of 64 Gy vs 74 Gy Dearnaley, 2007 ^{27,28}	<ul style="list-style-type: none"> • 64-Gy arm: GTV = prostate ± base of SVs (for phase 1 GTV) • 74-Gy arm: GTV = <ul style="list-style-type: none"> ◦ Prostate + SVs (for phase 1 GTV) ◦ Prostate ± base of SVs (for phase 2 GTV) • CTV = GTV + 5 mm 	<ul style="list-style-type: none"> • CTV + 5- to 10-mm margin
RTOG 0126: ²⁹ RCT of 70.2 Gy vs 79.2 Gy	<ul style="list-style-type: none"> • GTV = prostate • CTV = prostate and proximal SVs (up to 10 mm); may be reduced to prostate only after 55.8 Gy 	<ul style="list-style-type: none"> • CTV + a minimum of 5 mm in all directions. Superior and inferior margins should be 5-10 mm depending on spacing of planning CT
RTOG 0924: ³⁰ RCT of high-dose RT ± pelvic RT in intermediate- and high-risk patients	<ul style="list-style-type: none"> • GTV1 = all known disease on planning CT, urethrogram, clinical information • GTV2 = prostate + proximal SVs • CTV1 = prostate and SVs + LNs (obturator, external iliac, proximal internal iliac, common iliac) + 7-mm margins (excluding bone) • CTV2 = GTV2 	<ul style="list-style-type: none"> • PTV1 = CTV1 + 5-15 mm • PTV2 = CTV2 + 5-10 mm • Individual selection of PTV margin should be based on spacing of planning CT

CTV, clinical target volume; EBRT, external-beam radiation therapy; GETUG, Groupe d'Etude des Tumeurs Uro-Génitales; GTV, gross tumor volume; PTV, planning target volume; RCT, randomized controlled trial; SVs, seminal vesicles. Other abbreviations as in [Appendix 1](#). All studies listed use conventionally fractionated radiation therapy (ie, 1.8-2.0 Gy/fraction).

Appendix 3 Dose constraints for EBRT for low-risk prostate cancer

Fractionation	Structure	Constraint(s)	Comment/reference
Intact prostate, CFRT, assuming 1.8 Gy × 44 (79.2 Gy total)	PTV	V100 >98% Maximum point dose <107% of prescription dose	RTOG 9406 - level 3 ³³ ; RTOG 0126 - arm 2 ²⁹ ; RTOG 0415 - arm 1 ¹⁴⁹ ; RTOG 0924 ³⁰
	Bladder	V80 <15%	
		V75 <25%	
		V70 <35%	
		V65 <50%	
	Rectum	V75 <15%	
		V70 <25%	
		V65 <35%	
		V60 <50%	
	Femoral head	V50 <10% (each head evaluated separately)	
Small bowel	V45 <150 mL	RTOG 0534 - arm 3 ⁷¹	
Penile bulb	Mean <52.5 Gy	RTOG 9406 - level 3 ³³ RTOG 0126 - arm 2 ²⁹	
Intact prostate, HFRT, assuming 2.5 Gy × 25 fractions (70 Gy total)	PTV	V100 >98% Maximum point dose < 107% of prescription dose	RTOG 0415 - arm 2 ¹⁴⁹
	Bladder	V79 <15%	
		V74 <25%	
		V69 <35%	
		V64 <50%	
	Rectum	V74 <15%	
		V69 <25%	
		V64 <35%	
		V59 <50%	
	Penile bulb	Mean dose ≤51 Gy	
Intact prostate, SBRT, assuming 7.25 Gy × 5 fractions (36.25 Gy total)	PTV	D0.03 mL <107% of prescription dose (robotic arm)	RTOG 0938 - 5-fraction arm ¹⁵⁰
		D0.03 mL <120% of prescription dose (nonrobotic arm)	
		V100 >95%	
	Bladder	D0.03 >95% of prescription dose	
		D1 mL <105%	
		D90% <90% of prescription dose	
		D50% <50% of prescription dose	
	Rectum	D1cc <105%	
		D90% <90% of prescription dose	
		D80% <80% of prescription dose	
		D50% <50% of prescription dose	
	Femoral head	V20 <10 mL (both heads)	
	Penile bulb	D1 mL <81% of prescription dose	
		D1 mL <100% of prescription dose	
	Urethra	V20 <3 mL	
		D1 mL <107% of prescription dose	
	Penile shaft	Contoured as avoidance structure to avoid beams (robotic arm)	

X; Dose (X, in Gy; or as % of total dose) to 1 mL of structure; D90%, X Dose (X, in Gy; or as % of total dose) to 90% of structure.
 Note: For protons these dose constraints need to be interpreted as Gy (relative biological effectiveness). V100, X%; volume of structure (X%) receiving 100% of the dose. Other abbreviations as in [Appendixes 1 and 2](#).

VARIANT 1 A 67-y-old man diagnosed from a PSA screening program*

Treatment	Rating	Comments
Presimulation		This option is not required if performing image guidance but is an option that is not wrong for planning purposes.
Bowel preparation	7	Microenema is recommended. ⁹⁷ Oral stool softener and antiflatulent agents are also options. ^{89,95}
Supine position	8	See references ⁷⁶⁻⁷⁹
Prone position	5	See reference ⁸⁰
Custom immobilization (eg, with custom thermoplastic cast)	8	This option is per previously published reports. ^{81,82}
Bladder		This treatment is dependent on institution.
Full	7	
Comfortably full	8	
Empty	4	
Simulation tools		
CT simulation	8	CT alone is possible in the hands of an experienced clinician. ³⁶
MRI simulation and fusion to CT	7	This procedure may be most helpful if the prostate contour is uncertain or in instances of unusual anatomy. See references ^{41,44-48}
Treatment planning		
IMRT (nonarc)	8	
IMRT (arc)	8	
Proton beam	6	This reflects recognized controversy in the field. This procedure is unlikely to have worse outcomes than IMRT. Treatment on protocol is encouraged.
3D-CRT	5	This procedure is acceptable if dose-volume histogram constraints are met or if IMRT is not available.
Image guidance		
Use of radiofrequency transponders	7	See references ^{34,102,138,147,163-173}
CBCT with fiducial markers, aligned to PTV	8	
CBCT without fiducial markers, aligned to PTV	7	
CBCT, aligned to bony anatomy	3	The prostate gland is recognized to move independently of bony anatomy, so alignment based on the prostate PTV is recommended.
2D imaging with fiducial markers	7	
Ultrasound	7	
None	3	
RT fractionation		
CFRT (ie, 1.8-2.0 Gy/fraction)	8	
HFRT (ie, 2.1-3.5 Gy/fraction)	6	This procedure is per previous protocol (eg, RTOG 0415 ¹⁴⁹).
Stereotactic RT (ie, >3.5 Gy/fraction)	6	This procedure is probably acceptable, but head-to-head comparisons are limited currently. This procedure is per previous protocol (eg, RTOG 0938 ¹⁵⁰).

Rating scale: 1, 2, 3 = usually not appropriate; 4, 5, 6 = may be appropriate; 7, 8, 9 = usually appropriate.

CBCT, cone beam computed tomography; CFRT, conventionally fractionated radiation therapy; CT, computed tomography; 2D, 2-dimensional; 3D-CRT, 3-dimensional conformal radiation therapy; HFRT, hypofractionated radiation therapy; IMRT, intensity modulated radiation therapy; PSA, prostate-specific antigen; PTV, planning target volume; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group.

* PSA 5.2 ng/mL, prostate within normal limits on examination. Multiple needle biopsies of the prostate showed adenocarcinoma. Gleason score 3 + 3 = 6.

Variation 2 A 60-y-old man, asymptomatic in PSA screening program*

Treatment	Rating	Comments
Use current simulation	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel’s median rating. Distended rectum results in worse dosimetry ⁸⁸ and clinical outcome. ⁸⁹ It may be controversial to not resimulate, but some patients will always have a distended rectum and image guidance methods may protect against negative effects.
Resimulate this case after intervention:		
Patient walking, bowel movement, enema	8	Enema may be most appropriate. ⁹⁷

Rating scale: 1, 2, 3 = usually not appropriate; 4, 5, 6 = may be appropriate; 7, 8, 9 = usually appropriate.

Abbreviations as in Variation 1.

* PSA 5.2 ng/mL, prostate without palpable abnormalities. Multiple needle biopsies of the prostate showed adenocarcinoma. Gleason score 3 + 3 = 6. CT simulation reveals grossly distended rectum (gas and stool).

Variation 3 A 60-y-old man, asymptomatic in PSA screening program*

Treatment	Rating	Comments
Continue planning using current CT simulation	7	Definitive EBRT for large prostates without ADT is associated with low rates of GU or GI toxicity. ¹²²
Use ADT for downsizing of gland	4	Consider this option if dosimetric criteria are not met on initial plan due to large prostate volume.
Recommend for surgery rather than RT	5	This option is recommended if obstructive symptoms are present.
RT fractionation		
CFRT	8	
HFRT	5	
SBRT	4	The toxicities of SBRT in large prostate glands have not been fully characterized.
Simulation		
CT simulation (kV CT)	8	
MRI simulation and fusion to CT	8	Volume on MRI is noted to be smaller than that on CT.41

Rating scale: 1, 2, 3 = usually not appropriate; 4, 5, 6 = may be appropriate; 7, 8, 9 = usually appropriate.

ADT, androgen deprivation therapy; EBRT, external beam radiation therapy; GI, gastrointestinal; GU, genitourinary; HFRT, hypofractionated radiation therapy; MRI, magnetic resonance imaging; SBRT, stereotactic body radiation therapy. Other abbreviations as in Variation 1.

* PSA 5.2 ng/mL, prostate within normal limits, no palpable lesions. Multiple needle biopsies of the prostate showed adenocarcinoma. Gleason score 3 + 3 = 6. CT simulation reveals very large-volume prostate (100 mL).

Variant 4 A 60-y-old man, asymptomatic in PSA screening program*

Treatment	Rating	Comments
Treatment planning		
IMRT (nonarc)	8	Dosimetry may be improved by avoiding beams that pass through prostheses. ^{124,128,129}
VMAT (arc-based IMRT)	8	Dosimetry may be improved by using more arcs. ¹³⁷
IMRT (helical tomotherapy)	7	This procedure has been previously described. ¹³⁸
Proton beam	5	This procedure reflects recognized controversy in the field. Use anterior-oriented beams ¹³⁹ or oblique beams. ¹⁴⁰ CT simulation with kV and MV CT images improves range of uncertainties for planning. ¹⁴¹
IGRT		
Radiofrequency transponders	7	Hip implants have no meaningful effect on image guidance with this strategy. ¹³⁵
2D imaging with implanted fiducial markers	7	
MVCT/CBCT with fiducial markers	7	
Ultrasound	7	See reference ¹³⁴
Simulation		
CT simulation (kV CT)	8	Use a commercial algorithm to improve CT Hounsfield number accuracy and structure visualization. ¹²⁴⁻¹²⁶
Use MVCT to assist planning if available	7	This procedure may improve image resolution and permit calculation of electron density. ¹³¹
MRI simulation and fusion to CT	8	Bilateral hip implants are not a contraindication to CT/MRI simulation. ¹³³
None	3	
RT fractionation		
CFRT	8	This procedure is not a contraindication on previous protocol (ie, RTOG 9406 ³³).
HFRT	6	This procedure is not a contraindication on previous protocol (ie, RTOG 0415 ¹⁴⁹).
SBRT	6	This procedure is not a contraindication on previous protocol (ie, RTOG 0938 ¹⁵⁰).

Rating scale: 1, 2, 3 = usually not appropriate; 4, 5, 6 = may be appropriate; 7, 8, 9 = usually appropriate.

IGRT, image guidance radiation therapy; MVCT, megavoltage computed tomography; VMAT, volumetric modulated arc therapy. Other abbreviations as in Variants 1 and 3.

* PSA 5.2 ng/mL, prostate without palpable abnormalities. Multiple needle biopsies of the prostate showed adenocarcinoma. Gleason score 3 + 3 = 6. Patient has bilateral hip implants.

VARIANT 5 A 60-y-old man, asymptomatic in PSA screening program*

Treatment	Rating	Comments
Simulation	8	There is no effect on simulation.
Treatment planning		
IMRT (nonarc)	8	There are reportedly low complications with photon EBRT. ^{161,162}
IMRT (arc)	8	There are reportedly low complications with photon EBRT. ^{161,162}
Proton beam	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. This reflects recognized controversy in the field. Treatment on a clinical trial is encouraged.
IGRT		
CBCT with radiofrequency transponders	7	This is expert opinion. There is no published evidence on the optimal method for image guidance.
CBCT with fiducial markers, aligned to PTV	8	This is expert opinion. There is no published evidence on the optimal method for image guidance.
CBCT without fiducial markers, aligned to PTV	7	
CBCT, aligned to bony anatomy	3	The prostate gland is recognized to move independently of bony anatomy, so alignment based on the prostate PTV is recommended.
2D imaging with fiducial markers	7	
Ultrasound	7	
None	2	
RT fractionation		
CFRT	8	
HFRT	4	There is limited evidence regarding the safety of HFRT in inflammatory bowel disease.
SBRT	4	There is limited evidence in inflammatory bowel disease.

Rating scale: 1, 2, 3 = usually not appropriate; 4, 5, 6 = may be appropriate; 7, 8, 9 = usually appropriate.

Abbreviations as in Variants 1, 3, and 4.

* PSA 5.2 ng/mL, prostate without palpable abnormalities. Multiple needle biopsies of the prostate showed adenocarcinoma. Gleason score 3 + 3 = 6. Patient has a history of inflammatory bowel disease.

Variants 6 A 60-y-old man, asymptomatic in PSA screening program*

Treatment	Rating	Comments
IGRT		
Daily CT with soft-tissue alignment	7	There are no specific recommendations on RTOG 0534. ⁷¹ CBCT with fiducial markers is reasonable. ^{174,175}
Daily CT with implanted fiducial markers	6	It is uncertain if fiducial markers are stable, similar to the intact prostate setting.
Daily CT with surgical clips	7	This procedure may be used if other options are not available; however, clinicians should note that these clips may not appear clearly on CBCT.
Daily CT with alignment of bony anatomy	4	The prostate gland is recognized to move independently of bony anatomy, so alignment based on the prostate PTV is recommended.
Daily kV orthogonals	6	The prostate gland is recognized to move independently of bony anatomy, so alignment based on the prostate PTV is recommended.
Electromagnetic transponders	6	There are typically 3 beacons placed: 2 lateral to the ureterovesicular anastomosis and 1 distal in the retrovesical tissue where the SVs had been. The beacons are typically 1 cm apart from each other. ¹⁷⁶
None	3	

Rating scale: 1, 2, 3 = usually not appropriate; 4, 5, 6 = may be appropriate; 7, 8, 9 = usually appropriate.

Abbreviations as in Variants 1, 3, 4, and 5.

* PSA 5.2 ng/mL, prostate within normal limits, no palpable lesions. Multiple needle biopsies of the prostate showed adenocarcinoma. Gleason score 3 + 3 = 6. Patient has radical prostatectomy that reveals pT2 disease, positive apical margin, postoperative PSA of 0.2 ng/mL. Adjuvant EBRT recommended.

Variants 7 A 60-y-old man, asymptomatic in PSA screening program*

Treatment	Rating	Comments
Simulation		
Immobilization of pannus (eg, tape or cover sheet)	7	There may be considerable variability.
Treatment planning		
IMRT (nonarc)	8	Limiting beam angles can be considered. For low-risk patients, one can consider weight loss prior to starting treatment.
IMRT (arc)	8	
Proton beam	6	One can consider limiting arcs.
		Beam angles for proton beam therapy must be carefully considered because of limitations in proton beam path length.
IGRT		
Electromagnetic transponders	4	Obesity may obscure reading of transponders. In borderline cases, the transponders may be used as fiducial markers if the signal cannot be obtained.
Daily CBCT with fiducial markers	8	
Daily CBCT without fiducial markers	7	
Daily planar imaging with fiducial markers	7	
Daily ultrasound imaging	5	

Rating scale: 1, 2, 3 = usually not appropriate; 4, 5, 6 = may be appropriate; 7, 8, 9 = usually appropriate.

Abbreviations as in Variants 1 and 4.

* PSA 5.2 ng/mL, prostate with palpable abnormalities. Multiple needle biopsies of the prostate showed adenocarcinoma. Gleason score 3 + 3 = 6. Patient is obese, with pannus extending into radiation field.