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EXTERNAL BEAM RADIATION THERAPY TREATMENT PLANNING FOR CLINICALLY LOCALIZED PROSTATE CANCER

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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 (ACR) 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 al [9] and the National Comprehensive Cancer Network (NCCN) [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 10–20 ng/mL, or Gleason score 7; and high risk, for clinical stage T2c tumor, PSA >20 ng/mL, or Gleason score ≥8 [9]. The NCCN 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].

Radiation Therapy 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

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(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 I-III 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.

I. Definitions for Target Volumes and Organs at Risk (OARs)

The outcomes and toxicities with different EBRT technologies and fractionation techniques are shown in Appendix 1 [12-23]. To complement, 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 83 [31] of the International Commission on Radiation Units and Measurements for specifying dose prescription and are summarized as follows:

Gross tumor volume (GTV)

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 radiation treatment-planning process prior to the start of EBRT.

Clinical target volume (*CTV)*

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 where 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 subclinical 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 below 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-PTV (planning target volume) expansion margins may also provide some coverage of potential EPE.

Planning target volume (PTV)

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 below.

Contouring organs at risk (OARs)

The RTOG provides recommendations for contouring normal tissue structures in the form of a contouring atlas on the RTOG website and published consensus guidelines [35]. Adherence to these guidelines is recommended in

order 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) should be contoured, not just the anorectal wall. The penile bulb contour should encompass the portion of the bulbous spongiosum that is adjacent to the genitourinary (GU) diaphragm without extending the contour anteriorly into the penile shaft. The penile bulb may be visualized on a CT and a T2-weighted MRI. 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 (non-GI) normal structures using the treatment-planning software.

II. Determining Clinical Target Volumes 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

Computed tomography (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.

Magnetic resonance imaging (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 one 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, as it has been shown to decrease contouring variability when compared to 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 al [45] 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 al [46] reported improved sparing of the rectum and penile bulb with the use of MRI-based delineation of the prostate on 3-D conformal RT (3D-CRT) treatment plans. At this time, it is unclear whether sparing of the 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%–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 radiation treatment 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 in order to achieve high-quality MR-based imaging [52]. Consequently, MRI may become more readily employed [53]. However, the field strength of MRI is only 1 factor that may influence prostate cancer imaging [54]. Although a 3.0T MRI 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 MR-based imaging techniques currently 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 (EPE)

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 al [56] performed a detailed pathologic analysis of 371 prostatectomy specimens to determine CTV margins. EPE was present in a 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 al [57] 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 mm [58]. 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.

Seminal vesicle (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 al [60] 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 2.0–2.5 cm (approximately 60%) of the SVs be included in the CTV for intermediate-risk and high-risk patients (ie, PSA ≥10, Gleason ≥7, ≥T2b). Zlotta et al [57] 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.

Lymph nodes (LNs)

Lawton et al [61] conducted a study of CTV definition of pelvic LNs by radiation oncologists with expertise in prostate cancer and observed significant variation among physicians in the CTV structures contoured. In order to provide guidance for the safe and effective use of intensity-modulated RT (IMRT) for pelvic LN irradiation, the RTOG developed a contouring atlas for pelvic LN irradiation for prostate cancer [62]. When irradiating the pelvic

LNs for prostate cancer, the RTOG consensus guidelines recommend including the distal common iliac, presacral, external iliac, internal iliac, and obturator LNs. 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 (VUA), 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 guidelines [66] provide detailed guidance on CTV definition, including variation based upon pathological information, and are supplemented by an atlas available on the RTOG website (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 8–12 mm inferior to the VUA. The PF-CTV extends anteriorly to the posterior aspect of the pubis below the cranial border of the pubic symphysis and encompasses the posterior 1–2 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 to treating the prostate bed alone [70]. Whether to include pelvic LNs in postprostatectomy RT is an unresolved question and is currently being evaluated by the RTOG cooperative group in a phase III 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 al [73] 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 al [75] compared the prostate on preoperative MRI to 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. 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.

III. 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 as compared to 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 due to patient discomfort [79]. Furthermore, the prone position is more likely to be influenced by normal respiration [81,82], perhaps due to 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 al [85] 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, as 7 patients who started in the supine position refused to be treated in the prone position due to discomfort.

Shah et al [86] 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 patients 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 prior to EBRT, do not result in consistent bladder volumes [90]. It is not clear that variations in bladder filling status influence target position [91] or delivered doses [92] 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 antiflatulent 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 antiflatulent 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 casts [83] 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 to a nonimmobilized control group. Kneebone et al [83] 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<0.001). The use of a cast immobilization device reduced the incidence of major isocenter deviations (>10 mm). The average deviations in the anterior-posterior (AP), right-left, and superior-inferior 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. It is important to note that 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 prior to 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 al [104] 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 al [105] 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 al [103] 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 al [101] compared endoscopic examinations of patients treated with and without endorectal balloons and found that use of 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 I and II 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 preclinical 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 GI 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

A variety of 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, as 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 prior to brachytherapy to mitigate concerns regarding pubic arch interference and toxicity [119,120]. Likewise, Zelefsky et al [121] 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 since 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 since 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 (MVCT) 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 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 US [134] or radiofrequency transponders [135]. Recommendations, including those from a 2003 American Association of Physicists in Medicine (AAPM) 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 tomotherapy [138] and proton therapy [139-141].

Obesity

Obese patients may present a challenge for highly conformal EBRT since 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 due to 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 al [147] compared cone-beam CT (CBCT) with and without implanted gold fiducial markers and found that CBCT without fiducial markers provides a reasonably precise method of IGRT for prostate EBRT.

IV. Dose Constraints for Target Volumes and Organs at Risk (OARs)

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 0924 [30] 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 cc or more of the PTV is 107%, and the minimum allowable dose to 0.03 cc 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 al [148] 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 [33], 0126 [29]) 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 (OARs)

Safe delivery of EBRT requires care and attention to doses received by adjacent organs at risk (OARs), and this is particularly important for dose-escalated prostate EBRT. Emami et al [152] provided the first comprehensive set of dose-volume constraints for OARs 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 bladder [157] recommended the dose limits used for the conventional-fractionation arm of RTOG 0415 [149] (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 towards 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.

V. Organ Motion and Target Localization Methods

Prostate motion

Interfractional

Between fractions of conventionally fractionated EBRT, the prostate has been estimated to have translational and rotational movements. With respect to translational movements, Beltran et al [163] determined the necessary PTV margins based on both the intrafractional motion (which gives rise to internal margin) and interfractional motion (which gives rise to the setup margin) for 4 daily localization methods: skin marks with tattoos, pelvic bony anatomy, intraprostatic gold seeds using a 5-mm action threshold, and using no threshold. With tattoo localization, there is a setup error of 6.8 mm in the left-right axis, 7.2 mm in the superior-inferior axis, and 9.8 mm in the AP axis. Bone localization requires 3.1, 8.9, and 10.7 mm, respectively. The intraprostatic gold seed using a 5-mm threshold localization requires 4.0, 3.9, and 3.7 mm margins. No-threshold localization requires 3.4, 3.2, and 3.2 mm [163]. Wong et al [143] evaluated interfraction prostate shifts on 1870 CT-on-rails images from 329 patients treated with EBRT. They noted that the greatest interfractional motion was in the AP axis.

In addition, the prostate rotates between fractions. Graf et al [164] quantified the rotation of the prostate using kV x-ray imaging and intraprostatic fiducials. They report that the rotation in the plane of the treatment table, in superior-inferior direction (ie, roll), and left-right axis (ie, tilt/pitch) are on average 0.09°, −0.52°, and −0.01°, with standard deviations of 2.01°, 2.30°, and 3.95°, respectively. The largest rotational errors occurred around the left-right axis but without preferring a certain orientation.

Intrafractional

During a fraction of conventionally fractionated EBRT, the prostate has also been noted to have translational and rotational movements. Beltran et al [163] report that the intrafractional prostate motion requires a setup margin of 2.4 mm in the left-right axis and 3.4 mm in the inferior-superior and AP axes. Taken with their data on interfractional motion, they conclude that localizing on the bony anatomy leads to an increase in the required margins when compared with simple tattoo localization. Thus, they recommend that the PTV margin, including the intrafraction motion, interfraction motion, and interobserver uncertainty, needed for a 5-mm action threshold (ie, if a displacement of <5 mm is noted, then the displacement is recorded but a couch shift is not made) is 4.8 mm in the left-right direction, 5.4 mm in the inferior-superior direction, and 5.2 mm in the AP direction [163].

With respect to intrafractional rotational movements, Badakhshi et al [165] report that during a 14-minute fraction, the standard deviations of intrafractional rotation errors of the prostate around superior-inferior and left-right axes were on average 2.2° and 3.6°, respectively. Margins covering intrafractional motion were 4.5 and 4.3

mm in superior-inferior and AP axes without intrafractional correction. If they applied rotation correction above a threshold of 1° of displacement, the margins were 2.9 mm and 2.8 mm in superior-inferior and AP, respectively [165].

As the EBRT time increases, the risk of significant intrafraction prostate motion increases. Cramer et al [166] evaluated intrafraction prostate motion during IMRT and volumetric-modulated arc therapy (VMAT) using electromagnetic transponders and recommended patient repositioning when treatment duration exceeds 4–6 minutes. Shelton et al [167] observed a similar relationship between treatment duration and intrafraction prostate motion, with shorter treatment times achieved with VMAT (compared to IMRT), resulting in 30%–40% reduction in intrafraction prostate motion.

Seminal vesicles (SVs) and lymph nodes (LNs)

SVs can move during the delivery of a fraction of prostate EBRT, with a strong correlation to rectal volume [87]. SV movement during and between fractions is independent of the prostate and with respect to the contralateral SV. Thus, when the SVs are in the treatment volume, their interfractional motion must also be accounted for.

Gill et al [168] performed cinematic MRIs for 11 men undergoing RT to assess intrafraction SV motion. They report the displacements between the 2.5th percentile and 97.5th percentile (ie, the 2.5% trimmed range) of the prostate and SV centroids at different time points. At 3, 5, 10, and 15 minutes, the SV centroid measured in the superior-inferior direction 4.7 mm, 5.8 mm, 6.5 mm, and 7.2 mm, respectively. In the AP direction, it was 4.0 mm, 4.5 mm, 6.5 mm, and 7.0 mm. In the left-right direction for 3, 5, and 10 minutes: for the left SV it was 2.7 mm, 2.8 mm, and 3.4 mm, and for the right SV it was 3.4 mm, 3.3 mm, and 3.4 mm. Thus, the motion of the SVs increases with time, and the prostate and SV centroids do not move in unison in real time [168].

With respect to SV interfraction motion, Frank et al [169] used serial pretreatment CTs and demonstrated that the mean 3-D vector displacement for the prostate was 4.6 mm and for the SVs it was 7.6 mm. Similarly, Liang et al [170] studied SV interfraction motion and found that minimum margins of 3 mm for prostate and 4.5 mm for SV were required for IMRT.

Adamczyk et al [171] performed a retrospective analysis based on 253 CBCT studies of 28 patients to estimate the interfraction corrections on doses delivered to the prostate, SVs, and LNs and to determine the ideal PTVs to these targets with prostate-based position verification. They recommended margin sizes of 0.7 cm for the prostate, 0.8–0.9 cm for the SVs, and asymmetric 1.0 cm (vertically) and 0.5 cm (other axes) for the LNs [171].

Prostate bed

The prostate bed also has interfraction and intrafraction motion. In a prospective study of 14 patients undergoing adjuvant or salvage RT to the prostate bed, Huang et al [172] assessed the uncertainty and motion by offline analysis using 3 consecutive daily kV-CBCT images of each patient: 1) after initial setup to skin marks, 2) after correction for positional error/immediately before radiation treatment, and 3) immediately after treatment. They report that the magnitude of interfraction prostate bed motion was 2.1 mm and intrafraction prostate bed motion was 0.4 mm. The maximum interfraction and intrafraction prostate bed motion was primarily in the AP direction. The authors recommend margins of at least 3–5 mm with image guidance and 4–7 mm without image guidance (aligning to skin marks) to ensure 95% of the prescribed dose to the CTV in 90% of patients [172].

In a similar analysis, Klayton et al [173] assessed prostate bed motion using radiofrequency transponders in 2 patients undergoing IMRT. At localization, prostate bed displacement relative to bony anatomy exceeded 5 mm in 9% of fractions in the AP direction and 21% of fractions in the superior-inferior direction. During treatment, the target exceeded the 5-mm tracking limit for at least 30 seconds in 11% of all fractions, generally in the AP or superior-inferior directions. In the AP direction, target motion was twice as likely to move posteriorly, toward the rectum, than anteriorly [173].

VI. Methods for Image-Guided Radiation Therapy (IGRT)

The delivery of a high radiation dose to obtain tumor control is limited by the tolerance of the adjacent normal organs. Moreover, prostate movement can occur and influence dosimetric coverage. Prostate movements occur both between fractions and within fractions of delivery; the movements are translational, rotational, and deformational [102]. In theory, IGRT devices maximize the dose delivered to the tumor, improving patient outcomes, and minimize the dose delivered to surrounding critical structures, decreasing GI and GU toxicity. In practice, however, the use of IGRT systems varies widely. Commonly used IGRT systems include electronic

portal imaging with implanted fiducial markers, CBCT with or without implanted fiducial markers, and electromagnetic transponders [96,174,175].

There is evidence that IGRT improves clinical outcomes. A recent study found that IGRT eliminates the increased risk of biochemical failure associated with rectal distension on planning CT [176], suggesting a reduced rate of geometric misses of the prostate during EBRT. Additionally, de Crevoisier et al [89] found that patients with a distended rectum on planning CT for prostate EBRT had significantly lower rates of biochemical control, likely because of geographical misses during EBRT delivery. Since that initial observation, much work has been done to improve target localization for prostate EBRT through image-guidance strategies to address interfraction and intrafraction motion [177]. There is no consensus regarding the relative effectiveness of the various IGRT technologies [175], each of which has advantages and limitations [102].

Ultrasound

Transabdominal 3-D US has been used to localize the prostate for daily RT delivery with accuracy parallel to that of CT scanning of the pelvis. US-based methods do not require insertion of fiducials, and they allow localization without additional x-ray exposure. US has provided a useful tool for prostate localization with a suggested margin of 9-mm uniform PTV [178]. Although US methods avoid x-ray exposure and have comparable accuracy [179], they are sensitive to subjective and training variability, and hence their role in tracking may be less than that provided with either fiducial or MVCT methods. Moreover, the US procedure causes temporary prostatic displacement, such that some investigators have suggested that overall, the residual errors are not significantly less than with weekly or daily pelvic x-ray imaging based on bony anatomy.

2-D imaging with fiducial markers

Fiducial markers (eg, 1-mm-diameter gold seeds) implanted into the prostate gland prior to EBRT simulation appear on electronic portal imaging kV or MV devices (EPIDs) or CBCT. The use of fiducial markers has resulted in improved accuracy compared to alignment of bony anatomy using portal images and has allowed reduction of the PTV margin from 11–14 mm (with bony alignment) to 4–7 mm [180].

Using fiducial markers and EPIDs, Chung et al [181] demonstrated that after initial setup, displacements in the superior, inferior, anterior, and posterior directions were a maximum of 7 mm, 9 mm, 10 mm, and 11 mm, respectively. After identification and correction, prostate displacements were <3 mm in all directions. Others have reported similar reduction in errors using fiducial markers and daily position corrections [182]. If corrections with implantable fiducial markers are to be done daily, the PTV margins should be at least 4.9, 5.1, and 4.8 in left-right, superior-inferior, and AP directions, respectively. However, broader margins (6.7 mm, 8.2 mm, and 8.7 mm) are required if the correction is done weekly [183]. Care should be taken when adapting to prostate motion while pelvic LNs are treated, as this may lead to degradation of the dose to pelvic LN PTV [184]. In select patients, daily manual alignment to fiducials is one of the most reliable methods to maintain accuracy in prostate IGRT, more so than CBCT with soft-tissue–based automatic corrections [185]. Implanting fiducials through either a transperineal or transrectal approach is an invasive procedure but with a low rate of complications [186]. Although seeds may theoretically migrate, this is generally not a significant problem as fiducial markers have been shown to be stable within the prostate [187], even when implanted on the same day as the simulation [188]. Exposure to ionizing radiation with daily imaging and the inability to visualize normal tissues are limitations of using fiducial markers with planar imaging for tracking [189]. Thus, although implanted gold fiducial markers have benefits over non-use of IGRT, they have some limitations.

When fiducial markers are placed, either transrectal or transperineal insertion methods are appropriate. Fiducial markers have been typically placed at least 1 week prior to CT simulation in order to avoid marker migration between placement and simulation. However, recent evidence suggests that placement immediately prior to simulation on the same day would be reasonable, as migration of fiducial markers over a 1-week period is typically estimated to be 1 mm or less [188].

CBCT with or without implanted fiducial markers

Tomographic volumetric imaging capabilities allow daily capture of 3-D image data for the intact prostate and after prostatectomy [190,191]. Both MV and kV CT reconstructions can display the daily position of the prostate and adjacent OARs, thereby allowing treatment position to be adjusted to ensure that the entirety of the target is in the daily treatment volume [192]. It is important to note that CT-based methods of image guidance (whether kV or MV) may provide a spectrum of image quality and exposure levels [193]. These differences in image quality are due to the range of energies and geometries that subsequently lead to various levels of soft-tissue contrast and

spatial resolution. Furthermore, differences in imaging doses to the patient are also seen. In general, higher doses need to be applied to the patient when using MV systems to achieve the same image quality seen with some kV systems.

CBCT allows visualization of the prostate and OARs [147]. The convenience of CBCT is its ability to produce high-quality images of soft tissues with excellent spatial resolution in a relatively brief amount of time (ie, less than a few minutes). Daily online correction allows the use of the following suggested PTV margins: 4–5 mm in all directions and 3 mm posteriorly [194,195].

As compared to skin setup, MV CBCT can improve localization and justify a tighter margin [196]. In an assessment by Schubert et al [197], global systematic error with daily MV CBCT was found to be 4.7 mm in the vertical direction and largely caused by couch sag. In spite of low image quality, MV CBCT IGRT has a clear advantage in the presence of large artifacts, such as those caused by hip prostheses [138]. Also, it can allow direct dose calculation, dose-guided modifications, or adaptation to acquired images. However, of concern is the additional MV x-ray exposure. AAPM Task Group 75 provides further insight about the complexity of using MV CBCT [198].

Finally, the optimal use of the additional acquired information poses a challenge. Day-to-day organ position and shape changes may require adaptation of the dosimetry of the old plan or even development of a new plan. Nevertheless, image registration [199] and dose guidance [200,201] offer opportunities to maximize therapeutic ratio.

Electromagnetic transponders

Radiofrequency transponders can localize the prostate in a manner similar to gold markers but without additional radiation dose to the patient. These transponders can also be tracked in real time during a treatment session, allowing for immediate intervention if the prostate moves outside the radiation field [202]. A unique advantage of this method is correction of intrafraction error with possible reduction of PTV margin to 3 mm [34,203]. Some of the limitations of radiofrequency transponders include the subsequent difficulty of prostate post-treatment follow-up with MRI and the minimal displacement of transponders during MRI acquisition [204]. Furthermore, other limitations exist in the use of these transponders in patients with pacemakers and in very obese patients.

Impact of IGRT on PTV margins

Margins used to generate a PTV by expanding a CTV should consider magnitude of setup errors and other uncertainties of EBRT. This has been described in detail by van Herk [205], including conceptualization of how information regarding random and systematic errors can be used to estimate appropriate CTV-to-PTV expansions. Perez-Romasanta et al [206] measured interfraction prostate motion in the absence of intensive IGRT methods and calculated the CTV-to-PTV margins using the van Herk method. Their data suggest that localization based solely upon tattoo marks and weekly imaging requires a margin of 9–10.5 mm in the left-right direction, 15.2–17.8 mm in the AP direction, and 10.6–12.4 mm in the superior-inferior direction.

Margin reduction is an important benefit of online image guidance. Wu et al [207] evaluated CT images obtained in an online fashion during prostate EBRT and showed that CTV-to-PTV margins could be reduced with daily IGRT to a 3-mm margin to account for nonrigid and intrafraction motion. Similarly, Letourneau et al [208] suggested 3 mm as the minimal CTV-to-PTV margin for daily IGRT with CBCT, representing the residual error after correction of interfraction motion and intrafraction motion. In an ideal scenario, ignoring potential intrafraction motion, online IGRT can allow an average 13% higher EBRT dose to the prostate PTV without increasing the equivalent uniform dose to the rectum when compared to EBRT without IGRT [209].

A range of CTV-to-PTV expansion margins has been reported in treatment protocols for localized prostate cancer, as summarized in Appendix 2. For prostate bed treatment, Sidhom et al [63] recommended a uniform CTV-to-PTV margin of 10 mm. Song et al [112] recommended a 0.6- to 0.9-cm anisotropic PTV margin when setting up to bony anatomy, using data derived from surgical clips within the prostate bed and the van Herk method. The EORTC consensus guidelines recommend a minimum 5-mm margin [64].

An adaptive approach for patient-specific CTV-to-PTV margins has been proposed in which daily online CT scans from the first week of EBRT are evaluated to determine random and systematic setup errors. The observed errors are then considered to create a new plan using a patient-specific CTV-to-PTV margin [210]. Extending this an additional step, Schulze et al [211] have described an approach for online plan reoptimization to potentially increase the therapeutic ratio by performing online treatment planning with subsequent optimization.

It is important that PTV margins are appropriate for the level of precision in target localization and management of prostate gland motion. As an example of the importance of PTV margins, Engels et al [212] reported a higher rate of biochemical failure when a variable 3- to 5-mm CTV-to-PTV margin was used than when a 6-mm margin was used for patients receiving daily IGRT with implanted fiducial markers. They also noticed that biochemical failure rates were higher when patients had rectal distension with cross-sectional area >9 cm^2 on planning CT.

It is therefore important that radiation oncologists only consider tight CTV-to-PTV margins when matched by appropriately precise EBRT delivery methods and quality assurance. As a general rule, the ACR Radiation Oncology Prostate Cancer Expert Panel concludes that appropriate CTV-to-PTV margins should be ≥5 mm in routine practice and reduced to ≥3 mm only when methods are applied to monitor and correct for intrafraction motion of the prostate gland.

VII. Radiation Treatment Delivery Techniques

This section provides an overview of selected treatment delivery considerations for prostate EBRT, drawing from the available evidence. A separate set of ACR Appropriateness Criteria summarizes the clinical evidence to support the use of these various treatment approaches for prostate cancer [8].

Photons

3D-CRT

3D-CRT consists of EBRT delivery using forward-planned static fields with customized treatment planning and aperture design. Although there is limited evidence that directly compares 3D-CRT to IMRT or proton beam therapy, the available comparative data suggest that higher EBRT doses are more effective at achieving PSA failure-free survival for localized prostate cancer and that safe dose escalation can be more readily achieved with the increased conformity of IMRT relative to 3D-CRT [213].

Ongoing RTOG protocols 0815 [214] and 0924 [30] do allow for either 3D-CRT or IMRT, as long as specified EBRT planning objectives are satisfied. A minimum of 4 fields is recommended, as well as photon energy of at least 6 MV.

IMRT

Static fields

IMRT is widely used for prostate cancer treatment. IMRT achieves highly conformal dose distributions and demands a high level of precision in treatment planning and delivery [215]. Patient setup must be reproducible for IMRT, and daily image-guided target localization is recommended. Patient-specific quality assurance (QA) must be performed, including verification of treatment unit data, dose delivery, and independent monitor unit calculations [216]. Detailed guidance regarding delivery, treatment planning, and clinical implementation of IMRT is provided in a report from the AAPM [217]. Photon energy of at least 6 MV is recommended for prostate IMRT, and 5–9 fields are typically used for a plan encompassing the prostate gland.

Arcs

VMAT is an IMRT method that uses rotational arcs to deliver IMRT in a shorter time period [218]. VMAT provides dose distributions similar to static-field IMRT and has been shown to shorten the treatment time substantially, down to the range of 2–3 minutes [218]. Shorter treatment time with VMAT may reduce the risk of significant intrafraction prostate motion relative to static-field IMRT [167].

SBRT

Prostate SBRT requires attention to delivery of highly conformal RT and attention to precise target localization throughout the SBRT delivery process. SBRT may be delivered with either high-energy photons or protons [219,220]. The AAPM Task Group 101 report provides technical guidance on the general planning and delivery of SBRT, which is applicable to prostate SBRT [221]. Careful immobilization, highly conformal treatment, and image guidance is recommended with attention to monitoring and correcting for intrafraction motion during SBRT delivery [221].

Boike et al [107] published the results of their phase I clinical trial of prostate SBRT, in which radiation dose was escalated to 50 Gy in 5 fractions without dose-limiting toxicity. In that trial, patients were treated with implanted gold fiducial markers or electromagnetic transponder beacons. Endorectal balloons were also used for simulation and treatment, and a bowel regimen was prescribed including milk of magnesia the night before and a Fleet

enema 30–60 minutes prior to simulation and treatment. Patients were advised to have a full bladder for simulation and treatment [107]. The same approach was used for the subsequent phase II trial [106]. Notably, 5% of patients experienced a late toxicity that required placement of a colostomy [222].

Daily image-guidance strategies are necessary for SBRT to localize the prostate. Boike et al [107] reported using MV or kV CT before each fraction to confirm proper fiducial marker alignment, rectal balloon position, and bladder filling. SBRT fractions were separated by a minimum of 36 hours.

Prostate SBRT has also been delivered in a cooperative group trial, RTOG 0938 [150], for which accrual of over 270 patients has been completed and data are maturing. The RTOG 0938 trial required image guidance with implanted radiopaque fiducial markers or electromagnetic transponder beacons. A minimum of 72 hours and maximum of 96 hours were permitted between each fraction of SBRT, with no more than 2 fractions per week. Patients were advised to have a full bladder during simulation and treatment by drinking 16–24 ounces of fluid 2–3 hours before treatment. A bowel regimen was also followed, including a low-gas, low-motility diet starting 1 day prior to treatment; 1 tablespoon of milk of magnesia the night before simulation and each treatment; and, 1 Fleet enema 2–3 hours before simulation and each treatment.

ACR–American Society for Radiation Oncology (ASTRO) practice parameters provide additional guidance on SBRT planning and delivery [219]. A range of SBRT delivery options are permitted, including static fields or arc-based treatment, with or without IMRT planning. Interventions to limit or correct for target volume movement during SBRT are recommended. Stereotactic localization of the target volume is recommended, including imaging and/or the use of fiducial markers. Detailed QA is recommended to confirm IGRT image quality and SBRT treatment planning [223].

Protons

ACR-ASTRO practice parameters are available for proton beam EBRT delivery, which is an evolving technology for prostate cancer treatment [220]. Proton beam energies in clinical use typically range from 70 MeV to 250 MeV, with higher energies achieving deeper tissue penetration. Proton beam therapy delivery systems include scattered, uniform scanning, and pencil-beam scanning systems, with differences in the potential hazards and concerns among the various systems. It is recommended that margins used in treatment planning account for uncertainties in target volume localization, beam characteristics, and patient motion. Image-guidance strategies are recommended for proton beam therapy [220]. Most technical aspects of immobilization and image guidance for photon IMRT are also necessary for proton beam therapy, with additional emphasis on geometric uncertainties [216].

Other Guideline Documents for EBRT Planning and Prostate Cancer

There are several other guideline documents on the subject of EBRT planning that are relevant to this topic and may be of use to clinicians. The AAPM task group report to provide guidance on the delivery, treatment planning, and clinical implementation of IMRT in 2003 [217]. AAPM Task Group 101 provides guidance on SBRT planning and delivery, including technical aspects of treatment planning and delivery [221].

The ACR Technical Standard for the Performance of Radiation Oncology Physics for External Beam Therapy provides guidance on the required steps of EBRT planning, QA, and delivery [216]. The ACR-ASTRO Practice Parameters for the Performance of 3-D EBRT, IMRT, SBRT, and IGRT provide additional guidance regarding planning, delivery, QA, and personnel considerations [215,216,219]. Specific AAPM Task Group reports are also available for IGRT using CT-based methods [224] and for US-guided prostate EBRT [225], which include technical guidance regarding QA of these techniques.

Summary of Recommendations

- **Variant 1:** For the routine case of a patient with a low-risk, clinically localized prostate cancer who will be treated with EBRT, the following is recommended pretreatment: presimulation bowel prep [89,95,97], supine position [76-79] (though prone can sometimes be used [80]), with custom immobilization [81,82] and a full or comfortably full bladder. The patient should undergo a CT simulation [36]. An MRI simulation is also recommended; this may be most helpful if the prostate contour is uncertain, in instances of unusual anatomy, or in the hands of inexperienced clinicians [41,46,48]. Treatment planning can be performed with IMRT, either non-arcs (eg, step-and-shoot) or arcs. Proton beam RT is controversial, and recommendations for proton RT reflect controversy within radiation oncology. If protons are used, treatment on a protocol is encouraged. Notably, 3D-CRT is typically not appropriate if other options are available. Various options exist

for image guidance, including radiofrequency transponders [96,102,138,147,174,181,183,194-198]; CBCT with fiducials, aligned to the PTV; CBCT without fiducials, aligned to the PTV; 2-D imaging with fiducials; or US. On the other hand, it is generally not recommended to use CBCT aligned to bony anatomy or not use image guidance. RT fractionation is typically with conventionally fractionated RT (CFRT); additionally, HFRT and SBRT may be acceptable if the patient is treated per previous protocol.

- **Variant 2**: For a patient similar to the one in Clinical Variant 1 but with a CT simulation that reveals a **grossly distended rectum** (gas and stool), it is recommended that the patient walk, have a bowel movement, or have an enema [97]. Using a simulation that shows a grossly distended rectum results in worse dosimetry [88] and clinical outcome [89], but this may be unavoidable in certain patients.
- **Variant 3**: For a patient similar to the one in Clinical Variant 1 but with a CT simulation that reveals a **very large-volume prostate** (100 mL), continued planning using the current CT simulation is recommended. Using ADT to downsize the gland is not necessary [122]. Surgery can be considered if there are significant and intractable urinary obstructive symptoms or other options are unacceptable. MRI simulation and fusion to CT simulation is usually appropriate, as the CTV on MRI is noted to be smaller than that on CT. Fractionation with SBRT is less preferable, as the toxicities of SBRT in large glands have not been fully characterized.
- **Variant 4**: For a patient similar to the one in Clinical Variant 1 but with **bilateral hip implants**, treatment planning can still be performed with non-arc IMRT, arc-based IMRT (ie, VMAT), or with helical tomotherapy IMRT. For arc-based IMRT, dosimetry may be improved by using more arcs [137] and avoiding beams that pass through prostheses [124,128,129]. If protons are used, anterior-oriented beams [139] or oblique beams [140] are recommended; additionally, CT simulation with kV and MV CT images improves the range of uncertainties for planning [141]. IGRT can again be performed with radiofrequency transponders [135], 2-D imaging with implanted fiducials, MVCT/CBCT with implanted fiducials, or with US [134]. For simulation, CT simulation with kV CT can be used with a commercial algorithm to improve CT Hounsfield number accuracy and structure visualization [125,126]. Additionally, MVCT can be used to assist planning to improve image resolution and permit calculation of electron density [131]. Bilateral hip implants are not a contraindication to CT/MRI simulation [132]. Bilateral hip implants are not a contraindication to any fractionation (eg, CFRT, HFRT, and SBRT).
- **Variant 5**: For a patient similar to the one in Clinical Variant 1 but with **inflammatory bowel disease**, simulation is unchanged. Similarly, IMRT can be used [161,162]; proton beam therapy is controversial, and treatment on a clinical trial is encouraged. For IGRT, recommendations are largely unchanged. For RT fractionation, CFRT is recommended as there are limited published data regarding patients with inflammatory bowel disease on HFRT or SBRT protocols.
- **Variant 6**: For a patient similar to the one in Clinical Variant 1, **status postprostatectomy**, with a recommendation for adjuvant EBRT, the principal options for IGRT include daily CT with alignment to soft tissue or daily CT with surgical clips. Additionally, daily CT with implanted fiducials [190,191], daily CT with electromagnetic transponders [173], or daily kV orthogonal images can be used. Similar to image guidance for an intact prostate, daily CT with alignment to bony anatomy or lack of image guidance is not recommended.
- **Variant 7**: For a patient similar to the one in Clinical Variant 1 but with high body mass index and a **pannus extending into the radiation field**, immobilization of the pannus during simulation should be considered. IMRT can be used [122]; if proton therapy is used, beam angles must be carefully considered due to limitations in proton beam path length. For image guidance, the main differences (versus Variant 1) are that 1) a pannus may obscure reading of the transponders (the transponders can instead be used as fiducials if signal cannot be obtained) and 2) US imaging may be less appropriate than other options (eg, daily CBCT with or without fiducial markers).

Summary of Evidence

Of the 225 references cited in the *ACR Appropriateness Criteria® External Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer* document, 176 are categorized as therapeutic references including 26 well designed studies, 75 good quality studies, and 13 quality studies that may have design limitations. Additionally, 49 references are categorized as diagnostic references including 5 well designed studies,

10 good quality studies, and 19 quality studies that may have design limitations. There are 77 references that may not be useful as primary evidence.

The 225 references cited in the *ACR Appropriateness Criteria® External Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer* document were published from 1991-2015.

While there are references that report on studies with design limitations, 116 well designed or good quality studies provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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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 (months)	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	151	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
			3D-CRT: 70 Gy	150					
RTOG 9406 / Michalski [15,16]	1994–2000	Phase I/II 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
Zelefsky [17]	1992–1998	Clinical retrospective comparison of 3D-CRT vs IMRT	3D-CRT: 72 Gy + 9-Gy boost	61	L, I, H	12	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
			IMRT: 81 Gy	171			N/A		
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)	152	L, I, H	68	5-year 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.
			HFRT: 70.2 Gy in 2.7-Gy fractions (±ADT)	151					
Sheets 2012 [19]	2000–2008	SEER analysis of any late toxicity of protons vs IMRT, 3D-CRT	Proton	684	L, I, H	46–50	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).
			IMRT	684			N/A		
			3D-CRT	6310	L, I, H		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).
			IMRT	6666			N/A		
Zelefsky [20]	2006–2009	Retrospective cohort study of IMRT vs IMRT with IGRT	IMRT to 86.4 Gy	190	L, I, H	34	No differences in 3-year FFBF (88% to 94%) for L or I patients FFBF improved for H patients (97% vs 78%, SS) with IGRT	3-year Grade ≥2 GU toxicity: 20% vs 10.4%, respectively (SS) 3-year 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.
			+ IGRT kV imaging of implanted prostatic fiducial markers	186					
Katz [21-23]	2006–2009	Phase I/II dose-escalation study of robotic-arm SBRT	Robotic-arm SBRT: 35–36.25 Gy in 5 fractions	515	L, I > H	40	5-year Phoenix FFBFs: L: 98%, I: 93%, H: 75%	RTOG late Grade 3–4 toxicity: 0%	SBRT has promising rates of toxicity and efficacy.

Abbreviations: 3D-CRT = 3D conformal radiation therapy; ADT = androgen deprivation therapy; ASTRO = American Society for Radiation Oncology; 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; SEER = Surveillance, Epidemiology, and End Results; SBRT = stereotactic body radiation therapy (ie, >3.5 Gy/fraction in 5 fractions or less); 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]	• CTV = prostate and SVs	• 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 ant and in dimensions and 0.75 × 1.0 cm in post and sup dimensions
PROG 9509 RCT of 70.2 Gy vs 79.2 Gy Zietman, 2010 [24]	• CTV = prostate + 5-mm margin	• CTV + 7–10 mm
GETUG: RCT of 70 vs 80 Gy Beckendorf, 2004 [25]	• CTV = prostate ± SVs	• Phase I: prostate and SVs + 10-mm margin, reduced posteriorly to 5 mm • Phase II: prostate alone with same margins
Dutch CKVO96-10: RCT of 68 Gy vs 78 Gy Al Mamgami, 2008 [26]	• CTV = GTV ○ 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	• 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]	• 64-Gy arm: GTV = prostate ± base of SVs (for phase I GTV) • 74-Gy arm: GTV = ○ prostate + SVs (for phase I GTV) ○ prostate ± base of SVs (for phase II GTV) • CTV = GTV + 5 mm	• CTV + 5- to 10-mm margin
RTOG 0126 [29]: RCT of 70.2 Gy vs 79.2 Gy	• GTV = prostate • CTV = prostate and proximal SVs (up to 10 mm); may be reduced to prostate only after 55.8 Gy	• 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	• 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	• PTV1 = CTV1 + 5–15 mm • PTV2 = CTV2 + 5–10 mm • Individual selection of PTV margin should be based on spacing of planning CT

Abbreviations: CFRT = conventionally fractionated radiation therapy (ie, 1.8–2.0 Gy/fraction); 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; RTOG = Radiation Therapy Oncology Group; SVs = seminal vesicles.
Note: 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% Max 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)	RTOG 0534 – Arm 3 [71]
	Small bowel	V45 <150 cc	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% Max 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	D0.03cc <107% of prescription dose (robotic arm) D0.03cc <120% of prescription dose (nonrobotic arm) V100 >95% D0.03 >95% of prescription dose	RTOG 0938 – 5-fraction arm [150]
	Bladder	D1cc <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 <10cc (both heads) D1cc <81% of prescription dose	
	Penile bulb	D1cc <100% of prescription dose V20 <3cc	
	Urethra	D1cc <107% of prescription dose	
	Penile shaft	Contoured as avoidance structure to avoid beams (robotic arm)	

Abbreviations: CFRT = conventionally fractionated radiation therapy (ie, 1.8–2.0 Gy/fraction); EBRT = external-beam radiation therapy; HFRT = hypofractionated radiation therapy (ie, 2.1–3.5 Gy/fraction); PTV = planning target volume; RTOG = Radiation Therapy Oncology Group; SBRT = stereotactic body radiation therapy (ie, >3.5 Gy/fraction, in 5 fractions or less);
V100 = X%; volume of structure (X%) receiving 100% of the dose
D1cc = X; Dose (X, in Gy; or as % of total dose) to 1 cc 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 (RBE).

Clinical Condition: **External Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer**

Variant 1: **67-year-old man diagnosed from PSA screening program. PSA 5.2 ng/mL, prostate within normal limits on examination. Multiple needle biopsies of the prostate showed adenocarcinoma. Gleason score 3 + 3 = 6.**

Treatment	Rating	Comments
Presimulation		
Bowel prep	7	This option is not required if performing image guidance but is an option that is not wrong for planning purposes. 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 (non-arc)	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 [34,102,138,147,174,181,183,194-198,202-204].
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.
2-D 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**		

Clinical Condition: **External Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer**

Variant 2: **60-year-old man, asymptomatic in PSA screening program. 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).**

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		

Variant 3: **60-year-old man, asymptomatic in PSA screening program. 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).**

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		

Clinical Condition: **External Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer**

Variant 4: **60-year-old man, asymptomatic in PSA screening program. 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.**

Treatment	Rating	Comments
Treatment Planning		
IMRT (non-arc)	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].
2-D imaging with implanted fiducial markers	7	
MVCT/CBCT with fiducial markers	7	
Ultrasound	7	This procedure is for 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**

Clinical Condition: **External Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer**

Variant 5: **60-year-old man, asymptomatic in PSA screening program. 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.**

Treatment	Rating	Comments
Simulation	8	There is no effect on simulation.
Treatment Planning		
IMRT (non-arc)	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.
2-D 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**

Clinical Condition: **External Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer**

Variant 6: **60-year-old man, asymptomatic in PSA screening program. 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.**

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 [190,191].
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 [173].
None	3	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **External Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer**

Variant 7: **60-year-old man, asymptomatic in PSA screening program. 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.**

Treatment	Rating	Comments
Simulation		
Immobilization of pannus (eg, tape or cover sheet)	7	There may be considerable variability.
Treatment Planning		Limiting beam angles can be considered. For low-risk patients, one can consider weight loss prior to starting treatment.
IMRT (non-arc)	8	
IMRT (arc)	8	One can consider limiting arcs.
Proton beam	6	Beam angles for proton beam therapy must be carefully considered due to 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**