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Critical Review

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

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Abstract

Purpose: To present the most updated American College of Radiology (ACR) Appropriateness Criteria formed by an expert panel on the appropriate delivery of external beam radiation to manage stage T1 and T2 prostate cancer (in the definitive setting and post-prostatectomy) and to provide clinical variants with expert recommendations based on accompanying Appropriateness Criteria for target volumes and treatment planning.

Methods and materials: The ACR Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed annually by a panel of multidisciplinary experts. The guideline development and revision process includes an extensive analysis of current medical literature from peer-reviewed journals and the application of well-established methodologies (RAND/UCLA Appropriateness Method and Grading of Recommendations Assessment, Development, and Evaluation) to rate the appropriateness of imaging and treatment procedures for specific clinical scenarios. In instances in which evidence is lacking or equivocal, expert opinion may supplement available evidence to recommend imaging or treatment.

Results: The panel summarizes the most recent and relevant literature on the topic, including organ motion and localization methods, image guidance, and delivery techniques (eg, 3-dimensional conformal intensity modulation). The panel presents 7 clinical variants, including (1) a standard case and cases with (2) a distended rectum, (3) a large-volume prostate, (4) bilateral hip implants, (5) inflammatory bowel disease, (6) prior prostatectomy, and (7) a pannus extending into the radiation field. Each case outlines the appropriate techniques for simulation, treatment planning, image guidance, dose, and fractionation. Numerical rating and commentary is given for each treatment approach in each variant.

Conclusions: External beam radiation is a key component of the curative management of T1 and T2 prostate cancer. By combining the most recent medical literature, these Appropriateness Criteria can aid clinicians in determining the appropriate treatment delivery and personalized approaches for individual patients.

Introduction

This review complements other American College of Radiology (ACR) Appropriateness Criteria for localized prostate cancer by focusing on the practical and technical elements of external beam radiation therapy (EBRT).[1,2] This document provides guidance for EBRT treatment planning for localized, organ-confined prostate cancer; locally advanced node-negative disease; and post-prostatectomy radiation therapy (RT). Part II covers treatment delivery: organ motion, target localization, image guidance, and RT delivery techniques. Additionally, clinical variants are presented (see Variants 1-7).

RT fractionation definitions

This article relates mostly to men who are treated with dose-escalated conventionally fractionated EBRT (CFRT; a single 1.8-2.0 Gy fraction delivered in approximately 15 minutes per day, 5 days per week for 8-9 weeks, to a total dose of 76-80 Gy), which is an established treatment modality for men in all disease risk groups. Other fractionation techniques to treat patients with prostate cancer exist. For example, moderately hypofractionated RT (HFRT; 2.1-3.5 Gy per fraction for approximately 15 minutes per day, 5 days per week for approximately 4 weeks, to a total dose of approximately 52-72 Gy) has been tested in phase I-III trials since the 1990s.[3] Extremely fractionated RT, also termed stereotactic body RT (SBRT; 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 patients with low-risk prostate cancer.[4] HFRT and SBRT deliver a higher dose per fraction to the prostate; thus, these methods also require diligence in treatment planning.

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[5] determined the necessary planning target volume (PTV) margins on the basis of 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 anterior-posterior (AP) axis. Bone localization requires 3.1, 8.9, and 10.7 mm in each axis, respectively. The intraprostatic gold seed using a 5-mm threshold localization requires 4.0, 3.9, and 3.7 mm margins, respectively. No-threshold localization requires 3.4, 3.2, and 3.2 mm.[5] Wong et al[6] evaluated interfraction prostate shifts on 1870 computed tomography (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[7] quantified the rotation of the prostate using kV x-ray imaging and intraprostatic fiducials. They reported that the rotation in the plane of the treatment table, in superior–inferior direction (ie, roll), and the 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 preference for a certain orientation.

Prostate motion: Intrafractional

During a fraction of conventionally fractionated EBRT, the prostate has also been noted to have translational and rotational movements. Beltran et al[5] reported 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. From their data on interfractional motion, the researchers concluded that localizing on the bony anatomy leads to an increase in the required margins compared with simple tattoo localization. Thus, they recommended 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.[5]

With respect to intrafractional rotational movements, Badakhshi et al[8] reported that during a 14-minute fraction, the standard deviations of intrafractional rotation errors of the prostate around the superior–inferior and left–right axes were 2.2° and 3.6° on average, respectively. Margins that covered the intrafractional motion were 4.5 and 4.3 mm in the 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 the superior–inferior and AP axes, respectively.[8]

As the EBRT time increases, the risk of significant intrafraction prostate motion increases. Cramer et al[9] evaluated intrafraction prostate motion during intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) using electromagnetic transponders and recommended patient repositioning when treatment duration exceeds 4 to 6 minutes. Shelton et al[10] observed a similar relationship between treatment duration and intrafraction prostate motion, with shorter treatment times achieved with VMAT (compared with IMRT), which resulted in a 30% to 40% reduction in intrafraction prostate motion.

Seminal vesicles and lymph nodes

Seminal vesicles (SVs) can move during the delivery of a fraction of prostate EBRT, with a strong correlation to rectal volume.[11] 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 taken into account.

Gill et al[3] performed cinematic magnetic resonance imaging (MRI) for 11 patients undergoing RT to assess intrafraction SV motion. They reported displacements between the 2.5th percentile and 97.5th percentile (ie, 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 4.7, 5.8, 6.5, and 7.2 mm in the superior–inferior direction, respectively. In the AP direction, it was 4.0, 4.5, 6.5, and 7.0 mm, respectively. In the left–right direction for 3, 5, and 10 minutes, the left SV was 2.7, 2.8, and 3.4 mm, respectively; for the right SV, it was 3.4, 3.3, and 3.4 mm, respectively. Thus, the motion of the SVs increases with time, and the prostate and SV centroids do not move in unison in real time.

With respect to SV interfraction motion, Frank et al[4] used serial pretreatment CT scans and demonstrated that the mean 3-dimensional vector displacement was 4.6 mm for the prostate and 7.6 mm for the SVs. Similarly, Liang et al[12] studied SV interfraction motion and found that minimum margins of 3 mm for the prostate and 4.5 mm for SVs were required for IMRT.

Adamczyk et al[13] performed a retrospective analysis of 253 cone beam CT (CBCT) studies of 28 patients to estimate the interfraction corrections on doses delivered to the prostate, SVs, and lymph nodes (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 to 0.9 cm for the SVs, and asymmetric 1.0 cm (vertically) and 0.5 cm (other axes) for the LNs.[13]

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[14] 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 reported 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 recommended margins of at least 3 to 5 mm with image guidance and 4 to 7 mm without image guidance (ie, aligning to skin marks) to ensure 95% of the prescribed dose to the clinical target volume (CTV) in 90% of patients.[14]

In a similar analysis, Klayton et al[15] 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.[15]

Methods for image guided radiation therapy

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 and within fractions of delivery; the movements are translational, rotational, and deformational.[16] In theory, image guided radiation therapy (IGRT) devices maximize the dose delivered to the tumor to improve patient outcomes and minimize the dose delivered to surrounding critical structures to decrease gastrointestinal and genitourinary 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.[17-19]

There is evidence that IGRT improves clinical outcomes. A recent study found that IGRT eliminates the increased risk of biochemical failure that is associated with rectal distension on planning CT[20], which suggests a reduced rate of geometric misses of the prostate during EBRT. Additionally, de Crevoisier et al[21] 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.[22] There is no consensus with regard to the relative effectiveness of the various IGRT technologies,[19] each of which has advantages and limitations.[16]

Ultrasound

Transabdominal 3-dimensional ultrasound (US) is used to localize the prostate for daily RT delivery with an accuracy that parallels CT scanning of the pelvis. US-based methods do not require the insertion of fiducials, and they allow localization without additional x-ray exposure. US is a useful tool for prostate localization with a suggested margin of 9 mm uniform PTV.[23] Although US methods avoid x-ray exposure and have comparable accuracy,[24] they are sensitive to subjective and training variability; thus, their role in tracking may be less than that provided with either fiducial or megavoltage CT methods. Moreover, the US procedure causes temporary prostatic displacement, and 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-dimensional imaging with fiducial markers

Fiducial markers (eg, 1 mm diameter gold seeds) implanted in 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 with alignment of bony anatomy using portal images and has allowed for a reduction of the PTV margin from 11 to 14 mm (with bony alignment) to 4 to 7 mm.[25]

Using fiducial markers and EPIDs, Chung et al[26] demonstrated that after the initial setup, displacements in the superior, inferior, anterior, and posterior directions were a maximum of 7, 9, 10, and 11 mm, respectively. After identification and correction, prostate displacements were <3 mm in all directions. Other studies have reported a similar reduction in errors with fiducial markers and daily position corrections.[27] If corrections with implantable fiducial markers are done daily, the PTV margins should be at least 4.9, 5.1, and 4.8 mm in the left–right, superior–inferior, and AP directions, respectively. However, broader margins (6.7, 8.2, and 8.7 mm) are required if the correction is done weekly.[28] Care should be taken when adapting to prostate motion while pelvic LNs are treated because this may lead to a degradation of the dose to pelvic LN PTV.[29]

In select patients, daily manual alignment to fiducials is one of the most reliable methods of maintaining

accuracy in prostate IGRT, more so than CBCT with soft tissue–based automatic corrections.[30] Implanting fiducials through either a transperineal or transrectal approach is an invasive procedure but has a low rate of complications.[31] Although seeds may theoretically migrate, this is generally not a significant problem because fiducial markers have been shown to be stable within the prostate,[32] even when implanted on the same day as the simulation.[33] Exposure to ionizing radiation with daily imaging and the inability to visualize normal tissues are limitations of fiducial markers with planar imaging for tracking.[34] Thus, although implanted gold fiducial markers have benefits over nonuse of IGRT, they do have some limitations.

When fiducial markers are placed, either the transrectal or transperineal insertion method is appropriate. Fiducial markers typically have been placed at least 1 week prior to CT simulation to avoid marker migration between placement and simulation. However, recent evidence suggests that placement immediately prior to simulation on the same day is reasonable because migration of fiducial markers over a 1-week period is typically estimated to be 1 mm or less.[33]

CBCT with or without implanted fiducial markers

Tomographic volumetric imaging capabilities allow daily capture of 3-dimensional image data for the intact prostate and after prostatectomy.[35,36] 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.[37] 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.[38] 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 have also been observed. 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.[39] 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 suggested PTV margins of 4 to 5 mm in all directions and 3 mm posteriorly.[40,41]

Compared with skin setup, MV CBCT can improve localization and justify a tighter margin.[42] In an assessment by Schubert et al,[43] global systematic error with daily MV CBCT was found to be 4.7 mm in the vertical direction and largely caused by couch sag. Despite low image quality, MV CBCT IGRT has a clear advantage in the presence of large artifacts, such as those caused by hip prostheses.[44] Furthermore, it can allow direct dose calculation, dose-guided modifications, or adaptation to acquired images. However, the additional MV x-ray exposure is of concern. The American Association of Physicists in Medicine (AAPM) Task Group 75 provides further insight into the complexity of using MV CBCT.[45]

Finally, 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[46] and dose guidance[47,48] offer opportunities to maximize the therapeutic ratio.

Electromagnetic transponders

Radiofrequency transponders can localize the prostate in a manner similar to that of gold markers but without additional radiation dose to the patient. These transponders can also be tracked in real time during a treatment session and allow for immediate intervention if the prostate moves outside of the radiation field.[49] A unique advantage of this method is the correction of intrafraction error with possible reduction of PTV margin to 3 mm.[50,51] Limitations of radiofrequency transponders include the subsequent difficulty of prostate posttreatment follow-up with MRI and the minimal displacement of transponders during MRI acquisition.[52] 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 the magnitude of setup errors and other uncertainties of EBRT. This has been described in detail by van Herk,[53] including the conceptualization of how information regarding random and systematic errors can be used to estimate appropriate CTV-to-PTV expansions. Perez-Romasanta et al[54] measured the 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 on tattoo marks and weekly imaging requires a margin of 9 to 10.5 mm in the left–right direction, 15.2 to 17.8 mm in the AP direction, and 10.6 to 12.4 mm in the superior–inferior direction.

Margin reduction is an important benefit of online image guidance. Wu et al[55] evaluated CT images that were 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[56] suggested 3 mm as the minimal CTV-to-PTV margin

for daily IGRT with CBCT to represent the residual error after correction of interfraction and intrafraction motion. In an ideal scenario, ignoring potential intrafraction motion, online IGRT can allow an average of 13% higher EBRT dose to the prostate PTV without increasing the equivalent uniform dose to the rectum compared with EBRT without IGRT.[57]

A range of CTV-to-PTV expansion margins has been reported in treatment protocols for localized prostate cancer (Appendix 1). For prostate bed treatment, Sidhom et al[58] recommended a uniform CTV-to-PTV margin of 10 mm. Song et al[59] 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 consensus guidelines by the European Organization for Research and Treatment of Cancer recommend a minimum margin of 5 mm.[60]

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.[61] Extending this an additional step, Schulze et al[62] 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[63] reported a higher rate of biochemical failure when a variable 3 to 5 mm CTV-to-PTV margin was used compared with a 6 mm margin for patients who received daily IGRT with implanted fiducial markers. They also noticed that biochemical failure rates were higher when patients had rectal distension with a cross-sectional area of >9 cm^2 on the planning CT.

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

Radiation treatment delivery techniques

This section provides an overview of selected treatment delivery considerations for prostate EBRT, drawing on 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.[2]

Photons

3-dimensional conformal radiation therapy

Three-dimensional conformal radiation therapy (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 prostate specific antigen 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.[64]

Ongoing Radiation Therapy Oncology Group (RTOG) protocols 0815[65] and 0924[66] 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.[67] 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 the treatment unit data, dose delivery, and independent monitor unit calculations.[68] Detailed guidance with regard to delivery, treatment planning, and clinical implementation of IMRT is provided in a report from the AAPM.[69] Photon energy of at least 6 MV is recommended for prostate IMRT, and 5 to 9 fields are typically used for a plan that encompasses the prostate gland.

Arcs

VMAT is an IMRT method that uses rotational arcs to deliver IMRT in a shorter period of time.[70] VMAT provides dose distributions that are similar to static field IMRT and has been shown to shorten treatment time substantially, down to the range of 2 to 3 minutes.[70] Shorter treatment time with VMAT may reduce the risk of significant intrafraction prostate motion relative to static field IMRT.[8]

SBRT

Prostate SBRT requires attention to the 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.[71,72] The AAPM Task Group 101 report provides technical guidance on the general planning and delivery of SBRT, which is applicable to prostate SBRT.[73] Careful immobilization, highly conformal treatment, and image guidance is recommended, with attention to monitoring and correcting for intrafraction motion during SBRT delivery.[73]

Boike et al[74] published the results of their phase 1 clinical trial of prostate SBRT, in which the 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 to 60 minutes prior to simulation and treatment. Patients were advised to have a full bladder for simulation and treatment.[74] The same approach was used for the subsequent phase 2 trial.[75] Notably, 5% of patients experienced a late toxicity that required the placement of a colostomy bag.[76]

Daily image guidance strategies are necessary for SBRT to localize the prostate. Boike et al[74] 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,[77] for which accrual of more than 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 to 24 ounces of fluid 2 to 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 to 3 hours before simulation and each treatment.

The ACR–American Society for Radiation Oncology (ASTRO) practice parameters provide additional guidance on SBRT planning and delivery.[71] 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.[78]

Protons

ACR-ASTRO practice parameters are available for proton beam EBRT delivery, which is an evolving technology for prostate cancer treatment.[72] 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 the 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.[72] Most technical aspects of immobilization and image guidance for photon IMRT are also necessary for proton beam therapy, with additional emphasis on geometric uncertainties.[68]

Other guideline documents for EBRT planning and prostate cancer

There are several other guideline documents on 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 was issued in 2003.[69] AAPM Task Group 101 provides guidance on SBRT planning and delivery, including the technical aspects of treatment planning and delivery.[73]

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.[68] The ACR-ASTRO Practice Parameters for the Performance of 3-dimensional EBRT, IMRT, SBRT, and IGRT provide additional guidance with regard to planning, delivery, QA, and personnel considerations.[67,68,71] Specific AAPM Task Group reports are also available for IGRT using CT-based methods[79] and for US-guided prostate EBRT,[80] which include technical guidance regarding QA of these techniques.

Summary of recommendations

Variant 1

For the routine case of a patient with low-risk, clinically localized prostate cancer who will be treated with EBRT, the following pretreatment is recommended: presimulation bowel preparation,[21,81,82] supine position[83-86] (although prone can sometimes be used[87]), with custom immobilization[88,89] and a full or comfortably full bladder. The patient should undergo a CT simulation.[90]

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.[91-93] 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 the field of radiation oncology. If protons are used, treatment on a protocol is encouraged. Notably, 3D-CRT typically is not appropriate if other options are available. Various options exist for image guidance, including radiofrequency transponders[16-18,26,28,39-45]; 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 that is aligned to bony anatomy or not use image guidance. RT fractionation is typically used with CFRT. HFRT and SBRT may be acceptable if the patient was treated per a previous protocol.

Variant 2

For a patient similar to the one in 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.[81] Using a simulation that shows a grossly distended rectum would result in worse dosimetry[94] and clinical outcome,[21] but this may be unavoidable in certain patients.

Variant 3

For a patient similar to the one in variant 1 but with a CT simulation that reveals a very large-volume prostate (100 mL), continued planning with the current CT simulation is recommended. Using androgen deprivation therapy to downsize the gland is not necessary.[95] Surgery can be considered if there are significant and intractable urinary obstructive symptoms or if other options are unacceptable. MRI simulation and fusion to CT simulation is usually appropriate because the CTV on the MRI is noted to be smaller than that on CT. Fractionation with SBRT is less preferable because the toxicities of SBRT in large glands have not been fully characterized.

Variant 4

For a patient similar to the one in variant 1 but with bilateral hip implants, treatment planning can still be performed with non-arc IMRT, arc-based IMRT (ie, VMAT), or helical tomotherapy IMRT. For arc-based IMRT, dosimetry may be improved by using more arcs[96] and avoiding beams that pass through prostheses.[97-99] If protons are used, anterior-oriented beams[100] or oblique beams[101] are recommended. Additionally, CT simulation with kV and MV CT images improves the range of uncertainties for planning.[102] IGRT can again be performed with radiofrequency transponders,[103] 2-dimensional imaging with implanted fiducials, MV CT/CBCT with implanted fiducials, or with US.[104] For simulation, CT simulation with kV CT can be used with a commercial algorithm to improve the CT Hounsfield number accuracy and structure visualization.[105,106] Additionally, MVCT can be used to assist planning to improve image resolution and permit calculation of electron density.[107] Bilateral hip implants are not a contraindication to CT/MRI simulation.[108] 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 variant 1 but with inflammatory bowel disease, simulation is unchanged. Similarly, IMRT can be used[109,110]; 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 because limited published data exist with regard to patients with inflammatory bowel disease on HFRT or SBRT protocols.

Variant 6

For a patient similar to the one in 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,[35,36] daily CT with electromagnetic transponders,[15] or daily kV orthogonal images can be used. Similar to the 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 variant 1 but with high body mass index and a pannus that extends into the radiation field, immobilization of the pannus during simulation should be considered. IMRT can be used.[95] If proton therapy is used, beam angles must be carefully considered because of the limitations in proton beam path length. For image guidance, the main differences (vs variant 1) are that (1) a pannus may obscure reading of the transponders (transponders can instead be used as fiducials if the signal cannot be obtained); and (2) US

imaging may be less appropriate than other options (eg, daily CBCT with or without fiducial markers).

Supporting documents

Additional information on the ACR Appropriateness Criteria methodology and other supporting documents are available at www.acr.org/ac.

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Appendix 1 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 [111]	• 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 [112]	• CTV = prostate + 5-mm margin	• CTV + 7–10 mm
GETUG: RCT of 70 vs 80 Gy Beckendorf, 2004 [113]	• 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 [114]	• CTV = GTV o Group 1: prostate only o Group 2-3: prostate and SVs (for first 50–68 Gy), then prostate only for remainder o 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 [115,116]	• 64-Gy arm: GTV = prostate ± base of SVs (for phase I GTV) • 74-Gy arm: GTV = o prostate + SVs (for phase I GTV) o prostate ± base of SVs (for phase II GTV) • CTV = GTV + 5 mm	• CTV + 5- to 10-mm margin
RTOG 0126 [117]: 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 [66]: 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

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).

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		This option is not required if performing image guidance but is an option that is not wrong for planning purposes.
Bowel prep	7	Microenema is recommended.[81] Oral stool softener and antiflatulent agents are also options.[21,82]
Supine position	8	See references.[83-86]
Prone position	5	See reference.[87]
Custom immobilization (eg, with custom thermoplastic cast)	8	This option is per previously published reports.[88,89]
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.[90]
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.[91-93,118-120]
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.[16,18,26,28,39-45,49-52]
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 [121]).
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 [77]).

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

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 [94] and clinical outcome [21]. 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.[81]

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.[95]
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.[92]

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

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.[97-99]
VMAT (arc-based IMRT)	8	Dosimetry may be improved by using more arcs.[96]
IMRT (helical tomotherapy)	7	This procedure has been previously described.[44]
Proton beam	5	This procedure reflects recognized controversy in the field. Use anterior-oriented beams [100] or oblique beams.[101] CT simulation with kV and MV CT images improves range of uncertainties for planning.[102]
IGRT		
Radiofrequency transponders	7	Hip implants have no meaningful effect on image guidance with this strategy.[103]
2-D imaging with implanted fiducial markers	7	
MVCT/CBCT with fiducial markers	7	
Ultrasound	7	This procedure is for reference.[104]
Simulation		
CT simulation (kV CT)	8	Use a commercial algorithm to improve CT Hounsfield number accuracy and structure visualization.[99,105,106]
Use MVCT to assist planning if available	7	This procedure may improve image resolution and permit calculation of electron density.[107]
MRI simulation and fusion to CT	8	Bilateral hip implants are not a contraindication to CT/MRI simulation.[122]
None	3	
RT Fractionation		
CFRT	8	This procedure is not a contraindication on previous protocol (ie, RTOG 9406 [123]).
HFRT	6	This procedure is not a contraindication on previous protocol (ie, RTOG 0415 [121]).
SBRT	6	This procedure is not a contraindication on previous protocol (ie, RTOG 0938 [77]).

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

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 [109,110].
IMRT (arc)	8	There are reportedly low complications with photon EBRT [109,110].
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

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.[124] CBCT with fiducial markers is reasonable.[35,36]
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.[15]
None	3	

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

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