**American College of Radiology**

**ACR Appropriateness Criteria®**

**EXTERNAL BEAM RADIATION THERAPY TREATMENT PLANNING FOR CLINICALLY LOCALIZED PROSTATE CANCER**

Expert Panel on Radiation Oncology–Prostate: May Abdel-Wahab, MD, PhD; Omar Mahmoud, MD; Gregory Merrick, MD; I-Chow Joe Hsu, MD; V. Elayne Arterbery, MD; Jay P. Ciezki, MD; Steven J. Frank, MD; James Lloyd Mohler, MD; Brian J. Moran, MD; Seth A. Rosenthal, MD; Carl J. Rossi Jr, MD; Yoshiya Yamada, MD.

**Summary of Literature Review**

Advances in image-based treatment planning and localization have contributed to better targeting of the prostate. External beam radiation therapy (EBRT) leads to outcomes equivalent to those of radical prostatectomy and brachytherapy when case selection factors and quality of treatment delivery are controlled [1-3]. Newer radiation therapy (RT) techniques that allow better targeting of the prostate and greater sparing of normal tissues have led to an improved therapeutic ratio. Lowering doses to surrounding critical structures and simultaneous safe target dose escalation have become possible. This review will detail the practical elements of radiation dose delivery, including patient setup and immobilization, target volume definition, treatment planning, treatment delivery methods, and tools to verify target localization during a course of EBRT. (See Variant 1.)

**Patient Immobilization**

Immobilization devices are widely used to allow the use of smaller margins, thus reducing the dose to the surrounding normal tissues [4]. Although some studies suggest that they significantly reduce large day-to-day setup errors are significantly reduced with the use of patient immobilization devices, this conclusion is not universal [5].

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 [5] reported on a prospective randomized study which 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 immobilization devices reduced isocenter deviations >10 mm from 30.9% to 10.6% in the immobilized arm (P<0.001). The average deviations in the anteroposterior, right-left, and superior-inferior (SI) directions were reduced to 2.9 mm, 2.1 mm, and 3.9 mm, respectively, for the immobilized group.

However, the haphazard use of immobilization devices may be worse than none at all. A well-thought-out and 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. Furthermore, it is important to note that in the era of image guidance, the need for rigid fixation devices has been questioned [6]. Alternative options such as leg and ankle support, which may be more comfortable to the patient, have been suggested when positioning is later confirmed by image guidance.

**Patient Positioning**

Patient position during simulation treatment has been extensively studied. More recent studies have confirmed that there is no benefit to using the prone position as compared to the supine position [7,8]. In the prone position there may be greater rectal sparing, particularly in patients with large seminal vesicles (SVs). However, a larger percentage of the bladder may be included, which slightly increases the probability of complications [9]. There may also be more patient setup movement errors because some patients find the prone position less comfortable.

---

1Principal Author, Taussig Comprehensive Cancer Center, Cleveland Clinic, Cleveland, Ohio. 2Research Author, University of Miami, Miami, Florida. 3Panel Chair, Schiffler Cancer Center and Wheeling Jesuit University, Wheeling, West Virginia. 4Panel Vice-chair, University of California San Francisco, San Francisco, California. 5Karmans-Crittenton Cancer Center, Rochester Hills, Michigan. 6Cleveland Clinic Foundation, Cleveland, Ohio. 7MD Anderson Cancer Center, Houston, Texas. 8Roswell Park Cancer Institute, Buffalo, New York, American Urological Association. 9Chicago Prostate Cancer Center, Westmont, Illinois. 10Radiological Associates of Sacramento, Sacramento, California. 11Loma Linda University Medical Center, Loma Linda, California. 12Memorial Sloan Kettering Cancer Center, New York, New York.

The American College of Radiology seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.

Reprint requests to: Department of Quality & Safety, American College of Radiology, 1891 Preston White Drive, Reston, VA 20191-4397.
Furthermore, the prone position appears to be associated with greater prostate motion from normal breathing. The increased intra-abdominal pressure associated with breathing in a prone position results in significant movement of the prostate and SVs.

Dawson et al [11] evaluated the impact of breathing on the position of the prostate gland in four patients treated in four different positions in whom radiopaque markers were implanted in the periphery of the prostate using transrectal ultrasound (US) guidance prior to simulation. Fluoroscopy was performed in four different positions: prone in foam cast cradle, prone in thermoplastic mold, supine on a flat table, and supine with a false table under the buttocks. During normal breathing, maximum movement of prostate markers seen in the prone position (cranial-caudal) ranged from 0.9 to 5.1 mm and anterior-posterior (AP) movement ranged up to 3.5 mm. In the supine position, prostate movements during normal breathing were <1 mm in all directions. Deep breathing resulted in movements of 3.8 to 10.5 mm in the cranial-caudal direction in the prone position (with and without thermoplastic mold). This range was reduced to 2.7 mm in the supine position and to 0.5 to 2.1 mm with the use of a false tabletop. Deep breathing resulted in AP skeletal movements of 2.7 to 13.1 mm in the prone position, whereas in the supine position these variations were negligible.

Malone et al [12] also characterized inaccuracies in prostatic gland location due to respiration observed fluoroscopically in 28 patients in whom three gold fiducial markers were implanted under US guidance at the apex, posterior wall, and base of the prostate. Patients were immobilized on a customized thermoplastic shell placed on a rigid pelvic board. A second group of 20 patients were evaluated both prone (with or without thermoplastic shell) and supine (without immobilization shell). When the patients were immobilized prone in the thermoplastic shell, the prostate moved synchronously with respiration a mean distance of 3.3 ± 1.8 mm (range 1 to 10 mm). In 23% of the observations the displacements were ≥4 mm. The prostate movement decreased significantly when the thermoplastic shells were removed [11].

Bayley et al [13] conducted a prospective randomized trial of the supine versus prone position in patients undergoing conformal RT. 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 computed tomography (CT) simulation and treatment planning in both positions. Observed prostate motion was significantly less in the supine position than the prone position. Pretreatment positioning corrections were required more often for patients in 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. Seven patients who started in the supine position refused to be treated in the prone position due to discomfort. Other investigators have confirmed that prostate movement with respiration is significantly less with patients in a supine position [9,14].

Regardless of the type of immobilization device used or the treatment position chosen, there is no replacement for a careful setup and clear instructions to patients to get into the same position every day. Thus, no difference between the positions in set-up error reduction or in organs-at-risk (OAR) sparing in recent studies. The supine position was found to be more comfortable, however. In addition, the importance of patient education about bladder filling, rectal emptying, and adherence to recommended diet has been recognized [15,16].

**Retrograde Urethrography**

Retrograde urethrography (RUG) was commonly used in the past to help determine the level of the prostatic apex. However, it is no longer widely used, due to the possibility of complications [17] and apex displacement [18], even though a carefully administered RUG does not significantly alter the position of the prostate gland [19]. Magnetic resonance imaging (MRI) has largely superseded urethrography [20] as a tool to help delineate the prostatic apex. Nevertheless, RUG sometimes used in conjunction with CT scanning if an MRI is not available or in patients with contraindications to MRI (eg, pacemakers).

**Computed Tomography-Based Prostate Localization**

CT simulators are readily available in most radiation oncology departments. Typically the location of the apex can be resolved to two or three CT slices obtained at 3-5 mm intervals and, in the hands of experienced radiation oncologist, the use of CT may be adequate [21]. 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 [21]. The radiation oncologist should use multiplanar reconstructions to
facilitate prostate definition on a treatment planning CT and image registration of MRI images with CT images can aid apex definition on a CT scan.

**Magnetic Resonance Imaging-Based Prostate Localization**

MRI may be more accurate in delineating the prostate and SVs than CT [22]. CT overestimates the size of the gland approximately 27%-32%. The greatest systematic discrepancy between the gross tumor volumes (GTVs) is that the posterior apical prostate border was 3.6 mm more posterior on MRI than on CT-defined contouring [23]. Furthermore, MRI was found to be superior to CT or urethrography for localizing the prostatic apex [20].

Endorectal MRI may detect extracapsular tumor extension, SV invasion, or neurovascular bundle involvement with greater sensitivity, specificity, and accuracy than clinical findings alone [24]. Furthermore, endorectal MRI is associated with accuracy, sensitivity, and positive predictive values of 80%, 85%, and 93%, respectively, when the tumor foci exceed 1.0 cm. However, results are less accurate when the tumor is <1.0 cm [25].

Magnetic resonance spectroscopy (MRS) can detect variable concentrations of citrate, choline, and creatine in prostate tissue and improve the accuracy of detecting and localizing prostate cancer [26]. Coakley et al [27] reported improved accuracy of tumor volume prediction using MRS in 37 patients. In a series of 37 patients undergoing MRS prior to radical prostatectomy, Jung et al [28] reported a sensitivity of 93% in differentiating cancer from benign prostate tissue. These findings have led investigators at the University of California San Francisco to explore boosting the dominant intraprosthetic lesion with intensity-modulated radiation therapy (IMRT) using an MRS-defined tumor nodule [29].

MRI may also allow better identification of structures adjacent to the prostate that are associated with erectile function [30]. McLaughlin et al [31] described 25 patients with localized prostate cancer who underwent both CT- and MRI-based treatment planning. They 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. Better sparing of the penile bulb and corpora cavernosa with IMRT was achieved when MRI-based simulation rather than CT-based simulation was used for treatment planning [32]. In a similar analysis of 18 patients, Steenbakkers et al [33] reported improved sparing of the rectum and penile bulb with the use of MRI-based delineation of the prostate on 3D conformal radiation therapy (3DCRT) treatment plans. At this time it is unclear whether sparing of the erectile tissues with MRI-based radiation treatment planning will lead to better sexual outcome or quality of life. It also remains to be proven that sparing of these tissues will not compromise long-term tumor control.

New MRI techniques such as dynamic contrast-enhanced MRI (DCE-MRI) can further improve targeting and increase sensitivity when compared to T2-weighted MRI [34]. During DCE-MRI, a T1-weighted image is obtained before, during, and after bolus injection of the contrast agent. Prostate cancer has faster signal enhancement with higher washout rates than benign prostatic tissue on DCE-MRI, allowing better delineation of prostate tumors [35,36]. Thus, the technique has been used for detection, diagnosis, and staging of the tumor and for evaluating the response, as well as for guiding targeted biopsies in some patients [37].

The use of DCE-MRI in radiation oncology can allow better targeting of tumor, including areas of extracapsular extension/capsular penetration, SV invasion, and neurovascular bundle involvement, where the accuracies for detection were found to be 84%, 97%, and 97%, respectively. Furthermore, the availability of 3-Tesla (3T) MRI with abdominal coils has simplified the use of MRI with the ability to avoid the use of endorectal coils. The increase in signal-to-noise ratio with 3T DCE-MRI led to improved temporal and spatial resolution of dynamic images [38]. The ability to avoid endorectal coil is important in images that will be used for registration and radiation planning.

Furthermore, DCE-MRI may allow targeting of dominant tumor nodules for a boost [29,39]. Van Lin et al [40] combined DCE-MRI and MRS to aid in detection of dominant intraprostatic lesions during tumor volume delineation and planning prior to image-guided radiotherapy (IGRT) with promising preliminary results.

DCE-MRI has a role in evaluation of treatment response after RT. In this setting it has a significantly higher sensitivity (72% vs 38%), positive predictive value (46% vs 24%), and negative predictive value (95% vs 88%) than T2-weighted imaging and a similar specificity (85% vs 80%) [41]. Furthermore, the interobserver agreement is higher for DCE-MRI images than for T2-weighted and correlated with MRI-calculated tumor volumes and the mean biopsy core invasion rates [42].
CT or MRI detection of pelvic lymph node metastasis depends on the size of lymph nodes, with decreased detection rate if they are <1 cm [43]. Emerging imaging techniques which are not yet widely available include $^{11}$C-choline positron emission tomography (PET) which can identify potential metastasis in pelvic lymph nodes with a sensitivity of 80%, a specificity of 96%, and an accuracy of 93% [44].

The disadvantages of MRI-based prostate localization are its limited availability, CT-MRI fusion uncertainties, treatment planning warping, and a loss of radiographic density information for calculating radiation doses and reconstructing digital radiographs for treatment verification. Several centers are exploring methods to reduce the dosimetric and positional uncertainties associated with MRI simulation [45,46]. 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.

**Defining the Gross Tumor Volume and the Clinical Target Volume**

The entire gland is commonly considered the GTV for radiation treatment planning purposes because prostate cancer is often found to be multifocal at the time of radical prostatectomy. The clinical target volume (CTV) may expand the GTV to account for direct extension, or the CTV can be extended to encompass adjacent organs or regions of spread. In prostate cancer, the CTV may encompass the SVs and possibly the regional pelvic lymph nodes.

The standard terms recommended Report 50 of the International Commission on Radiation Units and Measurements (ICRU) for specifying dose prescription are summarized as follows [47]:

- **GTV (gross tumor volume):** Tumor only, no margin. The entire prostate gland as determined by a CT scan commonly defines the GTV. Gross extension beyond the gland in a patient with a clinical stage T3-4 cancer should be included as the GTV.
- **CTV (clinical target volume):** Includes margin around the GTV for regions of microscopic risk. This can include adjacent regions at risk of having subclinical disease, such as the SVs or pelvic lymph nodes.
- **PTV (planning target volume):** Includes margin around the CTV to allow for patient movement, setup error, and organ movement.

In another series of 712 prostatectomy specimens, Teh et al [48] reported that the mean radial distance from the capsule was found to be 2.93 mm. This study is unique in that it did account for formalin fixation effects. Nevertheless, the decision to add additional CTV margin may be most important in patients with high-risk features, such as a prostate-specific antigen (PSA) >20, Gleason score >7, or bulky tumors (T2c or greater).

In selected patients it is necessary to include the SVs in the CTV, which in most patients are well demonstrated on the cross-section CT scans of the pelvis. Nomograms [49,50] may be used to determine the probability of extraprostatic extension (EPE), SV, or pelvic lymph node involvement using clinical stage, pretreatment PSA, and Gleason score. Kestin et al [51] 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. They found an excellent correlation between the various prognostic parameters and the probability of SV involvement. Also, in 81 patients with positive SV involvement, the median length of tumor presence was 1 cm. In the entire population, 7% of patients had SV involvement beyond 1 cm. They concluded that in selected patients SVs should be treated and that only 2.5 cm (approximately 60% of the SV) should be included within the CTV unless there is radiographic evidence of involvement.

In cases where the disease is confined to the gland (clinical stages T1-2) but the risk of SV invasion exceeds 15%, two CTVs can be defined. The first encompasses the prostate and the SVs and the second boost CTV is the prostate alone. 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 (clinical stage T3), the SVs should be included for the total radiation dose prescription.

**Planning Target Volume Margins**

The magnitude of the PTV margin depends on several factors. Treatment setup errors can vary by the method of patient positioning and immobilization. Internal organs, including the prostate gland, can shift because of variable filling of the rectum and bladder. The shifts can be asymmetric, with most movement occurring in the AP directions. Langen et al [52] summarized setup errors and internal organ motion. In order to assure that an
adequate radiation dose treats the CTV, an appropriate PTV margin must be added. There is a tradeoff between assuring nearly 100% coverage during each treatment and the volume of adjacent organs irradiated unnecessarily. However, the method of localization must be taken into account when determining the PTV margin.

Methods that allow corrections for intra-fraction motion may allow smaller PTV margins. In addition, visual display tools in planning systems allow visualization of multileaf collimator (MLC) in respect to PTV. The MLC’s position to define beam apertures in 3DCRT or to create intensity maps in IMRT can be estimated on beam eye view. The magnitude of OAR sparing or PTV coverage can be visualized and judged accordingly.

**Localization for Prostate Radiation Therapy**

High precision is extremely important in limiting toxicity after dose escalation. IMRT has emerged as the most current available treatment planning technology [53-55]. IMRT planning begins in nearly an identical manner to that of forward planned 3DCRT; however, patient positioning and reproducibility are far more critical due to the sharp dose gradients that can be seen with this modality. Every effort is made to maintain accuracy while decreasing margin. The daily target localization method is critical in patients receiving IMRT for prostate cancer. Suitable methods include transabdominal US, intraprostatic fiducial markers with daily megavoltage portal or radiographic imaging, endorectal balloon immobilization, or daily in-room CT imaging. IMRT treatment planning requires defining dose constraints for the target and each critical structure. IMRT creates more heterogeneity of dose than 3DCRT, and the planning prescription needs to define a minimum dose to cover a predetermined volume of the PTV as well as a maximum dose to a small volume inside the PTV. Dose limits to OAR need to take into account both upper dose limits and the volume of those organs that are allowed to exceed those limits.

By definition, PTV accounts for setup error and internal organ motion [56]. Many studies have used different tools to define the optimum PTV margin, and this margin depends on the tracking technology used, as well as the method used to adapt to this motion. Use of IGRT in prostate cancer has improved results and allowed safe and effective dose escalation [57]. The quality assurance strategy differs by method of localization and institutional preference [58]. New strategies to reduce the uncertainty in daily treatment delivery and the magnitude of the PTV margin have been introduced. These methods employ daily imaging of the prostate in the treatment room.

Setup correction using bony landmarks, as opposed to skin marks, were the acceptable standard before wide use of implantable fiducial markers. The use of fiducial markers resulted in improved accuracy and has allowed reduction of the PTV margin from 11-14 mm with bone off-line setup to 4-7 mm with online fiducial markers [26]. If correction is to be done daily, the margins are 4.9, 5.1, and 4.8 in left-right, SI, and AP direction, respectively. However, broader margins (6.7, 8.2, and 8.7 mm) are required if the correction is done weekly [59]. Care should be taken when adapting to prostate motion while pelvic lymph nodes are treated, as this may lead to degradation of the dose to pelvic lymph node PTV [60]. Deformation of prostate shape, radiation exposure as well as inability to visualize OAR are some of the limitations of using fiducials alone for tracking [61].

Litzenberg et al [62] reported that margins could be reduced using daily fiducial marker localization and pretreatment position correction. After prostate localization and adjustment, the position errors were reduced to 1.3-3.5 mm left-right, 1.7-4.2 mm AP, and 1.6-4.0 mm inferior-superior in prone patients, and 1.2-1.8 mm left-right, 0.9-1.8 mm AP, and 0.8-1.5 mm inferior-superior in supine patients. Using fiducial markers and electronic portal images, Chung et al [63] 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 [64]. Radiopaque implanted fiducial markers can be imaged with electronic portal imaging or stereoscopic kilovoltage imaging devices. Crook et al [65] evaluated prostate motion in 55 patients in whom gold seeds were implanted at the base of the gland. Initial simulation was obtained in a supine position with a full bladder and repeated after patients received 40 Gy. Prostate motion was observed in the posterior direction (5.6 mm ± 4.1 mm) and in the inferior direction (5.9 mm ± 4.5 mm). In 30% of the patients the base of the prostate was displaced posteriorly and in 11% in the inferior direction by more than 10 mm.

**Transabdominal Ultrasound**

Transabdominal US has been used to localize the prostate for treatment planning and during daily RT delivery with accuracy parallel to that of CT scanning of the pelvis. Using an US-based system, Little et al [66] reported that without US localization, organ motion would have caused the CTV to move outside the PTV margin in 23.3%-41.8% of the treatments.
In a study of 26 patients, Trichter et al [67] demonstrated that daily setup to bony anatomy using electronic portal imaging did not accurately localize the prostate when compared to a transabdominal US system. The average residual shifts required to account for prostate position as measured by the US system were 0.32 \pm 0.46 cm in the lateral, 0.31 \pm 0.73 cm in the SI direction, and 0.32 \pm 0.56 cm in the AP direction. Suprapubic pressure required to obtain a good quality-image may cause the prostate to move during the localization procedure. Artignan et al [68] reported that a probe displacement of 1.2 cm will result in an average prostate displacement of 3.1 mm. In their study on healthy volunteers, a probe displacement of 2 cm would result in 40\% of them having their prostate move at least 5 mm. In a study of 16 prostate cancer patients, Serago et al [69] noted that pressure from the US probe displaced the prostate in 7 of 16 patients by an average of 3.1 mm.

In summary, 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 [70]. Although, US methods avoid x-ray exposure and have comparable accuracy [71], they are sensitive to subjective and training variability, and hence their role in tracking may be less than that provided with either fiducial or megavoltage CT (MVCT) methods [72-74].

**Computed Tomography**

Imaging with position correction can reduce the magnitude of systematic setup errors in daily EBRT. Tomographic volumetric imaging capabilities allow daily capture of 3D image data. Both megavoltage and kilovoltage CT reconstructions can display the daily position of the prostate and adjacent OAR, thereby allowing treatment position to be adjusted to ensure that the entirety of the target is in the daily treatment volume [75]. It is important to note that CT-based methods of image guidance (whether kilovoltage or megavoltage) provide a spectrum of image quality and exposure levels that depend on the method used [76]. 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 megavoltage systems to achieve the same image quality seen with some kilovoltage systems. Gildersleve et al [77] demonstrated in a randomized trial that an integrated megavoltage imaging system with repositioning during treatment would improve the accuracy of treatment from 4.3 mm to 2 mm and reduce the frequency of displacement errors >5 mm from 69\% to 7\%.

Cone beam computerized tomography (with or without fiducials) allows better visualization of the prostate and OAR [78]. Daily online correction allows the use of the following suggested PTV margins: 4 mm in all directions and 3 mm posterior [79] or 5 mm all around and 3 mm posterior [80].

As compared to skin setup, MVCT can provide a tighter margin [81]. In an assessment by Schubert et al [82], global systematic error with daily MVCT was found to be 4.7 mm in vertical direction and largely caused by couch sag. In spite of low image quality, MVCT IGRT has a clear advantage in the presence of large artifacts such as those caused by hip prostheses [83]. Also, it can allow direct dose calculation and dose-guided modifications or adaptation on acquired images. However, of concern is the additional megavoltage x-ray exposure. AAPM Task Group 75 approaches that subject and provides insight about its complexity [84].

In addition, 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 [85] and dose guidance [86,87] offer opportunities to maximize therapeutic ratio.

With the exception of electromagnetic transponder methods, all other methods only correct for interfraction and not intrafraction prostate motion, which is largely dependent on rectal filling [88].

**Endorectal Balloon**

An endorectal balloon can be used for prostate immobilization/fixedation and to ensure reproducibility of rectal filling. Reduction in organ motion as well as additional sparing has been observed with the rectal balloon [89-91]. However, deformation of prostate shape by introduction of balloon [92] patient compliance pose barriers to widespread use of balloons [93].

Use of an endorectal balloon during daily treatment potentially stabilizes the position of the gland. The balloon also moves the prostate anteriorly, allowing shielding of the posterior rectal wall. An endorectal balloon is a controlled intervention that can be reproduced during the course of RT. Air in the balloon may decrease the rectal surface dose by reducing the electronic buildup and equilibrium at the air–soft-tissue interface. Teh et al [94] reported results in 100 consecutive patients treated with IMRT and an endorectal rectal balloon. Ten of those
patients also participated in a prostate motion study following gold seed implantation. Each of these 10 patients underwent 10 CT scans during the course of their RT. The mean and standard deviations of SI target displacements were 0.92 mm and 1.78 mm, respectively. Of the 100 patients treated with a rectal balloon, 80% had no rectal complaints and 11% and 6% had grade 1 or 2 acute toxicity, respectively. The radiation dose was measured at a balloon-tissue interface using a phantom. The dose at the air-tissue interface was approximately 15% lower than the dose at the same point without an air cavity. The dose builds up rapidly so that at 1 and 2 mm away from the interface, the dose was only approximately 8% and 5% lower, respectively [94]. Wachter et al [95] 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 [96] demonstrated significant dosimetric sparing of the rectum with 3DCRT 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.

**Electromagnetic Transponders**

New 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 real-time during a treatment session, allowing for immediate intervention if the prostate moves outside the radiation field [97]. A unique advantage of this method is correction of intrafraction error with possible reduction of PTV margin to 3 mm [56,98]. 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 [99]. Furthermore, other limitations exist, such as in patients with pacemakers and in very obese patients.

**Dose Prescription and Dose Escalation for Localized Prostate Cancer**

Dose escalation has led to enhanced biochemical control with higher doses as discussed below. Dose escalation can be achieved through either standard fractionation or hypofractionation, which may have the additional benefit of taking advantage of the low α/β ratio of prostate cancer [100,101]. Biologic models support dose escalation beyond 80 Gy [102]; the adjusted 5-year biochemically no evidence of disease (bNED) rates (using the Phoenix definition) were 70%, 81%, 83%, and 89% for doses <70 Gy, 70-75 Gy, 75-80 Gy, and >80 Gy, respectively. Similarly, Cheung et al [103] showed that the TCD50 (the radiation dose to achieve 50% tumor control, using the ASTRO definition) was 57.3 Gy with plateauing of the dose-response curves at 78 Gy for low-risk disease. However, for intermediate-risk disease, the TCD50 was 67.5 Gy with a plateau after >78 Gy. The high-risk group had a TCD50 of 75.5Gy. The steep portion of the curve from 78 Gy to 83 Gy may improve PSA control by 10% [104]. The TCD50 for high-risk patients is ~10 Gy higher than for low-risk patients, and the TCD95 is 78 Gy, 83 Gy, and 88 Gy for low-, intermediate-, and high-risk groups, respectively [105].

An ultra-high dose of 86.4 Gy used in the Memorial Sloan-Kettering Cancer Center (MSKCC) dose escalation study resulted in 5-year bNED of 98% in low-risk, 85% in intermediate-risk and 70% in high-risk disease [106].

A dose response was also demonstrated in patients with an initial PSA level of 10-20 ng/ml. The disease-free survival rates were 19%, 31%, and 84% in patients receiving <70 Gy, 70-72 Gy, and >72 Gy, respectively (P=0.003). Higher or lower value groups didn’t show significant benefit from dose escalation [107]. On the other hand, the Medical Research Council (MRC) RT01 trial showed that 5-year biochemical progression-free survival (bPFS) rates with the higher 74 Gy dose were 85% for low-risk patients, 79% for intermediate-risk patients, and 67% for high-risk patients, compared to 79%, 70%, and 43%, respectively, for patients receiving the 64 Gy dose [108].

In the MD Anderson Cancer Center (MDACC) trial, the 8-year freedom from biochemical or clinical failure rates improved significantly with dose escalation to 78 Gy (78% vs 59%). Furthermore, if PSA was >10 ng/ml, dose escalation led to a significant improvement in freedom from biochemical or clinical failure to 78% versus 39% in the 78 Gy and 70 Gy arms respectively [109]. In this trial, all patients began with radiation to a limited pelvic field with a standard 4-field arrangement. Patients were then randomized to receive a conventional field boost to a total isocenter dose of 70 Gy or a 3DCRT boost to a total isocenter dose of 78 Gy. The largest gain from this 8 Gy dose increase was seen in the patients with pretreatment PSA >10 ng/ml. In those intermediate-risk patients the 5-year biochemical disease-free survival (bDFS) rates were 72% for 78 Gy and 44% for 70 Gy.

A collaborative study by the Massachusetts General Hospital and Loma Linda University compared 70.2 GyE to 79.2 GyE (GyE=Gray equivalent) using highly conformal proton beams as the boost modality. The Proton
Radiation Oncology Group (PROG) 95-09 trial also confirmed the importance of dose escalation, using protons for the boost portion of the treatment. The boost doses of 19.8 GyE versus 28.8 GyE were given in addition to the standard photon treatment of 50.4/28 [110]. Significant differences in the 10-year ASTRO bPFS rates were seen for the overall group, as well as the low-risk patients of 68% and 83% for the low doses versus high doses given to the whole group, respectively. For low-risk disease a significant difference in 10-year bPFS rates of 72% versus 93% was seen. The differences were not significant for the intermediate-risk group with a 10-year bPFS rate of 58% versus 70% (P=0.06). Unlike the MDACC trial, this study demonstrated an advantage to high-dose RT in both low-risk and high-risk patients [111]. It is important to note, however, that proton radiotherapy and photon radiotherapy were not directly compared in this trial, since protons were only used as a boost. As a method of dose escalation, the clinical benefit of proton radiotherapy over photon radiotherapy may not be pronounced despite the dosimetric advantage in body integral dose [112]. Jabbari et al found that equivalent biochemical control and lower PSA nadir is seen after permanent prostate seed implant brachytherapy as compared to high-dose 3DCRT and high-dose conformal proton beam radiotherapy boost.

Higher doses may be needed even in the presence of androgen deprivation therapy (ADT) as shown in the Grupo de Investigación Clínica en Oncología Radioterápica (GICOR) study [113] where low-risk patients were assigned to 3DCRT only, intermediate-risk to 3DCRT and 4-6 months ADT, high-risk to 3DCRT and 2 years ADT. The 5-year bDFS rates by dose (<72 vs ≥72 Gy) were as follows: low-risk, 66% versus 96%; intermediate-risk, 56% versus 94%; and high-risk, 63% versus 84%, with significant differences in the low- and high-risk patients.

In some reports, there has not been a benefit for dose escalation above 70 Gy for low-risk prostate cancer [114-116]. The Fox Chase Cancer Center series reported no benefit to doses >77 Gy compared to 67-77 Gy for low-risk patients and did not show a dose response for doses >72 Gy. Hurwitz et al did not see a difference in bDFS rates for patients receiving more than 68 Gy. This lack of benefit to higher doses may be due to the small local tumor burden that is readily controlled with conventional doses. On the other hand, investigators from the Cleveland Clinic and MSKCC have shown a bDFS benefit for patients with low risk disease who receive escalated doses with 3DCRT or IMRT [117-119]. In the MSKCC dose escalation trial, Zelefsky et al reported a 5-year bDFS rate of only 77% for patients receiving 64.8-70.2 Gy compared to 90% for low-risk patients receiving 75.6-86.4 Gy. Khuntia et al from the Cleveland clinic reported 5-year bDFS rates of 52%, 82%, and 93% for low-risk patients receiving ≤68Gy, 68-72Gy, and >72Gy, respectively.

Intermediate-risk patients benefited from escalated radiation doses in most retrospective analyses [114,115,117-119]. Pollack et al [115] reported 5-year bDFS rates of 24%, 65%, and 79% for patients receiving isocenter doses of <72 Gy, 72-75.9 Gy, and ≥76 Gy, respectively. Khuntia et al [117] reported 5-year bDFS rates of 27%, 51%, and 83% for doses of ≤68 Gy, 68-72 Gy, and ≥72 Gy, respectively. In the Cleveland Clinic series the low-dose patients were treated with either standard techniques or 3DCRT with doses prescribed to the isocenter. The intermediate-dose and high-dose patients were treated with either 3DCRT or IMRT. Radiation dose at the Cleveland clinic was prescribed to an isodose line that covered the PTV when IMRT was used. At MSKCC, Zelefsky reported 5-year bDFS rates of 50% and 70% in intermediate-risk patients receiving 64-70.2 Gy and 75.6-86.4 Gy, respectively.

Patients with high-risk disease do not uniformly demonstrate a benefit from escalated radiation doses [115,116]. This may be due to the greater burden of subclinical metastases in patients with high presenting PSA or high-grade disease. From the Cleveland Clinic, Khuntia et al [117] reported improved 5-year bDFS rates for high-risk patients of 21%, 29%, and 71% for radiation doses of ≤68 Gy, 68-72 Gy, and >72 Gy, respectively. Zelefsky reported 5-year bDFS rates in intermediate-risk patients of 21% and 47% in patients receiving 64-70.2 Gy and 75.6-86.4 Gy, respectively [105,120]. Cheung et al [104] from MDACC suggested a dose response for bDFS for high-risk patients. They suggested that a 5 Gy dose increase beyond 78 Gy may improve PSA control for these patients. Several randomized trials have been undertaken to demonstrate whether there is a benefit to high-dose 3DCRT.

**Toxicity**

Normal tissue tolerance plays an important role in 3DCRT and is critical in IMRT treatment planning. In the Radiation Therapy Oncology Group® (RTOG®) prospective dose escalation trial, Michalski et al and Ryu et al reported the administration of minimum PTV doses from 64.8 Gy to 79.2 Gy in 1.8 Gy/day fractions and 74 Gy to 78 Gy in 2 Gy/day fractions. Dose escalation in the RTOG® 94-06 trial included the following levels: 68.4 Gy (1.8 Gy/fractions; level I), 73.8 Gy (1.8 Gy/fractions; level II), 79.2 Gy (1.8 Gy/fractions; level III), 74 Gy (2
Gy/fractions; level IV), and 78 Gy (2 Gy/fractions; level V). A lower than expected incidence of grade 3 or worse intestinal or urinary toxicity was found based on comparisons to historical controls [121-124]. The late grade 3+ gastrointestinal or genitourinary (GI/GU) toxicity rates for different doses were reported as follows:

- For patients receiving prostate-only RT: 68.4 Gy, 3%; 73.8 Gy, 4%; 79.2 Gy, 6%; 74 Gy, 7%; and 78 Gy, 9%.
- For patients receiving both prostate and SV RT: 68.5 Gy, 6%; 73.8 Gy, 2%; 79.2 Gy, 6%; 74 Gy, 9%; and 78 Gy, 12%.

In both groups the differences were statistically significant. More toxicity was observed with 2 Gy fractions than with 1.8 Gy [125].

Based on their review of rectal toxicity in patients who received 3DCRT in the MSKCC dose escalation study, Jackson et al [126] recommended that ≤60% of the rectal wall receive 40 Gy and ≤30% of the rectal wall should receive ≥75.6 Gy to minimize the risk of grade 2 or greater rectal toxicity. In an update on their IMRT experience, Zelefsky reported that the rate of late grade 2 rectal bleeding was 1.5%, and only 0.5% experienced grade 3 toxicity requiring one or more transusions or laser cauterization procedures. Late grade 2 urethritis occurred in 10% of patients, and another 0.5% experienced grade 3 urethral stricture. Dose constraints for this study were 100% of the prescription to the PTV (excluding overlap with normal organs) and limits of 40% and 58% of the prescription dose to the rectal wall and bladder wall, respectively. In the overlap region between the PTV and these critical organs, the constraint was set at 88% of the prescription dose for the rectum and 98% for the bladder. The prescription doses to the PTV ranged from 81.0 to 86.4 Gy in 1.8 Gy fractions [120]. The reported toxicity rates in the updated MSKCC retrospective [106] review of 478 patients treated in the ultra-high-dose radiation to 86.4 Gy arm (weekly electronic portable imaging device [EPID] with PTV 1 cm except posteriorly 6 mm) were as follows:

- Acute toxicity rates: grade 3+ GI, none; grade 3 GU, 0.6%; grade 2 GI, 8%; grade 2 GU, 22%.
- Late toxicity was as follows: grade 3 GI, <1%; grade 3 GU, <5%; grade 2 GI, 3%; grade 2 GU, 13%.

Erectile dysfunction occurred in 30% of patients (80% received ADT), and diminished erectile strength in 25% (60% received ADT).

The MDACC dose escalation trial [109] reported significant differences in 10-year GI toxicity rates between high-dose and low-dose arms, but not in GU rates. The differences were as follows: grade 3 GI, 7% versus 1%; grade 2 GI, 26% versus 13%; grade 3 GU, 5% versus 4%; grade 2+ GU, 13% versus 8%.

Concern about toxicity with dose escalation was addressed in several recently published trial toxicity updates as well. The Groupe d’Etude des Tumeurs Uro-Génitales study (GETUG) randomized 306 intermediate-risk patients to 70 Gy/35 fractions versus 80 Gy/40 fractions. The rectal wall Dmax was 76 Gy and the bladder wall Dmax was 80 Gy [127]. No significant differences were seen in GI toxicity. The acute grade 2 and grade 3 GI toxicity rates were 27%, and 2% in low-dose arm versus 28% and 2% in the high-dose arm, respectively.

Radiation toxicity in the Dutch CKVO96-10 study comparing 68 Gy versus 78 Gy was reported [128]. At a median follow-up of 4.2 years, no significant differences in GI toxicity were seen. The GI grade 2 toxicity rates were 32% in the high-dose arm and 27% in the low-dose arm, the GI grade 3 toxicity rates was 5% versus 4%. The GU grade 2 toxicity rates was 39% versus 41% and GU grade 3+ toxicity rates was 13% versus 12%.

Analysis of sexual function from the same trial [129] demonstrated that erectile dysfunction increases with time; at 1 year 27%, at 2 years 36%, at 3 years 38% of pretreatment potent men got erectile dysfunction, with no difference between the low and high dose group.

A retrospective review of a multicenter dataset has shown that for low- and intermediate-risk patients treated with doses >70 Gy, overall treatment time, as well as, dose significantly affected outcome, but not in high-risk patients [130]. Similar conclusions on low risk patient were reported by others [131]. Arcangeli et al [132] reported on a phase III randomized trial of hypofractionation versus conventional fractionation in 168 patients with high-risk prostate cancer. Patients received neoadjuvant/concurrent/adjuvant ADT for 9 months, and 3DCRT 80 Gy/40 fractions (Arm 1) versus 3DCRT 62 Gy/20 fractions (Arm 2). CTV was prostate + SV. Significant differences in bPFS were seen, in spite of the short median follow-up of 2.7 years. Three-year bPFS for the conventional arm (Arm 1) was 79% versus 87% in the hypofractionated arm. Three-year late GI and GU Grade 2 toxicity were similar at 16% versus 17%, and 11% versus 14% for the conventional versus the hypofractionated arm, respectively.
Of note, however, is the slight increase in acute GI toxicity (but no difference in GU toxicity) for the Fox Chase Cancer Center randomized study seen in the first 100 reported intermediate- and high-risk patients who were randomized to conventional versus hypofractionated (70.2 Gy/26 fractions) RT. No biochemical outcomes have been reported to date [133]. In conclusion, the use of appropriate doses and simulation techniques and close monitoring for verification of field setup are essential for accurate delivery of RT.

Summary

- The use of CT is recommended for simulation of patients with prostate cancer.
- MRI has an important role and should be considered to aid in volume determination. The type of MRI (eg, DCE or body coil) depends on the available equipment and expertise. Endorectal coil can cause deformation of the prostate and make fusion difficult.
- Daily localization is recommended with techniques that require smaller margins. Different localization techniques have advantages and disadvantages and should be chosen after thoughtful consideration of patient and tumor characteristics as well as the experience of the treating staff.
- The use of intensity modulation may be beneficial. 3-D blocks should be used in the absence of IMRT.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

References


The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient’s clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient’s condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.
### Clinical Condition: External Beam Radiation Therapy Treatment Planning for Clinically Localized Prostate Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Simulation Imaging Tools</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Immobilization devices (external)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>X-ray retrograde urethrography</td>
<td>5</td>
<td>If MRI is not available or possible.</td>
</tr>
<tr>
<td>MRI endorectal coil</td>
<td>5</td>
<td>Endorectal coil may displace prostate anatomy and make image fusion more difficult.</td>
</tr>
<tr>
<td>MRI body coil</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>MRI body coil with DCE (dynamic contrast enhancement)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Immobilization devices (internal, rectal balloon)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bony anatomy 2D x-ray simulations</td>
<td>3</td>
<td>To verify isocenter only.</td>
</tr>
<tr>
<td><strong>Treatment Planning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMRT</td>
<td>8</td>
<td>Most appropriate for patients treated with dose escalation.</td>
</tr>
<tr>
<td>3D-CT based plan</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Proton beam RT</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2D-CT based plan</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Non-CT based computerized plan</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Field Shaping</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMRT</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>3D-designed blocks</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Manually designed blocks from x-ray simulation films or diagnostic CT scans</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>No blocks</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment Localization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily localization with implanted fiducial markers (stereoscopic)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>In room CT-based localization</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Daily monitoring through electromagnetic transponders</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Daily transabdominal ultrasound</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Daily port film or electronic image localization: bony landmarks</td>
<td>5</td>
<td>Use with wider PTV margins.</td>
</tr>
<tr>
<td>Weekly port films or electronic images</td>
<td>4</td>
<td>Appropriateness depends on size of margins and type of immobilization device used.</td>
</tr>
<tr>
<td>Port film or image with initial treatment only</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

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