Prostate Cancer

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19.1 Introduction

1. In the USA, other than skin cancer, prostate cancer is the leading cancer diagnosis in men, estimated to represent 21% of new cancer diagnoses in men in 2016. Due to improvements in early detection and treatment, prostate cancer mortality has been decreasing since the 1990s [1]. Most patients are diagnosed with non-metastatic disease, and those who opt for intervention are typically managed with radiation therapy (RT) with or without androgen deprivation therapy (ADT) or surgery.
2. The NCCN classification system stratifies patients into pretreatment risk groups based on risk of disease progression and to assist decision-making. This includes very low-, low-, intermediate-, and high-risk groups.

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3. RT may be delivered by external beam (intensity-modulated radiation therapy or particle therapy), brachytherapy, or a combination of the two. High-risk and unfavorable intermediate-risk disease is typically managed with RT and ADT [2]. Some patients who opt for surgery may go on to have adjuvant RT and/or ADT.
4. Control rates after RT for prostate cancer are excellent. Significant improvements in local control and/or toxicity have been made with dose-escalated RT, intensity-modulated RT (IMRT), image-guided RT (IGRT), hypofractionated RT, and addition of ADT to patients with intermediate- or high-risk disease [3–5]. Five-year biochemical relapse-free survival after dose-escalated RT is 98%, 85%, and 70% for low-, intermediate-, and high-risk groups, respectively [6].
5. The most common acute and late genitourinary (GU) toxicity during and after prostate RT is irritative urinary symptomatology including urgency, frequency, and hesitancy, all of which may be exacerbated by pretreatment lower urinary tract symptoms or benign prostatic hyperplasia. Erectile dysfunction may occur in approximately one third of men [7]. The Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 gastrointestinal toxicity (rectal bleeding) is encountered in approximately 5% of patients 10 years after treatment [8]. Severe late toxicity including urinary stricture, rectal fistula, and secondary malignancy is relatively uncommon.
6. The benefit of proton therapy in the definitive treatment of prostate cancer may be best realized with potential reduction in acute and late GU and GI toxicities [9]. Rates of Grade 2+ late GU and GI toxicities with IMRT may approach 10–15% and 5–10%, respectively [6, 10]. IMRT/IGRT have allowed for the safe delivery of high-dose RT. Proton therapy may improve the therapeutic ratio by reducing GI toxicity including rectal bleeding, potentially reducing the risk of secondary, radiation-induced malignancy due to the markedly reduced integral dose from lack of exit dose.

19.2 Simulation

1. To aid in daily prostate image guidance, three fiducial markers are implanted in the prostate under transrectal ultrasound guidance (Figs. 19.1 and 19.2). Markers should be radiographically visible and cause minimal streak artifact on CT scan [11]. In our practice, we generally recommend markers that have <10% dose perturbation [12]. These markers should ideally be placed approximately 3–5 days prior to simulation to allow time for resolution of prostate hemorrhage/edema and any fiducial migration.
2. At the time of fiducial placement, a hydrogel spacer (e.g., Augmenix SpaceOAR™) can be inserted to provide temporary physical separation of the anterior wall of the rectum from the prostate (Fig. 19.3). This allows for improved sparing of the anterior rectal wall from the high-dose region of treatment.
3. CT simulation is required in all patients. For dose calculation, a non-contrast CT should be obtained. Intravenous contrast is not required but may assist with target delineation of pelvic nodal volumes.

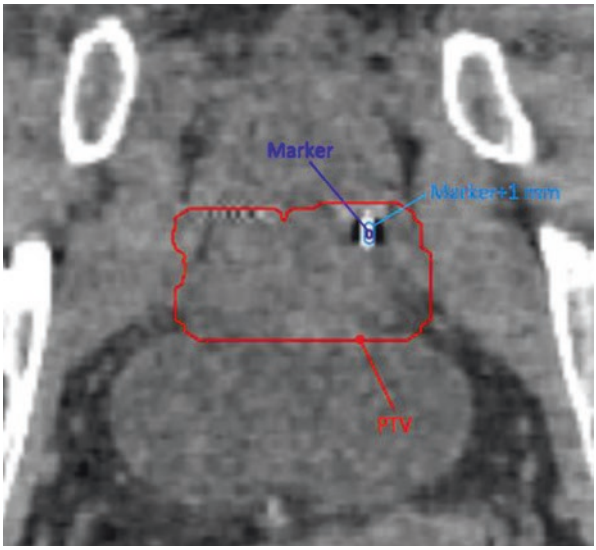

Fig. 19.1 The fiducial marker and an expansion structure expanded from the marker by 1 mm for daily fiducial registration

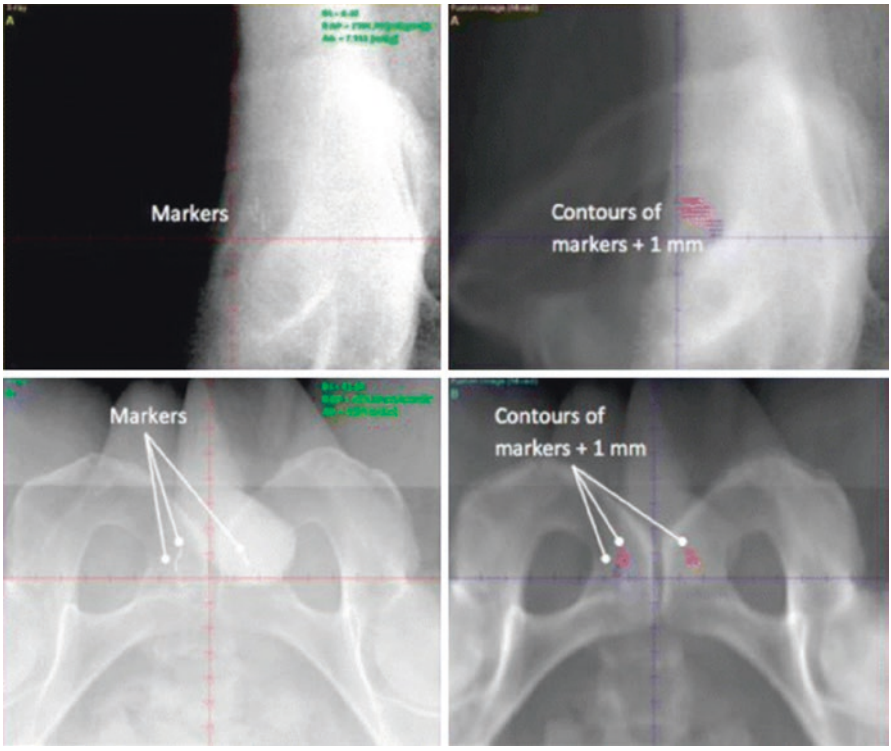

Fig. 19.2 Orthogonal X-ray images for a prostate patient with three fiducial markers. The markers can be aligned with the expanded contour with a 1-mm margin to account for a 2-mm setup uncertainty

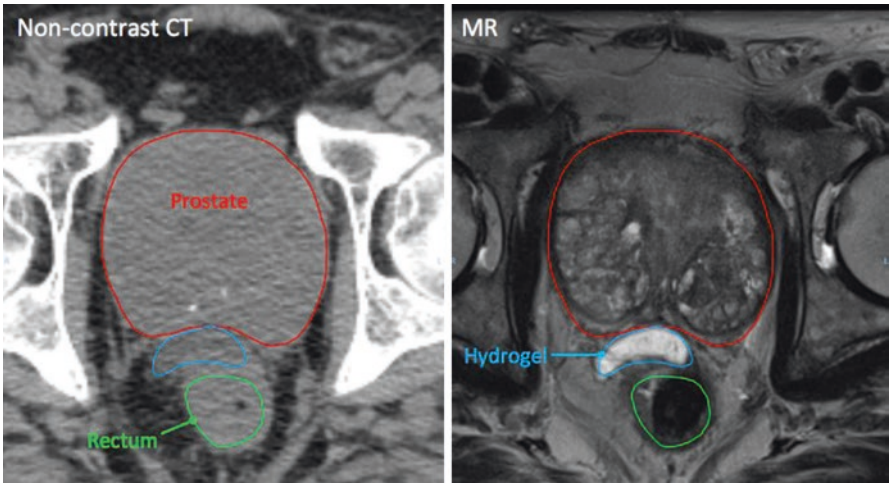

Fig. 19.3 Prostate contoured using the ancillary magnetic resonance (MR) image registered to the non-contrast computed tomography (CT) image. In this case, a hydrogel spacer had been placed between the prostate and rectum, which can be clearly discriminated on the MR images

4. Axial CT images at 1.25-mm intervals are captured from approximately the top of L4 to 5 cm below the ischial tuberosities. The patient is supine on the table immobilized in an indexed customized vacuum-lock cushion or alpha-cradle. Orthopedic metal artifact reduction (OMAR) technology may be helpful in reducing CT streak artifact in patients with prosthetic hips; however, the accuracy of the Hounsfield unit (HU) numbers will still have to be validated.
5. Multiparametric magnetic resonance imaging (MRI) is highly recommended to assist in prostate contouring in all patients. MRI may be particularly helpful in patients with orthopedic hip prostheses as metal streak artifact may make it difficult to contour the prostate accurately.
6. High-resolution, T2 axial MR images through the pelvis/prostate should be registered to the non-contrast planning CT for accurate target delineation paying special attention to soft-tissue alignment.

19.3 Target Delineation and Prescription

1. For low-risk prostate cancer patients, the clinical target volume (CTV) includes the entire prostate. For intermediate-risk patients, we typically include the proximal seminal vesicles (SV) as part of the initial CTV54 and boost the prostate alone in CTV79.2 (Fig. 19.4). If OAR constraints are not exceeded, the entire initial volume may be treated to the full prescription dose. Dose-escalated radiation is certainly recommended, but dose used may vary with institution from 74 to 82 Gy(RBE) [13, 14].

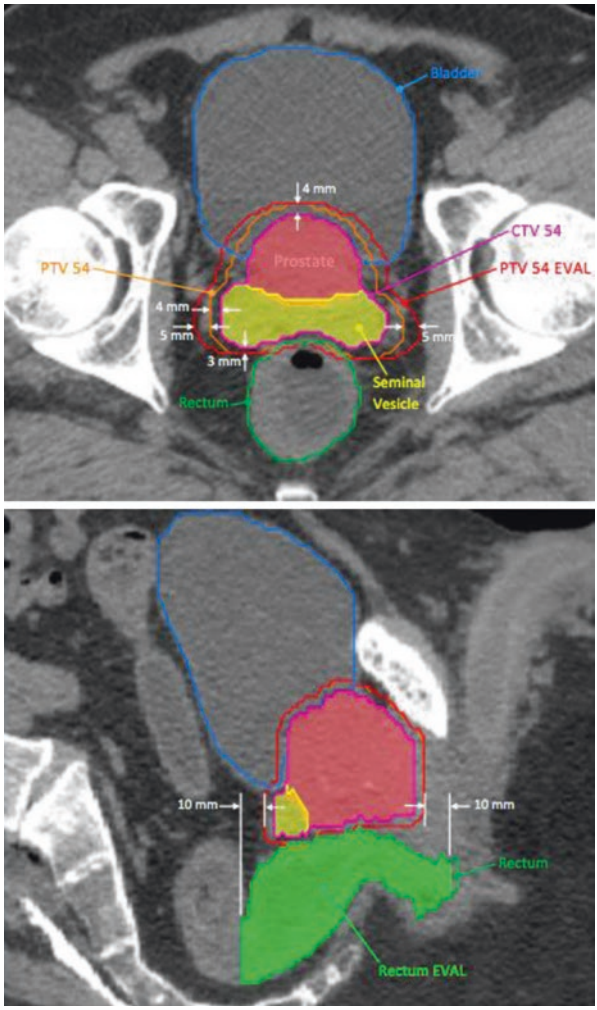

Fig. 19.4 Target volumes and organs at risk for the initial phase (54 Gy(RBE) in 30 fractions) of an intermediate-risk prostate cancer

2. For high-risk prostate cancers, the initial CTV45 includes the entire prostate and SVs. The CTV45 may also include the pelvic nodes for physicians who treat the pelvis. The pelvic volume includes the external and internal iliac nodes and obturator nodes contoured as per the Radiation Therapy Oncology Group (RTOG) Pelvic Lymph Node Atlas.
3. When contouring the CTV, every effort should be made to include suspicious lesions and areas of extracapsular penetration (ECE) or seminal vesical invasion (SVI). ECE and SVI are best visualized on the fusion MRI. Review of contours with a diagnostic radiologist can be helpful in distinguishing areas of tumor from normal structures. The prostate apex can be difficult to see clearly on CT, so correlation with MRI is typically helpful in ensuring adequate coverage of the prostate apex. MR imaging is also helpful in the identification of and contouring of

spacer hydrogels. Uncertainties related to image fusion should be considered in the treatment planning process.

4. To aid in image guidance registration, fiducial markers should be contoured with the use of the appropriate window and level setting to allow for proper visualization. Fiducial marker contours should correlate reasonably with the physical dimension specifications provided by vendors. An extra 1-mm margin is then added to the fiducial contour for the low- and intermediate-risk patients, and a 2-mm margin is added for high-risk patients to create registration structures in the IGRT software. On the DRRs, these "grape" or "cloud" structures will represent the region to which fiducial markers should be registered for correct prostate alignment.
5. Setup uncertainty is estimated to be up to 2–3 mm with the use of two to three implanted fiducial markers. The planning target volume (PTV) considering the setup uncertainty would be expanded from the CTV depending on the stage. For low-risk patients, the PTV margin expansion should be 2 mm posteriorly and 3 mm in other directions. For intermediate- and high-risk prostate patients, the PTV margin expansion around prostate is 3 mm posteriorly and 4 mm elsewhere. However, this may vary with institutional practice and difference in patient setup. For example, an alternative approach is to use a 5-mm uniform expansion for optimization and an additional institution-specific 1 mm for range uncertainty [10, 13].
6. Additional margin for range uncertainty is added to the PTV in the lateral directions when an opposed lateral beam arrangement is utilized, creating a PTV-EVAL structure. Adequate dose coverage of the PTV-EVAL is used to assess plan robustness and adequacy of coverage. In our clinical practice, an additional margin of 5 mm is added to the PTV along the beamline axis to create to the PTV-EVAL. Figure 19.5 shows a composite margin 9 mm expanded from the CTV to the PTV-EVAL to account for range uncertainty. Alternatively the margins can be calculated as indicated in Chap. 3.
7. Required normal structures to be contoured include the rectum, bladder, left and right femoral heads, large intestine, small bowel, and penile bulb. A RECTUM-EVAL structure is also created as a plan evaluation structure that is defined as the circumferential rectal wall extending 1 cm superior and inferior to the PTV.

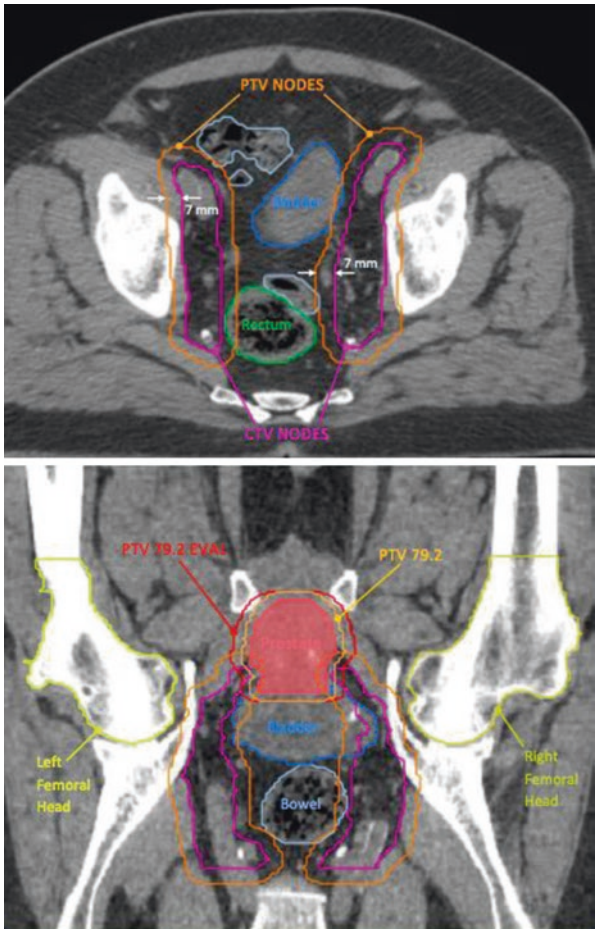

Fig. 19.5 The delineations of tumor/treatment volumes and organ at risks for a high-risk prostate cancer. The nodes will receive a dose of 45 Gy(RBE), and there is no PTV NODE EVAL since the range uncertainty is considered with the 7-mm margin expanded from CTV NODE

19.4 Patient Positioning, Immobilization, and Treatment Verification

1. Bladder filling is practiced at most institutions to help keep as much of the bladder wall away from the high-dose region and also to help move the small bowel superiorly, away from the target region. Patients are instructed to drink 20 ounces of water 30–60 min prior to simulation and daily treatment. The volume and timing may need to be adjusted at the time of simulation based on the adequacy of bladder filling seen on the simulation CT.
2. Simulation and treatment with an endorectal balloon or rectal saline instillation is recommended as a method of maintaining a consistent rectal shape and for prostate immobilization (Fig. 19.6) [9]. The rectal balloon is typically filled with 50–60 cm^3 of saline. However, other institutions may use 100 cm^3 of saline in a rectal balloon [10]. With saline instillation, up to 100 cm^3 of saline is inserted into the rectum via a lubricated, flexible rubber catheter. If necessary, bowel gas can be removed via the catheter, as well. Daily setup accuracy should be assessed with a daily pair of orthogonal X-ray images using the implanted fiducial markers or cone beam

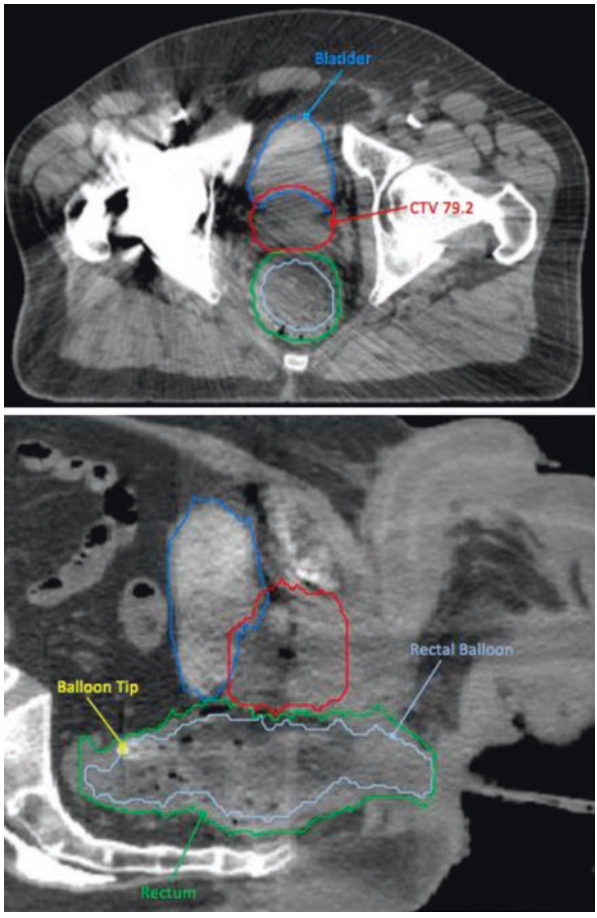

Fig. 19.6 Use of a rectal balloon for an intermediate-risk prostate cancer with right-sided hip prosthesis

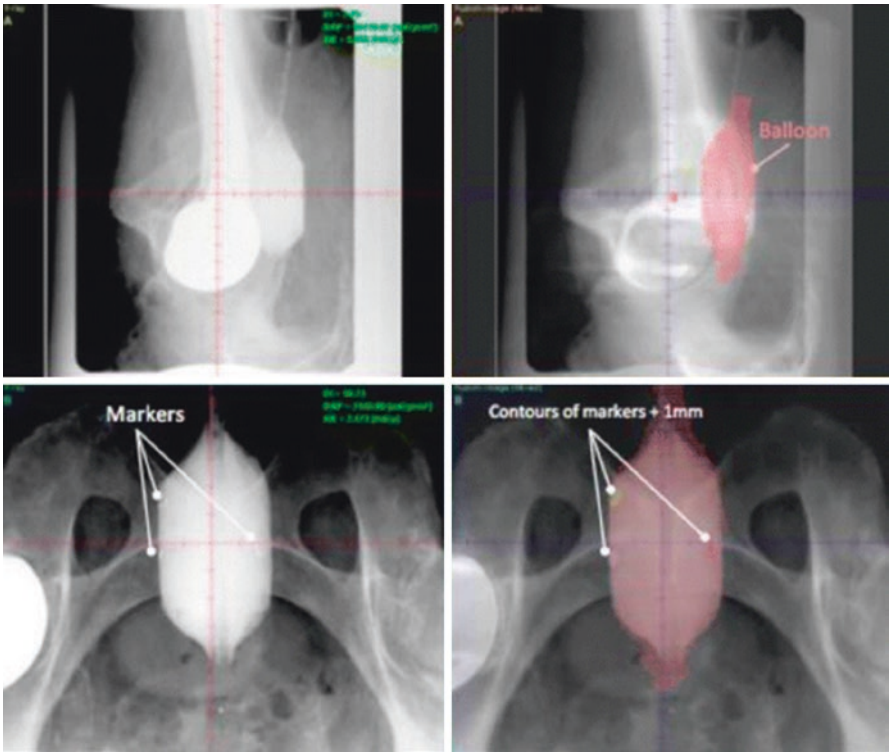

Fig. 19.7 A rectal balloon filled with diluted contrast is used to aid in daily setup for a prostate patient with a hip prosthesis. The fiducial markers are clearly visible on the PA film, and the contrast-filled balloon assists in the lateral view

CT. Cone beam CT can also verify bladder volume and endorectal balloon placement. In patients with prosthetic hips, fiducial markers may be difficult to visualize through the metallic hip, and a contrast-filled rectal balloon may be helpful in identifying the prostate/anterior rectal wall interface on a daily basis (Fig. 19.7).

3. Large discrepancies between fiducial registration and approximate bony registration may indicate an issue with setup. An effort to reduce bony anatomy discrepancy should be attempted to limit this discrepancy to <5–7 mm. Quality assurance or "QA" CTs may be helpful in understanding the nature of setup inconsistency whether it be related to bladder/rectal filling, patient positioning, or bowel gas.

19.5 Treatment Planning

1. The prostate ± seminal vesicles are typically treated with coplanar, opposed left and right lateral fields with a single isocenter. Two fields or a single alternating lateral field can be treated on a daily basis [15]. Patients who require treatment to the pelvic nodes are treated also with opposed lateral fields. The superior portions of the nodal volumes require treatment with two fields daily, with each

lateral field treating the ipsilateral nodal volumes. These fields are then matched inferiorly with beams that treat the central prostate volume (Fig. 19.8).

2. An alternative approach for patients with a metallic hip prosthesis is to use anterior oblique-oriented beams [16]. A typical beam arrangement for a patient with a right hip prosthesis may be a left lateral, right anterior oblique, and left anterior oblique beams. Anteriorly oriented beams may be sensitive to changes in rectal or bladder filling (Fig. 19.9). Alternatively a posterior oblique can be used in combination with a lateral beam. Thus, QA CTs may be relatively more important in these cases to ensure that the rectal and bladder anatomy remains consistent.
3. Whichever approach is used, daily coverage of the CTV considering the setup and range uncertainty is critical to minimize risk of local failure. In addition,

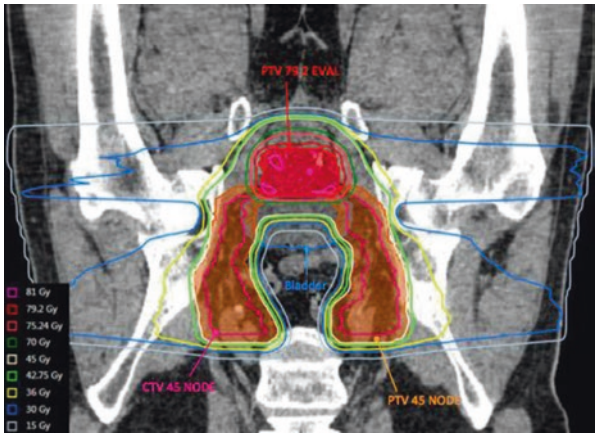

Fig. 19.8 The dose distributions of a high-risk prostate treatment plan using two matched opposed lateral pencil beam scanning (PBS) fields

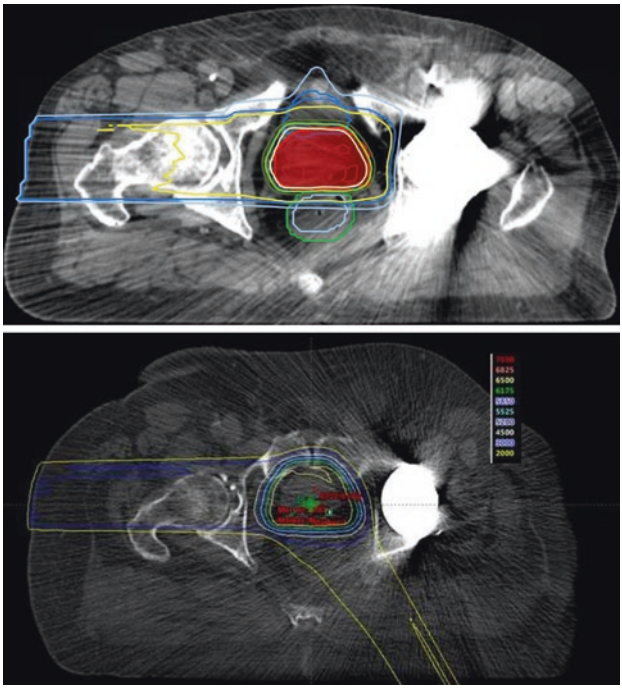

Fig. 19.9 The dose distributions of the treatment plan of a low-risk prostate patient with femur prosthesis using horizontal and anterior oblique (superior image) or horizontal and posterior oblique fields (inferior image)

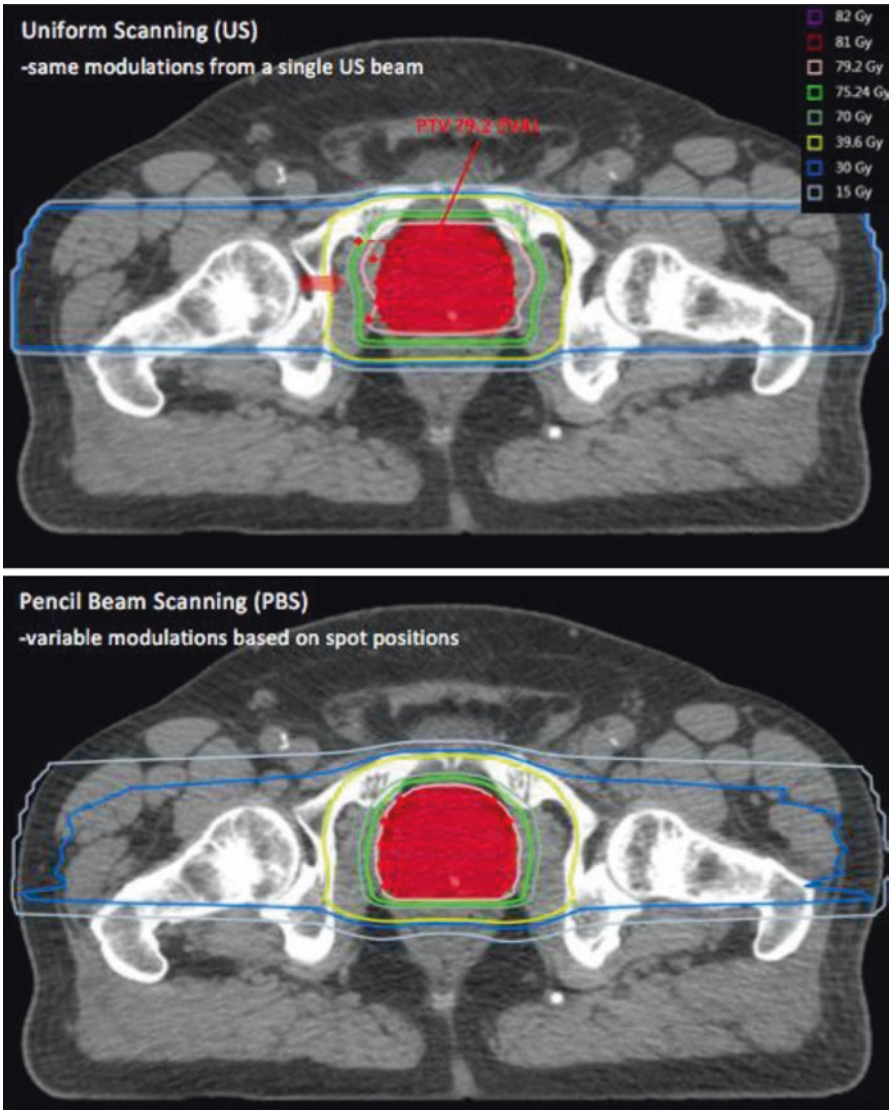

Fig. 19.10 The comparison of dose distributions of prostate treatment plans using uniform scanning (US) and pencil beam scanning (PBS) techniques. The *red dash lines* represent the spread-out Bragg peak (modulation) in the US plan and spot positioning in the PBS plan, respectively

every attempt should be made to reduce the volume of bladder and rectal wall that receives high-dose radiation [17].

4. Pencil beam scanning (PBS) allows treatment of the target volume spot by spot along a 3D grid without the use of tissue compensators or custom apertures. PBS in general provides highly conformal dose distributions as compared to uniform scanning techniques. PBS allows for variable modulation distances as compared to uniform scanning in which range modulation is the same for all spots, resulting in reduced proximal conformality of the beam (Fig. 19.10) [18–20].

Table 19.1 Target volume coverage goals and normal tissue dose constraints in proton treatment planning for prostate cancer

Target		Recommended coverage		
PTV-EVAL V98		≥99.5%		
PTV-EVAL V100		≥95%		
OAR	Normal organ tolerances	Prescription		
		All Rx's	≤ 60 Gy(RBE)	> 60 Gy(RBE)
		Gy(RBE)		Hard constraints
Bladder	Bladder $V_{81Gy(RBE)}$	<1 cm^3		
	Bladder $V_{70Gy(RBE)}$	<25%		
Bladder (post prostatectomy)	Bladder $V_{65Gy(RBE)}$	<40%		
	Bladder $V_{40Gy(RBE)}$	<60%		
Rectum	Rectum-EVAL $V_{70Gy(RBE)}$	<13%		<70Gy(RBE)
	Rectum $V_{70Gy(RBE)}$	<10%		
	Rectum $V_{65Gy(RBE)}$	<17%		
	Rectum $V_{81Gy(RBE)}$	<1 cm^3		
	Rectum $V_{50Gy(RBE)}$	<55%		
Rectum (post prostatectomy)	Rectum $V_{65Gy(RBE)}$	<25%		
	Rectum $V_{40Gy(RBE)}$	<45%		
Penile bulb	Mean dose	<52.5Gy(RBE)		
Femoral heads	Femoral heads $V_{50Gy(RBE)}$	<1.0 cm^3		
Bowel	Bowel 1.0 cm^3		≤55Gy(RBE)	≤ 60Gy(RBE)
	Bowel 0.03 cm^3			≤ 64Gy(RBE)

19.6 Planning Constraints

1. Target volume coverage goals and normal tissue dose constraints for prostate proton therapy are summarized in Table 19.1. Trade-offs between target coverage and normal tissue dose should be determined by the treating physician and take into account the unique clinical factors of the individual case.

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