High Dose Rate Prostate Brachytherapy

6

Alexander A. Harris, Kyle Stang, Matthew M. Harkenrider, Mitchell Kamrava, Derrick Lock, Gerard Morton, Michael L. Mysz, Timothy Showalter, Anthony C. Wong, and Abhishek A. Solanki

Contents

A. A. Harris · K. Stang · M. M. Harkenrider · D. Lock · M. L. Mysz · A. A. Solanki (✉)
Department of Radiation Oncology, Loyola University Chicago, Maywood, IL, USA

Loyola University Medical Center, Stritch School of Medicine, Loyola University Chicago, Maywood, IL, USA
e-mail: Alexander.Harris@lumc.edu; kstang1@lumc.edu; MHARKENRIDER@lumc.edu; MMYSZ2@lumc.edu; asolanki@luc.edu

M. Kamrava
Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA
e-mail: Mitchell.Kamrava@cshs.org

G. Morton
Department of Radiation Oncology, Sunnybrook Health Sciences Center, Toronto, ON, Canada

T. Showalter
Department of Radiation Oncology, University of Virginia School of Medicine, Charlottesville, VA, USA
e-mail: TNS3B@hscmail.mcc.virginia.edu

A. C. Wong
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA
e-mail: anthony.wong2@ucsf.edu

A. A. Solanki, R. C. Chen (eds.), *Radiation Therapy for Genitourinary Malignancies*, Practical Guides in Radiation Oncology,
https://doi.org/10.1007/978-3-030-65137-4_6

6.1 Introduction

- The goal of brachytherapy is to deliver ablative doses of radiation directly to a tumor with relative sparing of surrounding normal tissues by placing the radioactive source in close proximity to the tumor.
- High dose rate (HDR) brachytherapy is the use of radioactive isotopes to deliver radiation dose at a rate ≥20 cGy/min (12 Gy/h, usually much higher) [1]. It is performed by temporarily inserting a radioactive source through catheters that are directly inserted in a tumor via a remote afterloader. The total dose is delivered over the course of one or several fractions—either as a single implant or multiple implants.
- In prostate cancer, HDR brachytherapy is commonly used as monotherapy in men with low and favorable intermediate risk prostate cancer, as a boost when combined with external beam radiation therapy (EBRT) for men with unfavorable intermediate or high risk prostate cancer, or as salvage local therapy in men with local recurrence after prior curative-intent radiotherapy [2].
- Biochemical and clinical outcomes with HDR brachytherapy are similar to those seen with surgery and EBRT [3–7].
- In this chapter, we will discuss the history and rationale for prostate HDR brachytherapy, key anatomy, optimal patient selection, implantation and treatment delivery considerations, treatment-related toxicity, and patient follow-up considerations.

6.2 History of Prostate HDR Brachytherapy

- Prostate HDR was pioneered in the late 1980s and early 1990s as a boost treatment to EBRT in men with intermediate and high-risk prostate cancer at multiple centers across the world [8–10]. These regimens used 2–4 fractions delivered using 1–2 implants.
- Following the encouraging outcomes seen with HDR boost, HDR as monotherapy was pioneered at Osaka University, Japan, in the mid-1990s. This initial regi-

men consisted of one implant and a subsequent 5-day hospitalization. Patients received 48 Gy in 8 fractions or 54 Gy in 9 fractions delivered twice daily >6 h apart [11]. Around this time, 4 and 6 fraction regimens were also developed [12–14].

- Like other forms of prostate cancer radiation therapy, there has been a trend toward the use of more hypofractionated regimens for monotherapy and boost treatment delivery. Current regimens are delivered using 1–2 implants (delivering 1–2 fractions per implant) as outpatient procedures.
- Initial prostate HDR brachytherapy strategies employed ultrasound or CT-based treatment planning, but MRI has become increasingly available for contouring and treatment planning.
- Salvage local therapy for locally radiorecurrent disease after initial curative-intent radiation represents the most novel role of prostate HDR brachytherapy and is actively being studied.

6.3 Rationale for Prostate HDR Brachytherapy

- The initial rationale for the use of HDR brachytherapy was to overcome the variability of dosimetry seen with low dose rate (LDR) brachytherapy due to seed displacement/misplacement. Given the relatively fixed nature of the catheters and the post-implantation plan optimization, the radiation dose could be reliably delivered according to the treatment plan. Additionally, the rapid complete dose delivery of HDR was hypothesized to offer a radiobiologic advantage in the setting of prostate cancer, which has a low alpha/beta ratio.
- Both LDR and HDR brachytherapy have dosimetric advantages over EBRT. Comparative series suggest more consistent dosimetry with HDR compared to LDR [15, 16]. A dosimetric comparison from a randomized trial demonstrated improved urethral and rectal dosimetry with HDR [17] compared to LDR. Additionally, HDR may allow for improved coverage of extracapsular extension and seminal vesicle involvement compared to LDR [18].
- Retrospective comparisons suggest similar biochemical control with LDR and fractionated HDR but less severe urinary and bowel toxicity and similar or decreased sexual toxicity with HDR [13, 19, 20].
- A small Phase II randomized pilot study of 31 patients developed through CHU de Quebec-Universite Laval compared definitive single fraction HDR with LDR. HDR demonstrated less severe detriment and more rapid resolution in International Prostate Symptom Score (IPSS). Additionally, the HDR group had improved IPSS and Expanded Prostate Cancer Index Composite (EPIC)-26 urinary incontinence scores compared to the LDR group in the first year [21]. However, as discussed below, single fraction HDR may not be the optimal form of HDR monotherapy due to a higher risk of recurrence compared to fractionated HDR.

- Several trials are ongoing comparing definitive HDR and LDR brachytherapy (NCT02692105, NCT02960087, NCT03426748, NCT02628041, NCT02960087).
- Disadvantages to HDR include:
  - Compared to EBRT, HDR requires a surgical procedure. In fact, depending on the regimen that is used, multiple implantation surgical procedures may be required, which increases the risk of complications from anesthesia and the implant procedures themselves (e.g., infection). This contrasts with LDR, which requires only a single implant procedure. However, the current NCCN guideline-endorsed HDR regimens are 13.5 Gy × 2 fractions as monotherapy and 15 Gy × 1 as a boost, decreasing the number of treatments/implants [2].
  - Compared to LDR, there are higher initial capital costs (i.e., to purchase the remote-afterloader system and building a shielded room). However, this can be mitigated by the ability to use the remote-afterloader system and shielded room for many patients with various malignancies.
  - From a staffing perspective, HDR typically requires more time and resources than LDR.

6.4 Pertinent Anatomy for Prostate HDR Brachytherapy

- Comprehensive understanding of the key anatomic structures and their appearance on the various imaging modalities is critical to deliver safe and effective HDR brachytherapy. Similar to other forms of radiation therapy, these include the urethra, rectum, bladder neck, neurovascular tissue, external urethral sphincter, and penile bulb. Similar to LDR brachytherapy, the pubic arch, formed by the inferior rami and pubis, should be identified as it may lead to interference during the transperineal implantation procedure, although this is typically a lesser concern than with LDR.
- The brachytherapist must have comfort with identifying and delineating these anatomic structures prior to the implant, intraoperatively during the implantation and during treatment planning in the axial and sagittal dimensions.
- Pre-operative MRI is particularly helpful in preparing and strategizing for the implant in several ways:
  - It can identify sites of gross extracapsular extension (ECE) and seminal vesicle involvement (SVI), which can be incorporated into the overall treatment plan and implant procedure and brachytherapy treatment.
  - MRI can aid in identifying a prominent median lobe.
  - MRI can better identify anteriorly located tumors which may require modification of the brachytherapy implant approach for appropriate coverage.
  - Some centers are incorporating preoperative MRI or an MRI during the implantation or treatment planning into the workflow to better delineate the boundaries of the prostate, particularly at the apex in order to spare the external urethral sphincter, which may be associated with urinary toxicity.

  - Some institutions are using gross tumor noted on MRI to create a focal simultaneous integrated boost [22].
- Please refer to Chap. 2 for a detailed discussion about functional and imaging anatomy relevant for prostate cancer radiotherapy. Chapter 5 also discusses the use of MRI with LDR brachytherapy in detail. We discuss the use of MRI for treatment planning with HDR brachytherapy as follows.

6.5 Patient Selection

- The American Brachytherapy Society has consensus guidelines that can be used as a tool for patient selection [23].
- Table 6.1 describes selection criteria for HDR brachytherapy.
- It is important to note that many of the criteria used to select for HDR brachytherapy are extrapolated from those used for LDR brachytherapy. We discuss some of these considerations in Table 6.1.

Table 6.1 Selection criteria for prostate HDR brachytherapy

Selection criteria	Comments
Optimal candidates	
HDR monotherapy: Low risk and favorable intermediate risk prostate cancer patients	At many institutions, select patients with unfavorable intermediate risk may also be included as long as there is no MRI evidence of unencompassable extracapsular extension (ECE) or seminal vesicle invasion (SVI)
HDR boost: Unfavorable intermediate risk and high risk prostate cancer patients	Patients with low and favorable intermediate risk prostate cancer who have unexpected ECE that cannot be encompassed with an implant or unexpected SVI on MRI are also candidates for HDR as a boost
Limited obstructive urinary symptoms	Frequently used cutoffs for this include an IPSS score $\leq$20 and a post-void residual urine $\geq$100 cc
Life expectancy $\geq$10 years	
Limited comorbidity burden	
Relative contraindications	
Prior transurethral resection of the prostate (TURP)	TURP has traditionally been considered a relative contraindication in LDR brachytherapy due to the difficulty of placing seeds in the TURP defect as well as reports of increased urinary obstruction [24–26]. These concerns carried over to HDR brachytherapy and were confirmed in early HDR series that showed increased toxicity in patients treated with prior TURP [10]. However, more recent studies show no difference in toxicity between patients with and without a history of TURP treated with HDR brachytherapy [27, 28].

(continued)

Table 6.1 (continued)

Selection criteria	Comments
Prostate gland size >60 cc	Large gland size has been considered a relative contraindication in LDR brachytherapy due to concern for pubic arch interference resulting in potentially compromised coverage and due to increased urinary toxicity [24, 29]. Pubic arch interference can be overcome in HDR brachytherapy by using a free hand or mobile template approach as opposed to a fixed stepper-based approach [30]. Furthermore, recent studies in HDR brachytherapy show no difference in dosimetric coverage, biochemical control, or urinary toxicity in men with a large prostate [31–34].
Moderate to severe urinary symptoms	Typically defined as IPSS >20, high pre-treatment urinary symptoms have been considered a relative contraindication in LDR brachytherapy due to concern for increased post-treatment urinary retention [24, 35, 36]. Similar to prior TURP and large gland size, a relative contraindication for patients with elevated baseline urinary symptoms were carried over from LDR to HDR. However, recent studies in HDR brachytherapy show no difference in post-implant urinary toxicity in men with high baseline urinary symptoms compared to those with limited symptoms [37–39].
Large median lobe	Median lobe hyperplasia is considered a relative contraindication due to concerns for increased risk of post-implant urinary retention as well as concerns over difficulty implanting intravesicular tissue [40]. One small study showed adequate coverage of the gland, but with high levels of post implant toxicity [41]. Another small study showed a numerical but no statistically significant increase in urinary post-implant toxicity in men with enlarged median lobes [42].
Prior radiotherapy	Salvage HDR is an emerging treatment modality for radiorecurrent prostate cancer. See Sect. 6.14. Salvage prostate HDR brachytherapy for local recurrence after curative-intent radiotherapy below. Prior dose to the prostate, rectum, and bladder will be important considerations in any patient with a history of prior radiation.
Anticoagulation use (potential bleeding risk)	There are few men who absolutely cannot be off anticoagulation, and therefore the brachytherapist should work with the patient's care team to determine whether anticoagulation can be temporarily held.
Inflammatory bowel disease (IBD)	Those with inflammatory bowel disease may be at risk of increased acute and late toxicity after radiation-based therapy [43]. There are small, single institutional experiences reported in LDR brachytherapy with mixed bowel toxicity results [44, 45]. There are no such series with HDR brachytherapy, and some advocate for the use of HDR brachytherapy in patients with IBD due to the potentially improved rectal sparing.
Generally absolute contraindications	
Inability to tolerate any form of anesthesia	
Nodal or distant metastases	
Pre-existing rectal fistula	

6.6 Pre-operative Assessments and Procedures

- Patients should be counseled about the risk and benefits of treatment and alternatives to HDR brachytherapy.
- Staging work-up should be completed according to NCCN guidelines [2].
- As discussed above, preoperative MRI can help with implant/treatment planning.
- A volume study can be conducted prior to the implant procedure. The volume study is critical for LDR brachytherapy when pre-implant treatment planning methods are used but is less critical for HDR. In the setting of HDR, it may help direct needle placement or identify anatomic concerns that may make the implant technically difficult or impossible (i.e., pubic arch interference, large gland size, large median lobe, excessive calcifications). Many clinicians choose to omit the volume study for prostate HDR brachytherapy.
- The brachytherapist should work with the patient's care team (i.e., primary care physician and/or cardiologist) and anesthesia team to obtain preoperative clearance for the selected form of anesthesia and the implant procedure.
- Anticoagulation should be held prior to the surgical procedure based on recommendations from the provider(s) managing the anticoagulation. Each case is unique and requires clinical judgment in determining the duration. Antiplatelet therapy can be held as well, but the incremental risk of bleeding is relatively low.
- Some centers use tamsulosin prophylactically beginning ~1 week prior to the implant to help with acute urinary symptoms from the implant procedure and treatment. Similarly, some centers use prophylactic phospodiesterase inhibitors to prevent erectile dysfunction. However, there are no data available that suggest these practices effectively reduce the risk of toxicity in these domains, and some centers choose not to use prophylactic medications.
- Fleets enemas can be used the night prior to the procedure and morning of the procedure to improve visualization of the prostate under transrectal ultrasound.

6.7 Operative Procedure

- Preoperative antibiotics can be delivered in the operating room. Intravenous cefazoloin × 1 prior to the procedure is a common choice for this purpose. For patients with an allergy, a single dose of clindamycin can be used.
- The patient is then placed under anesthesia. Many centers use general anesthesia, while other centers use a spinal block or epidural anesthesia. For centers with CT or MRI-based post-implant planning, a spinal nerve block or spinal epidural can limit discomfort with adjustments and potentially reduce the risk of displacement. However, the recovery of lower extremity neurologic function after the procedure may take some time and delay discharge if only a single fraction is being delivered. A spinal epidural may offer more durable pain control for patients who are being admitted overnight for multiple fractions. Ultimately, local workflow and unique patient considerations should be used to determine the optimal form of anesthesia.

- Positioning:
  - Place the patient into the dorsal lithotomy position. The goal is to begin the implant with the knees and hips at 90° flexion using stirrups. Caution should be taken in patients with arthritic conditions and one can consider positioning such patients while awake when possible.
  - Ensure that the patient is in the center of the table laterally, and there is no roll or yaw translational rotation.
- Scrub, prep, and drape procedural area including lower abdomen, inner thighs, perineum, penis. Ensure adequate sterilization, visualization, and access for implantation to the transperineal region posterior to the pubic arch to the anus. However, brachytherapy is not a sterile procedure.
- Insert Foley catheter into the urethra. There is no agreed upon ideal Foley size. ABS guidelines recommend using the smallest gauge catheter [23]. This minimizes distortion of the urethra, which may be particularly important for smaller glands. A 12F catheter can be used for this purpose. Another option used at multiple centers is the use of a 16F catheter. The Foley bulb can be filled with diluted contrast (i.e., 1 cc isovue and 6 cc sterile water) to help with subsequent treatment planning if using CT-based planning.
- Fill the bladder in order to allow appropriate visualization of the bladder neck. 120 cc normal saline is a common choice.
- Immobilize the scrotum and penis out of the perineal implant field. A sterile adhesive surgical drape can be used, or a wet surgical towel tucked into the inguinal folds to elevate the scrotum away from the perineum.
- Place the transrectal ultrasound into the anus and visualize the prostate in the axial and sagittal dimensions.
  - Evaluate the prostate size and dimensions and ensure the posterior aspect of the prostate is parallel to the ultrasound probe and the urethra is as midline as anatomically possible on axial ultrasound over the course of the prostate.
  - Evaluate for any unexpected anatomy.
  - Evaluate the rectal wall anatomy (i.e., thickened rectal wall, anterior protrusion of the rectum near the prostate apex that must be avoided with the implant).
  - Assess for a large median lobe.
  - Follow the urethral trajectory to plan for any special considerations during the implant for a deviating urethra within the prostate.
- Some institutions, particularly those using CT-based planning, place fiducial markers at the base and/or apex to help with target delineation as well as to confirm no displacement of the implant at the time of treatment. This can be placed using a transperineal approach.
- For centers using ultrasound-based planning, a stepper-based system with a grid template is typically used. This fixed set up (similar to the LDR setup) allows for intraoperative treatment planning. Other institutions use a technique in which a mobile perineal template is held against the perineum to guide and space the catheters. Finally, other institutions use no template at all for catheter placement but use putty to immobilize the catheters at the end of the procedure. The free

hand and mobile template techniques allow for more freedom to change the angles of catheter insertion to allow for implanting larger glands and in patients with more narrow pubic arches.

- Brachytherapy catheter placement
  - Progression from anterior to posterior is commonly done to avoid ultrasound artifact from catheters already in place.
  - When placing the catheters, always "follow" the catheters as you place them with the ultrasound through the perineum, into the subcutaneous tissues inferior to the prostate, past the bulbar urethra, into the prostate, and up to the bladder neck. This allows the brachytherapist to avoid trauma to critical structures such as the urethra and rectum.
  - Be very cautious when placing the medial catheters in the area of the bulbar urethra to avoid urethral perforation. If a catheter appears to perforate the urethra at any time, remove it and replace it.
  - Visualize the positioning of the catheters in axial and sagittal dimensions to ensure appropriate placement.
  - As more catheters are placed, the prostate tends to be deflected superiorly from the pressure. Continuously ensure that all previously placed catheters remain at the optimal depth and the template is tight against the skin.
  - Be cautious to avoid anterior rectal protrusion near the apex when placing the posterior catheters. Posterior pressure on the TRUS probe can help displace this.
  - The goal is to have catheters 0.7–1 cm apart and distributed throughout the prostate (and proximal seminal vesicles if determined to be at risk). Figures 6.1 and 6.2 depict an example of appropriate catheter placement on CT and MRI, respectively.
  - During placement, take any ECE or SVI identified on pre-operative or intra-operative imaging into consideration to ensure adequate coverage.
  - If a rectal spacer is planned to be used, this can be placed after completion of catheter placement to avoid artifact from the spacer making visualization difficult, as well as to avoid perforation of the spacer with catheters. If multiple implant procedures are indicated, rectal spacer placement may make subsequent procedures difficult (inability to clearly see the prostate on ultrasound).
- There can be displacement of the catheters when the patient's legs are brought down to the supine position at the end of the procedure. To assess this, the legs can be brought down past flexion with the ultrasound still in place. Additionally, if cystoscopy or fluoroscopy are being used post-treatment, these can be performed with the legs down as well. The catheters can be adjusted based on any changes noted during these evaluations.
- Upon completion of the implant, if using post-implant planning and treatment delivery (i.e., CT or MRI-based planning), the template is sutured to the skin to minimize the risk of displacement with movement. At least a suture in all four corners of the implant should be used. Suturing to the skin is not necessary if the patient will not be moved for these later aspects of treatment (i.e., if intraoperative ultrasound-based planning is used).

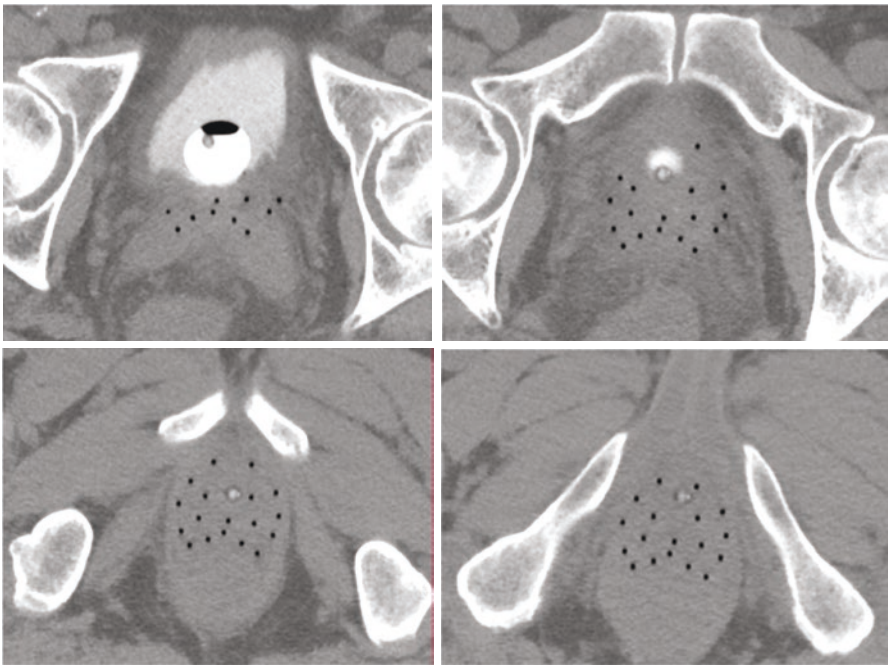

Fig. 6.1 Catheter placement at seminal vesicles, prostate base, mid and distal gland on CT

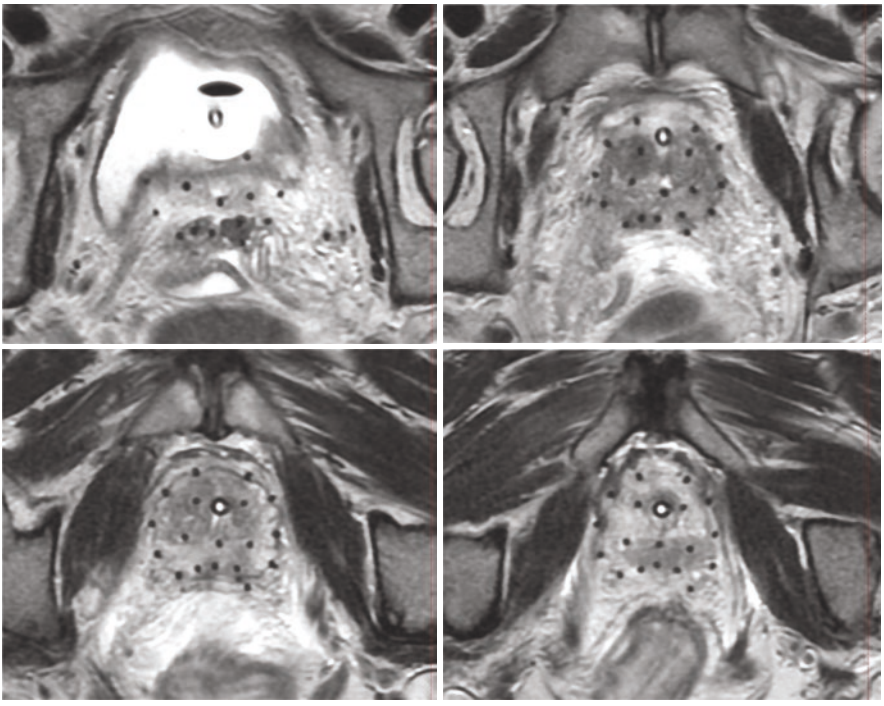

Fig. 6.2 Catheter placement at seminal vesicles, prostate base, mid and distal gland on MRI

- Some institutions perform a secondary imaging modality to confirm appropriate placement of catheters (i.e., fluoroscopy). Alternatively, cystoscopy can be performed in collaboration with our urology colleagues after all the catheters are placed. During cystoscopy, one can evaluate for any urethral perforation as well as ensure the catheters are at the optimal depth at the bladder neck. A sign that the catheters are at the appropriate depth is evidence of bladder mucosal "tenting" without perforation at the bladder neck on cystoscopy. This is seen by retroflexing the cystoscope.
- At centers with intraoperative treatment planning and delivery workflows, these occur in the OR and then implant is removed.
- At centers with post-operative treatment planning. The patient is awoken from anesthesia with the catheters still in place for post-anesthesia recovery and subsequent treatment planning and delivery.

6.8 Treatment Planning

- There are two primary treatment planning approaches for prostate HDR brachytherapy:
  - Ultrasound-based planning (intraoperative planning).
  - CT-based planning (post-implant planning).
- Both treatment planning approaches have advantages and disadvantages and are discussed in detail below.
- Ultrasound-based planning [46]
  - *Technique*: At the conclusion of the implant, there is an immediate transition to the planning process. TRUS images are obtained and critical structures (prostate, urethra, bladder wall, and rectal wall) are contoured (similar to the delineation defined below). Catheters are reconstructed, and anatomy-based inverse planning is used to generate an optimized plan. The afterloader is connected to the respected catheters and treatment delivered with the TRUS probe in place. After treatment delivery, the catheters are removed, the anesthesia is reversed, and the patient is transferred to post-anesthesia recovery. The entire process takes about 60–120 min.
  - *Advantages*: Intraoperative planning allows minimization of anatomic changes from edema and real-time imaging during planning. There is no/limited patient transfer, which minimizes the risk of catheter displacement. This also allows for efficient utilization of time and resources. Finally, TRUS provides excellent soft tissue delineation for prostate contouring.
  - *Disadvantages*: Ultrasound-based intraoperative planning is best done with all steps in the same room. This necessitates either an OR with appropriate shielding, or anesthesia delivery in an HDR suite. This process also relies on high quality ultrasound imaging, which may be difficult to obtain in patients with calcifications, or other artifacts. Finally, it can be difficult to identify the prostate apex on ultrasound [47, 48].
- CT-based planning
  - *Technique*: At the conclusion of the implant, the catheters/template are fixed to the perineum and the patient proceeds to post-anesthesia recovery.

- After completion of post-anesthesia recovery, the patient undergoes CT simulation in the supine position to obtain the image dataset for planning. 1.5–2 mm image slices are obtained from above the bladder to below the template. During CT, the bladder is typically filled with dilute contrast to visualize the bladder neck (2 cc isovue and 28 cc normal saline is an option to allow contrast between the Foley bulb, prostate, and filled bladder). Additionally, ensure that the Foley bulb is pulled down to the bladder neck to aid in treatment planning.

  There are several aspects for the brachytherapist to review at the time of CT simulation. If the brachytherapy catheters are advanced too cranially (i.e., into the bladder) or are too shallow, adjustments can be made to ensure optimal depth. Confirmation of appropriate spacing between catheters (~0.7–1 cm), avoidance of the urethra and rectum, and adequate coverage of the prostate and seminal vesicles are also important to assess during CT simulation.

  Upon completion of any adjustments, the catheters should be marked with a pen/marker to be able to assess for movement prior to the subsequent treatment delivery.

  Of note, both plastic and metal catheters are available for implantation. Plastic catheters cause less CT artifact than metal catheters and can allow for easier target and normal tissue delineation.
- The catheters are then digitized by the medical physicist on the CT and the target and organs at risk (OARs) are delineated by the physician (discussed below).
- Treatment planning is performed using inverse planning. There are resources to help improve treatment planning efficiency [15].
- *Advantages*: CT-based planning minimizes OR procedure time, which may be important for centers that do not have a brachytherapy suite and utilize the general OR resources.
- *Disadvantages*: With ultrasound-based planning, the patient can undergo implantation, treatment planning, treatment, and removal while under anesthesia. With CT-based planning, most workflows require the patient to wake up with the catheters in place and the patient remains awake during treatment planning and delivery and catheter removal. This can lead to more pain from the patient's perspective (although this can be managed with pain medications or spinal nerve block) and makes for a longer treatment day. As part of this, extra resources are needed in the clinic (nursing staff, availability on the CT simulator). Additionally, the soft tissues of the prostate can be difficult to identify on CT due to the catheters, particularly the apex. A major disadvantage is that there could be implant displacement due to patient transfers from surgical table to CT sim to treatment table. This risk requires multiple imaging studies to exclude, and if it occurs, it requires multiple potential readjustments to correct.

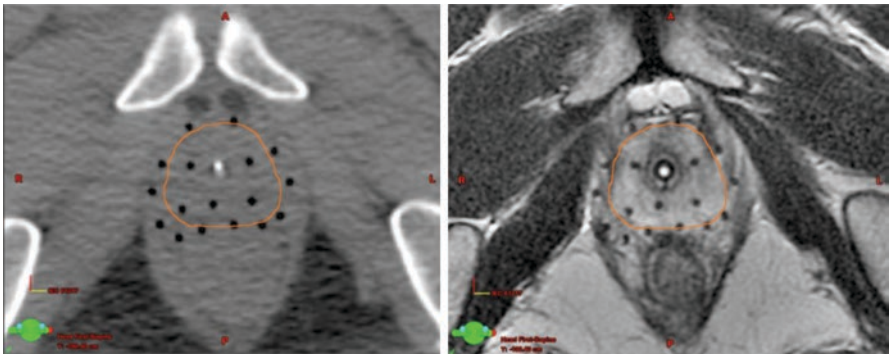

Fig. 6.3 Implanted catheters visualized via CT (left) vs. MRI (right) demonstrating enhanced soft tissue visualization and prostate delineation with MRI

- MRI-based Planning
  - Some institutions have transitioned to using MRI-based planning. This can be performed either with a MRI simulator or separate T2 MRI after implant and CT simulation to help with target delineation. The improved visualization of the prostate, rectum, and bladder neck allow for more precise target and OAR delineation. The clinical target volume (CTV) contents remain the same. One can consider the same or smaller planning target volume (PTV) margins due to improved target delineation compared to CT alone. Several series have compared CT and MRI-based planning and demonstrated that MRI-based planning is associated with a smaller target volume and improved OAR doses [49, 50].
  - An example of catheter distribution seen on MRI is shown in Fig. 6.2.
  - Figure 6.3 displays a comparison in prostate visualization utilizing CT imaging and MRI imaging.
- An example of the finalized HDR brachytherapy treatment plan performed with MRI imaging is shown in Fig. 6.4.

6.9 Target and Organ at Risk Delineation

- There is no consensus regarding CTV, PTV, or treatment margins.
  - The CTV is typically the prostate with or without the seminal vesicles. All areas of extracapsular extension and seminal vesicle invasion should be encompassed in the CTV.
  - The role and optimal PTV expansion are unknown. In the EBRT setting, the PTV is used for set-up uncertainties, which are less of an issue with HDR. At many institutions, the CTV = PTV. At other institutions, an asymmetric expansion of 0–5 mm is added to the CTV, limiting expansions in the area of OARs (i.e., rectum and bladder neck).

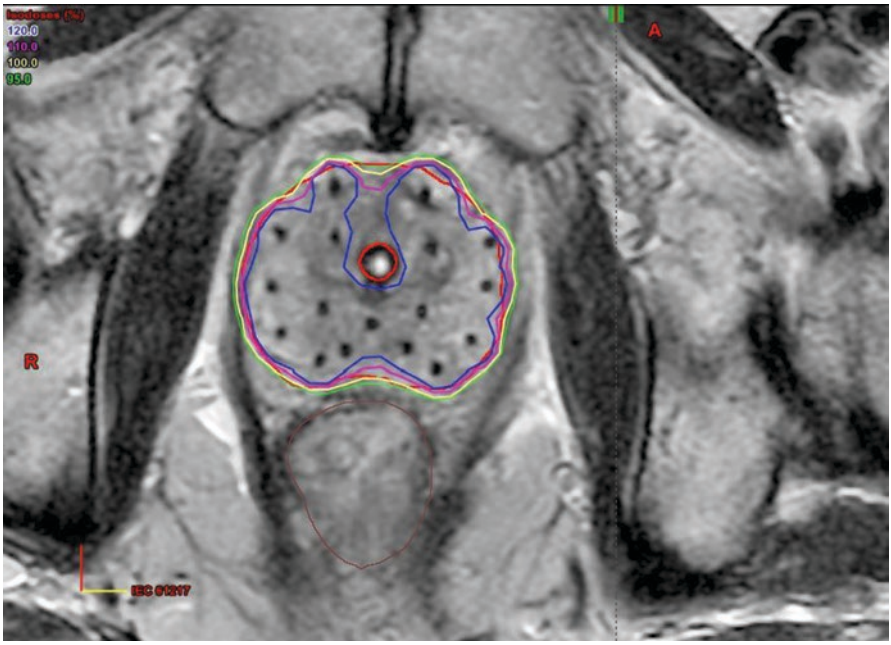

Fig. 6.4 Catheter placement at prostate mid-gland on MRI with isodose lines (in % of prescription dose of 13.5 Gy)

- The knowledge about the patient's anatomy and the relative anatomic placement of the catheters during the implant should be used in target delineation.
- The rectum, urethra, and bladder should be contoured as OARs.
- The preoperative MRI can be fused to aid in target delineation. However, due to displacement and distortion of the normal prostate position from the implant, the fusion can be difficult. It can be used side by side to help guide target delineation when helpful, particularly in cases where a clear GTV is identified (i.e., when a tumor can be visualized on MRI).
- An example of catheter distribution seen on CT is shown in Fig. 6.1.

6.10 Treatment Delivery Using the Remote Afterloading System

- The patient is treated in a shielded room with the afterloader. In the setting of intraoperative planning and treatment delivery, this is conducted in a shielded OR. Other centers do this in a shielded room in the radiation oncology department.
- The remote afterloading system is connected to the catheters with appropriate quality assurance (including but not limited to): double-check of catheter and remote–afterloader connections, and visual inspection of template and catheters. Some centers conduct fluoroscopy to confirm the appropriate positioning of the

catheters has been maintained if the patient has been moved. Treatment is delivered under physicist and physician supervision.

- If only a single fraction is to be delivered after the implant, then the patient moves on to catheter removal and discharge as below. If the patient is to receive multiple fractions with the same implant, these should be delivered a minimum of 6 h apart. At some centers, 2 fractions are delivered the same day. Other centers require overnight admissions if the 2 fractions will be delivered on separate days or more than 2 fractions are planned. In this scenario, the inpatient team must be educated on the importance of minimizing the risk of catheter displacement, and the positioning should be assessed prior to each treatment.
- Upon completion of the brachytherapy fraction(s) to be delivered with the implant, catheters are removed with appropriate analgesia (e.g., at Loyola IV dilaudid is used) and hemostasis ensured.
- Then, the bladder is typically filled and the Foley is removed. Following spontaneous voiding (approximately how much the bladder was filled with), the patient is sent home.
- Some institutions discharge patients with prophylactic medications (e.g., tamsulosin), antibiotics (e.g., 3 days of ciprofloxacin), and/or an anti-inflammatory medication (e.g., 2 weeks of naproxen). However, like the discussion about prophylactic medications above, other centers do not prescribe these medications, and there are no data demonstrating the need or efficacy of this practice. Opioid pain medications are not usually required.

6.11 Dose and Fractionation Considerations

- There have been many different dose/fractionations used with prostate HDR, both as monotherapy and as a boost. There is no current consensus on the ideal dose/fractionation, but most institutions are moving toward the more hypofractionated regimens (i.e., 13.5 Gy × 2 for monotherapy, 15 Gy × 1 as a boost).
- Monotherapy dose/fractionation options:
  - A randomized trial compared 13.5 Gy × 2 vs. 19 Gy × 1 as monotherapy and demonstrated inferior biochemical and local control with single fraction HDR. Therefore, single fraction HDR for monotherapy should be avoided [51].
  - Monotherapy Dose/fractionations supported by guidelines include [2, 23]
    34 Gy in 4 fractions
    36–38 Gy in 4 fractions
    31.5 Gy in 3 fractions
    26–27 Gy in 2 fractions
    Current NCCN Guidelines recommend [2]:
    - 27 Gy in 2 fractions
    - 34 Gy in 4 fractions
  - Interfraction interval:
    Fractions delivered BID as part of the same implant should be delivered ≥6 h apart.

Fractions delivered as separate implants are usually delivered 1–2 weeks apart. The duration between implants does not appear to be associated with toxicity [52].

- Boost dose/fractionations supported by guidelines include [2, 23]:
  - 15 Gy in 3 fractions
  - 11–22 Gy in 2 fractions
  - 12–15 Gy in 1 fraction
  - Current NCCN guidelines recommend [2]:
    15 Gy in 1 fraction
    21.5 Gy in 2 fractions
- HDR Sequencing with EBRT: HDR boost can be delivered before, during, or after external beam radiotherapy. There are no strong data demonstrating any clinical impact to sequencing.
  - The THEPCA trial (NCT02618161) was a trial that compared HDR before EBRT with HDR after EBRT, but the results are not yet available [53].
  - A common method is to deliver the HDR boost ~2 weeks prior to EBRT in order to manage brachytherapy-related toxicity during EBRT as well as place fiducial markers.
- EBRT Dose: Typically, 45–50.4 Gy in 25–28 fractions is used. A hypofractionated option is 37.5 Gy in 15 fractions [54]. Studies are ongoing testing ultra-hypofractionated supplemental EBRT doses (i.e., 5 Gy × 5) (NCT04236752). Depending on the risk of pelvic nodal involvement, the pelvic lymph nodes can be included.
- Dose Constraints
  - Given the significant heterogeneity in dose/fractionation schedules used in prostate HDR brachytherapy, no consensus guidelines currently exist for DVH planning goals. Consequently, there is variability among institutions in regard to the planning goals.
  - Several studies have suggested that larger volumes of the urethra receiving higher doses are correlated with increased genitourinary toxicity [55–57].
  - The GEC/ESTRO consensus guidelines provide constraints based on the EQD2 (Table 6.2) [54].
  - Examples of planning goals used in RTOG, the Sunnybrook and the CHU de Quebec-Universite Laval Randomized Trials are listed in Table 6.2 [21, 51, 58, 59].

6.12 Toxicity

- In general, acute and late toxicities from prostate HDR brachytherapy are similar to other forms of radiation therapy in nature and frequency. The exceptions to this are the risks of the operative implant procedure.
- It is frequent for patients receiving monotherapy to have very limited subjective acute toxicities after the first implant, but a significant increase after the second implant.

Table 6.2 HDR brachytherapy planning goals from GEC/ESTRO and Key prospective trials

	Planning goals		
Target	GEC/ESTRO [54]	Sunnybrook and CHU de Quebec-Universite Laval randomized trials [21, 51]	RTOG 0321 and RTOG 0924 [58, 59]
PTV	V100 ≥ 95%	V100 > 95% D90 between 105% and 115% V150 ≤ 35% V200 ≤ 12%	V100 ≥ 90%
Bladder	None specified	None specified	V75 < 1 cc
Urethra	D0.1 cc ≤ 120 Gy EQD2 D10 ≤ 120 Gy EQD2 D30 ≤ 105 Gy EQD2	Max dose <120% D10 < 115%	V125 < 1 cc V150 = 0 cc
Rectum	D2 cc ≤ 75 Gy EQD2	Max dose <90% V80 < 0.2 cc	V75 < 1 cc

- The risk of acute urinary retention after the implantation procedure is ~5% [51, 60–62]. This usually occurs either immediately or within a few days of the implant procedure. It can be managed with a temporary catheter placement until acute inflammation resolves. In this scenario, we frequently add a 5-alpha reductase inhibitor and a steroid to the tamsulosin to help reduce acute inflammation that is contributing to the obstruction.
- Acute hematuria occurs in ~2% of patients [51, 60–62]. This can be managed with temporary urinary catheter placement. In rare severe cases, hospitalization may be indicated as well as continuous bladder irrigation.
- Dysuria and other obstructive symptoms are common, with reported rates ranging from 20% to 60% [60–62]. Management with tamsulosin, naproxen, or phenazopyridine are good first options.
- After approximately 1-month, patients begin noticing improvement in acute urinary toxicities, with most patients returning to baseline ~2 months after treatment [21]. However, it can take upwards of 12 months for patients to have their urinary function return to baseline [63].
- Late genitourinary toxicities include persistent obstructive/irritative urinary symptoms. Late grade 2 GU toxicity occurs in 10–40% of patients [60–62]. Tamsulosin can be continued for obstructive urinary symptoms as needed. In refractory cases, a 5-alpha reductase inhibitor can be considered, and thereafter referral to an urologist for potential surgical options if still bothersome. Late cystitis can lead to irritative symptoms or hematuria. Irritative urinary symptoms can be managed with anticholinergics or phenazopyridine.
- Severe, late, grade 3 urinary toxicities are rare, occurring in <5% of cases [60–62]. Gross hematuria should prompt referral to a urologist. Late strictures are rare and should prompt referral to a urologist.
- Acute and chronic GI toxicity are rare with reported rates of <5% [51, 52, 60–63]. Steroid suppositories can be used for acute or chronic proctitis. Severe proc-

titis is extremely rare. However, if it occurs, consider hyperbaric oxygen, silver nitrate/formaldehyde cauterization, or partial colectomy if refractory.
- Erectile Dysfunction is common, occurring in up to 50% of patients, either acutely due to the trauma from catheter placement or chronically due to radiation-related neurovascular late effects [51, 52, 63]. A phosphodiesterase inhibitor can be used with escalation to a penile pump, penile injection therapy, intraprostatic phosphodiesterase inhibitor therapy as needed.

6.13 Follow-Up

- A short-term follow-up (2–4 weeks) post-implant assessment may be useful to assess for significant post-implant acute toxicity and treat it appropriately.
- Standardized patient and physician reported toxicities tools, including IPSS, EPIC Quality of life forms, and CTCAE can be utilized at each follow-up to standardize treatment-related toxicity assessment and management.
- PSA levels should be taken at regular intervals after treatment to assess biochemical control.
  - PSA bounce occurs in ~25–40% of patients and typically occurs 12–30 months post treatment [64, 65].
  - There is no definite long-term correlation between PSA bounce and biochemical control with HDR [64].
- The PSA kinetics post-HDR are relatively dynamic. The PSA nadir + 2 ng/ml definition of biochemical failure is used for HDR brachytherapy, although many argue that it may not be sensitive after brachytherapy due to the ablative nature of treatment, and may not be specific due to the relatively variable PSA kinetics within the first several years post-HDR. Continually rising PSA levels that approach, meet, or exceed the nadir + 2 ng/ml definition of biochemical recurrence should be evaluated via diagnostic imaging with bone scan, MRI, and/or novel molecular imaging (i.e., fluciclovine, choline, or PSMA PET/CT).

6.14 Salvage Prostate HDR Brachytherapy for Local Recurrence After Curative-Intent Radiotherapy

- Salvage local therapy is an option for select patients with biopsy-proven local recurrences after prior curative-intent radiotherapy [66].
- NCCN provides general guidelines for selection of patients for salvage local therapy.
  - Candidates include those with biopsy-proven, local-only recurrent disease who have no nodal or metastatic disease on restaging imaging and no significant morbidity from prior radiotherapy [2].
- Both LDR [67–77] and HDR [77–85] brachytherapy have been used in the treatment of local recurrence of prostate cancer after either EBRT or brachytherapy.

- Data describing outcomes with salvage HDR brachytherapy are primarily retrospective. A single phase II trial has reported results with 5-year biochemical relapse-free, distant metastases-free and cause-specific survival of 68.5%, 81.5%, and 90.3% respectively, and with 1 patient developing grade 3 GU toxicity and no grade 3 GI and no grade 4 toxicities [85].
- Pre-salvage brachytherapy MRI can delineate the area of recurrence for brachytherapy planning [86].
- When possible, novel molecular imaging (e.g., fluciclovine PET scan) should be performed to rule-out patients for distant metastatic disease [87].
- Use of rectal spacer may be considered to reduce rectal dose from re-irradiation [88, 89].
- There is no standard dose/fractionation for salvage HDR. Some reported regimens include 8 Gy × 4 fractions, 6 Gy × 6 fractions, and 10–13.5 Gy × 2 [79, 80, 82, 83, 85, 89].
- Some institutions target the whole gland, while others perform focal salvage brachytherapy.
- *Focal salvage brachytherapy*:
  - In the setting of focally recurrent prostate cancer, often the recurrent disease is not detected in all parts of the prostate gland.
  - Focal brachytherapy to the specific area of disease recurrence may allow recurrent disease control while minimizing toxicity by avoiding repeat irradiation to the entire gland [90, 91].
  - New imaging techniques such as multiparametric MRI, saturation biopsies, and novel molecular PET imaging may allow better detection of specific disease location within the gland [87].
  - There have been a few phase I/II trials as well as retrospective studies investigating focal HDR brachytherapy [91–97]. Murgic et al. in a prospective trial of 15 patients with locally recurrent prostate cancer after EBRT delivered 27 Gy divided in 2 implants to CTV defined as quadrant of prostate with MRI-visible recurrent lesion, showing 3-year PSA failure-free rate of 61%, 1 patient with grade 3 GU toxicity and no changes in EPIC composite bowel or urinary scores [91].

6.15 Conclusions

- Prostate HDR brachytherapy remains an effective component of prostate cancer care as a method of optimal conformal dose-escalation.
- There are a variety of clinical scenarios in which HDR brachytherapy is an appropriate treatment option, including in the definitive setting as monotherapy or in combination with androgen deprivation therapy and/or EBRT, as well as in the salvage setting for local recurrence after prior curative-intent radiotherapy.
- In each of these settings, appropriate patient selection and attention to treatment preparation, technique, and planning are crucial to the delivery of successful brachytherapy.

References

1. Erickson BA, Bittner NH, Chadha M, Mourtada F, Demanes DJ (2017) The American College of Radiology and the American Brachytherapy Society practice parameter for the performance of radionuclide-based high-dose-rate brachytherapy. Brachytherapy 16(1):75–84. https://doi.org/10.1016/j.brachy.2016.05.006
2. National Comprehensive Cancer Network (2020) NCCN clinical practice guidelines in oncology (NCCN Guidelines®) prostate cancer 2020 Version 1.2020. National Comprehensive Cancer Network, Fort Washington, PA
3. Chen RC, Basak R, Meyer AM et al (2017) Association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. JAMA 317:1141. https://doi.org/10.1001/jama.2017.1652
4. Grimm P, Billiet I, Bostwick D et al (2012) Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high-risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. BJU Int 109(Suppl 1):22–29. https://doi.org/10.1111/j.1464-410X.2011.10827.
5. Hamdy FC, Donovan JL, Lane JA et al (2016) 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 375(15):1415–1424. https://doi.org/10.1056/NEJMoa1606220
6. Donovan JL, Hamdy FC, Lane JA et al (2016) Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 375(15):1425–1437. https://doi.org/10.1056/NEJMoa1606221
7. Sanda MG, Dunn RL, Michalski J et al (2008) Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 358(12):1250–1261. https://doi.org/10.1056/NEJMoa074311
8. Stromberg J, Martinez A, Gonzalez J et al (1995) Ultrasound-guided high dose rate conformal brachytherapy boost in prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. Int J Radiat Oncol Biol Phys 33(1):161–171. https://doi.org/10.1016/0360-3016(95)00035-w
9. Mate TP, Gottesman JE, Hatton J, Gribble M, Van Hollebeke L (1998) High dose-rate afterloading 192Iridium prostate brachytherapy: feasibility report. Int J Radiat Oncol Biol Phys 41(3):525–533. https://doi.org/10.1016/s0360-3016(98)00097-2
10. Demanes DJ, Rodriguez RR, Schour L, Brandt D, Altieri G (2005) High-dose-rate intensity-modulated brachytherapy with external beam radiotherapy for prostate cancer: California endocurietherapy's 10-year results. Int J Radiat Oncol Biol Phys 61(5):1306–1316. https://doi.org/10.1016/j.ijrobp.2004.08.014
11. Yoshioka Y, Nose T, Yoshida K et al (2000) High-dose-rate interstitial brachytherapy as a monotherapy for localized prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. Int J Radiat Oncol Biol Phys 48(3):675–681. https://doi.org/10.1016/s0360-3016(00)00687-8
12. Martinez AA, Pataki I, Edmundson G, Sebastian E, Brabbins D, Gustafson G (2001) Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: a feasibility report. Int J Radiat Oncol Biol Phys 49(1):61–69. https://doi.org/10.1016/s0360-3016(00)01463-2
13. Martinez AA, Demanes J, Vargas C, Schour L, Ghilezan M, Gustafson GS (2010) High-dose-rate prostate brachytherapy: an excellent accelerated-hypofractionated treatment for favorable prostate cancer. Am J Clin Oncol 33(5):481–488. https://doi.org/10.1097/COC.0b013e3181b9cd2f
14. Martin T, Baltas D, Kurek R et al (2004) 3-D conformal HDR brachytherapy as monotherapy for localized prostate cancer. A pilot study. Strahlenther Onkol 180(4):225–232. https://doi.org/10.1007/s00066-004-1215-4
15. Solanki AA, Mysz ML, Patel R et al (2018) Transitioning from a low-dose-rate to a high-dose-rate prostate brachytherapy program: comparing initial dosimetry and improving work-

flow efficiency through targeted interventions. Adv Radiat Oncol 4(1):103–111. https://doi.org/10.1016/j.adro.2018.10.004
16. White EC, Kamrava MR, Demarco J et al (2013) High-dose-rate prostate brachytherapy consistently results in high quality dosimetry. Int J Radiat Oncol Biol Phys 85(2):543–548. https://doi.org/10.1016/j.ijrobp.2012.03.035
17. Major T, Polgár C, Jorgo K, Stelczer G, Ágoston P (2017) Dosimetric comparison between treatment plans of patients treated with low-dose-rate vs. high-dose-rate interstitial prostate brachytherapy as monotherapy: initial findings of a randomized clinical trial. Brachytherapy 16(3):608–615. https://doi.org/10.1016/j.brachy.2017.02.003
18. Skowronek J (2013) Low-dose-rate or high-dose-rate brachytherapy in treatment of prostate cancer - between options. J Contemp Brachytherapy 5(1):33–41. https://doi.org/10.5114/jcb.2013.34342
19. Hentz C, Mark K, Martin B et al (2017) HDR prostate brachytherapy is associated with lower urinary toxicity and more rapid resolution over the first year compared to LDR brachytherapy. Int J Radiat Oncol 99(2):E238. https://doi.org/10.1016/j.ijrobp.2017.06.1173
20. Grills IS, Martinez AA, Hollander M et al (2004) High dose rate brachytherapy as prostate cancer monotherapy reduces toxicity compared to low dose rate palladium seeds. J Urol 171(3):1098–1104. https://doi.org/10.1097/01.ju.0000113299.34404.22
21. Hathout L, Mahmoud O, Wang Y et al (2019) A phase 2 randomized pilot study comparing high-dose-rate brachytherapy and low-dose-rate brachytherapy as monotherapy in localized prostate cancer. Adv Radiat Oncol 4(4):631–640. https://doi.org/10.1016/j.adro.2019.04.003
22. Carlone M, Rink A, Beiki-Ardakani A et al (2016) MR-guided high-dose-rate (HDR) brachytherapy: simultaneous integrated focal boost to intra-prostatic GTV(s). Brachytherapy 15(2016):S51–S52. https://doi.org/10.1016/j.brachy.2016.04.065
23. Yamada Y, Rogers L, Demanes DJ et al (2012) American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy. Brachytherapy 11(1):20–32. https://doi.org/10.1016/j.brachy.2011.09.008
24. Davis BJ, Horwitz EM, Lee WR et al (2012) American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. Brachytherapy 11(1):6–19. https://doi.org/10.1016/j.brachy.2011.07.005
25. Blasko JC, Ragde H, Grimm PD (1991) Transperineal ultrasound-guided implantation of the prostate: morbidity and complications. Scand J Urol Nephrol Suppl 137:113–118
26. Talcott JA, Clark JA, Stark PC, Mitchell SP (2001) Long-term treatment-related complications of brachytherapy for early prostate cancer: a survey of patients previously treated. J Urol 166:494–499
27. Luo HL, Fang FM, Chuang YC, Chiang PH (2009) Previous transurethral resection of the prostate is not a contraindication to high-dose rate brachytherapy for prostate cancer. BJU Int 104(11):1620–1623. https://doi.org/10.1111/j.1464-410X.2009.08664.
28. Peddada AV, Jennings SB, Faricy PO, Walsh RA, White GA, Monroe AT (2007) Low morbidity following high dose rate brachytherapy in the setting of prior transurethral prostate resection. J Urol 178(5):1963–1967. https://doi.org/10.1016/j.juro.2007.07.028
29. Pham YD, Kittel JA, Reddy CA et al (2016) Outcomes for prostate glands >60 cc treated with low-dose-rate brachytherapy. Brachytherapy 15(2):163–168. https://doi.org/10.1016/j.brachy.2015.12.002
30. Gibbons EP, Smith RP, Beriwal S et al (2009) Overcoming pubic arch interference with free-hand needle placement in men undergoing prostate brachytherapy. Brachytherapy 8:74–78
31. Le H, Rojas A, Alonzi R et al (2013) The influence of prostate volume on outcome after high-dose-rate brachytherapy alone for localized prostate cancer. Int J Radiat Oncol Biol Phys 87(2):270–274. https://doi.org/10.1016/j.ijrobp.2013.05.022
32. Monroe AT, Faricy PO, Jennings SB et al (2008) High-dose-rate brachytherapy for large prostate volumes (> or =50cc)-uncompromised dosimetric coverage and acceptable toxicity. Brachytherapy 7:7–1

33. Press RH, Morgan TM, Cutrell PK et al (2019) Patient-reported health-related quality of life outcomes after HDR brachytherapy between small (<60 cc) and large (≥60 cc) prostate glands. Brachytherapy 18(1):13–21. https://doi.org/10.1016/j.brachy.2018.08.009
34. Harris AA, Martin B, Stang K et al (2018) Impact of prostate gland size ≥60 cc on physician and patient-reported toxicity after high dose rate prostate brachytherapy. Int J Radiat Oncol 102(3):e116. https://doi.org/10.1016/j.ijrobp.2018.07.315
35. Crook J, McLean M, Catton C et al (2002) Factors influencing risk of acute urinary retention after TRUS-guided permanent prostate seed implantation. Int J Radiat Oncol Biol Phys 52:453–460
36. Terk M, Stock R, Stone N (1998) Identification of patients at increased risk for prolonged urinary retention following radioactive seed implantation of the prostate. J Urol 160:1379–1382
37. Morgan TM, Rossi PJ, Cutrell PK et al (2019) High-dose-rate prostate brachytherapy appears safe in patients with high baseline International Prostate Symptom Scores. Brachytherapy 18(6):793–799. https://doi.org/10.1016/j.brachy.2019.06.001
38. Yamada Y, Bhatia S, Zaider M et al (2006) Favorable clinical outcomes of three-dimensional computer-optimized high-dose-rate prostate brachytherapy in the management of localized prostate cancer. Brachytherapy 5:157–164
39. Harris AA, Baldea K, Farooq A, Flanigan R, Harkenrider MM, Solanki AA (2019) Exploring the impact of high baseline IPSS on urinary, bowel, and sexual function in the first year after prostate high dose rate brachytherapy. Brachytherapy 18(3):S75. https://doi.org/10.1016/j.brachy.2019.04.157
40. Pedley ID (2002) Transperineal interstitial permanent prostate brachytherapy for carcinoma of the prostate. Surg Oncol 11(1–2):25–34. https://doi.org/10.1016/s0960-7404(02)00010-5
41. Wallner K, Smathers S, Sutlief S, Corman J, Ellis W (2000) Prostate brachytherapy in patients with median lobe hyperplasia. Int J Cancer 90(3):152–156
42. Amin PP, Naslund M, Vyas S (2011) Permanent brachytherapy of prostates with median lobe hyperplasia. Brachytherapy 10(2011):S89. https://doi.org/10.1016/j.brachy.2011.02.177
43. Song DY, Lawrie WT, Abrams RA et al (2001) Acute and late radiotherapy toxicity in patients with inflammatory bowel disease. Int J Radiat Oncol Biol Phys 51:455–459
44. Pai HH, Keyes M, Morris WJ, Christie J (2013) Toxicity after (125)I prostate brachytherapy in patients with inflammatory bowel disease. Brachytherapy 12(2):126–133. https://doi.org/10.1016/j.brachy.2012.04.008
45. Mohammed W, Hoskin P, Henry A, Gomez-Iturriaga A, Robinson A, Nikapota A (2018) Short-term toxicity of high dose rate brachytherapy in prostate cancer patients with inflammatory bowel disease. Clin Oncol 30(9):534–538. https://doi.org/10.1016/j.clon.2018.06.007
46. Morton GC (2015) Prostate high-dose-rate brachytherapy: transrectal ultrasound based planning, a technical note. Pract Radiat Oncol 5(4):238–240. https://doi.org/10.1016/j.prro.2014.12.009
47. Sandler HM, Bree RL, McLaughlin PW, Grossman HB, Lichter AS (1993) Localization of the prostatic apex for radiation therapy using implanted markers. Int J Radiat Oncol Biol Phys 27(4):915–919. https://doi.org/10.1016/0360-3016(93)90468-b
48. Mitterberger M, Horninger W, Aigner F et al (2010) Ultrasound of the prostate. Cancer Imag 10(1):40–48. https://doi.org/10.1102/1470-7330.2010.0004
49. Saigal K, All S, Potrebko P et al (2019) Incorporating routine magnetic resonance imaging-based planning for the delivery of high-dose-rate brachytherapy for prostate cancer: an evaluation of clinical feasibility and dosimetric outcomes. Cureus 11(2):e4085. https://doi.org/10.1016/j.brachy.2020.09.002
50. Harris AA, Wu M, Deirmenjian JM et al (2020) Computed tomography versus magnetic resonance imaging in high-dose-rate prostate brachytherapy planning: The impact on patient-reported health-related quality of life. Brachytherapy S1538-4721(20):30203–8. https://doi.org/10.1016/j.brachy.2018.04.142
51. Morton G, McGuffin M, Chung HT et al (2020) Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: efficacy results from a randomized

phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. Radiother Oncol 146:90–96
52. Harris AA, Korpics M, Sherwani Z, Farroq F, Baldea K, Flanigan R, Harkenrider M, Solanki AA (2020) Patient and physician reported toxicity with two-fraction definitive high dose rate prostate brachytherapy: the impact of implant interval. J Contemp Brachytherapy 12:216. https://doi.org/10.5114/jcb.2020.96861
53. Palvai S, Harrison M, Shibu Thomas S et al (2015) Timing of High-Dose Rate Brachytherapy With External Beam Radiotherapy in Intermediate and High-Risk Localized Prostate CAncer (THEPCA) patients and its effects on toxicity and quality of life: protocol of a randomized feasibility trial. JMIR Res Protoc 4(2):e49. https://doi.org/10.2196/resprot.4462
54. Hoskin PJ, Colombo A, Henry A et al (2013) GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: an update. Radiother Oncol 107(3):325–332
55. Ghadjar P, Oesch SL, Rentsch CA et al (2014) Late toxicity and five year outcomes after high-dose-rate brachytherapy as a monotherapy for localized prostate cancer. Radiat Oncol 9:122. https://doi.org/10.1186/1748-717X-9-122
56. Hsu IC, Hunt D, Straube W et al (2014) Dosimetric analysis of radiation therapy oncology group 0321: the importance of urethral dose. Pract Radiat Oncol 4(1):27–34. https://doi.org/10.1016/j.prro.2013.02.011
57. Cendales R, Alwers E, Cifuentes J et al (2015) High-dose-rate brachytherapy delivered in two fractions as monotherapy for low-risk prostate cancer. J Contemp Brachytherapy 7(1):10–16. https://doi.org/10.5114/jcb.2015.48838
58. Hsu IC, Bae K, Shinohara K et al (2010) Phase II trial of combined high-dose-rate brachytherapy and external beam radiotherapy for adenocarcinoma of the prostate: preliminary results of RTOG 0321. Int J Radiat Oncol Biol Phys 78(3):751–758. https://doi.org/10.1016/j.ijrobp.2009.08.048
59. Radiation Therapy Oncology Group RTOG 0924. Androgen deprivation therapy and high dose radiotherapy with or without whole-pelvic radiotherapy in unfavorable intermediate or favorable high risk prostate cancer: a phase III randomized trial. https://clinicaltrials.gov/ct2/show/NCT01368588 (identification No. NCT02285855)
60. Morton G, Chung HT, McGuffin M et al (2017) Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: early toxicity and quality-of life results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy. Radiother Oncol 122:87. https://doi.org/10.1016/j.radonc.2016.10.019
61. Jawad MS, Dilworth JT, Gustafson GS et al (2016) Outcomes associated with 3 treatment schedules of high-dose-rate brachytherapy monotherapy for favorable-risk prostate cancer. Int J Radiat Oncol Biol Phys 94(4):657–666. https://doi.org/10.1016/j.ijrobp.2015.10.011
62. Barkati M, Williams SG, Foroudi F et al (2012) High-dose-rate brachytherapy as a monotherapy for favorable-risk prostate cancer: a phase II trial. Int J Radiat Oncol Biol Phys 82(5):1889–1896. https://doi.org/10.1016/j.ijrobp.2010.09.006
63. Gaudet M, Pharand-Charbonneau M, Desrosiers MP, Wright D, Haddad A (2018) Early toxicity and health-related quality of life results of high-dose-rate brachytherapy as monotherapy for low and intermediate-risk prostate cancer. Brachytherapy 17(3):524–529. https://doi.org/10.1016/j.brachy.2018.01.009
64. Åström L, Sandin F, Holmberg L (2018) Good prognosis following a PSA bounce after high dose rate brachytherapy and external radiotherapy in prostate cancer. Radiother Oncol 129(3):561–566. https://doi.org/10.1016/j.radonc.2018.08.011
65. Burchardt W, Skowronek J (2018) Time to PSA rise differentiates the PSA bounce after HDR and LDR brachytherapy of prostate cancer. J Contemp Brachytherapy 10(1):1–9. https://doi.org/10.5114/jcb.2018.73786
66. Tisseverasinghe SA, Crook JM (2018) The role of salvage brachytherapy for local relapse after external beam radiotherapy for prostate cancer. Transl Androl Urol 7(3):414–435
67. Grado GL, Collins JM, Kriegshauser JS et al (1999) Salvage brachytherapy for localized prostate cancer after radiotherapy failure. Urology 53:2–10

68. Wong WW, Buskirk SJ, Schild SE et al (2006) Combined prostate brachytherapy and short-term androgen deprivation therapy as salvage therapy for locally recurrent prostate cancer after external beam irradiation. J Urol 176:2020–2024
69. Aaronson DS, Yamasaki I, Gottschalk A et al (2009) Salvage permanent perineal radioactive-seed implantation for treating recurrence of localized prostate adenocarcinoma after external beam radiotherapy. BJU Int 104:600–604
70. Lee HK, Adams MT, Motta J (2008) Salvage prostate brachytherapy for localized prostate cancer failure after external beam radiation therapy. Brachytherapy 7:17–21
71. Burri RJ, Stone NN, Unger P et al (2010) Long-term outcome and toxicity of salvage brachytherapy for local failure after initial radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 77:1338–1344
72. Moman MR, van der Poel HG, Battermann JJ et al (2010) Treatment outcome and toxicity after salvage 125-I implantation for prostate cancer recurrences after primary 125-I implantation and external beam radiotherapy. Brachytherapy 9:119–125
73. Vargas C, Swartz D, Vashi A et al (2014) Salvage brachytherapy for recurrent prostate cancer. Brachytherapy 13:53–58
74. Nguyen PL, Chen MH, D'Amico AV et al (2007) Magnetic resonance image-guided salvage brachytherapy after radiation in select men who initially presented with favorable-risk prostate cancer. Cancer 110:1485–1492
75. Peters M, Maenhout M, van der Voort van Zyp JRN et al (2014) Focal salvage iodine-125 brachytherapy for prostate cancer recurrences after primary radiotherapy: a retrospective study regarding toxicity, biochemical outcome and quality of life. Radiother Oncol 112:77–82
76. Henríquez I, Sancho G, Hervás A et al (2014) Salvage brachytherapy in prostate local recurrence after radiation therapy: predicting factors for control and toxicity. Radiat Oncol 9:102
77. Kollmeier MA, McBride S, Taggar A et al (2017) Salvage brachytherapy for recurrent prostate cancer after definitive radiation therapy: a comparison of low-dose-rate and high-dose-rate brachytherapy and the importance of prostate-specific antigen doubling time. Brachytherapy 16:1091–1098
78. Tharp M, Hardacre M, Bennett R et al (2008) Prostate high-dose-rate brachytherapy as salvage treatment of local failure after previous external or permanent seed irradiation for prostate cancer. Brachytherapy 7:231–236
79. Chen CP, Weinberg V, Shinohara K et al (2013) Salvage HDR brachytherapy for recurrent prostate cancer after previous definitive radiation therapy: 5-year outcomes. Int J Radiat Oncol Biol Phys 86:324–329
80. Lee B, Shinohara K, Weinberg V et al (2007) Feasibility of high-dose-rate brachytherapy salvage for local prostate cancer recurrence after radiotherapy: the University of California–San Francisco experience. Int J Radiat Oncol Biol Phys 67:1106–1112
81. Kukiełka AM, Hetnał M, Dąbrowski T et al (2014) Salvage prostate HDR brachytherapy combined with interstitial hyperthermia for local recurrence after radiation therapy failure. Strahlenther Onkol 190:165–170
82. Wojcieszek P, Szlag M, Głowacki G et al (2016) Salvage high-dose-rate brachytherapy for locally recurrent prostate cancer after primary radiotherapy failure. Radiother Oncol 119:405–410
83. Lyczek J, Kawczyńska MM, Garmol D et al (2009) HDR brachytherapy as a solution in recurrences of locally advanced prostate cancer. J Contemp Brachytherapy 1:105–108
84. Jiang P, van der Horst C, Kimmig B et al (2017) Interstitial high-dose-rate brachytherapy as salvage treatment for locally recurrent prostate cancer after definitive radiation therapy: toxicity and 5-year outcome. Brachytherapy 16:186–192
85. Yamada Y, Kollmeier MA, Pei X et al (2014) A phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy. Brachytherapy 13:111–116
86. Hsu CC, Hsu H, Pickett B et al (2013) Feasibility of MR imaging/MR spectroscopy-planned focal partial salvage permanent prostate implant (PPI) for localized recurrence after initial PPI for prostate cancer. Int J Radiat Oncol Biol Phys 85(2):370–377

87. Boustani A, Pucar D, Saperstein L et al (2018) Molecular imaging of prostate cancer. Br J Radiol 91(1084):20170736
88. Nguyen P, Devlin P, Beard C et al (2013) High-dose-rate brachytherapy for prostate cancer in a previously radiated patient with polyethylene glycol hydrogel spacing to reduce rectal dose: case report and review of the literature. Brachytherapy 12(1):77–83
89. Hepp R, Eggert T, Schabl G et al (2018) Salvage high-dose-rate brachytherapy for prostate cancer persistence after brachytherapy: repeated use of a polyethylene glycol hydrogel spacer. J Contemp Brachytherapy 10:169–173
90. Peach M, Trifiletti D, Libby B (2016) Systematic review of focal prostate brachytherapy and the future implementation of image-guided prostate HDR brachytherapy using MR-ultrasound fusion. Prostate Cancer 2016:4754031
91. Murgic J, Morton G, Loblaw A et al (2018) Focal salvage high dose-rate brachytherapy for locally recurrent prostate cancer after primary radiation therapy failure: results from a prospective clinical trial. Int J Radiat Oncol Biol Phys 102(3):561–567
92. Chung HT, Loblaw A, D'Alimonte L et al (2016) Toxicities, quality of life and MRI response to focal salvage HDR prostate brachytherapy for locally recurrent prostate cancer after external-beam radiotherapy. Brachytherapy 15(2016):S179–S180. https://doi.org/10.1016/j.brachy.2016.04.329
93. Guerif S, Didas O, Vallee M et al (2014) Focal salvage HDR brachytherapy for local prostate cancer recurrence after a primary radiation therapy: early experience of prospective study. Brachytherapy 13(2014):S116–S117. https://doi.org/10.1016/j.brachy.2014.02.419
94. Zamboglou C, Rischke H-C, Meyer PT et al (2016) Single fraction multimodal image guided focal salvage high-dose-rate brachytherapy for recurrent prostate cancer. J Contemp Brachytherapy 8(3):241–248
95. Maenhout M, Peters M, van Vulpen M et al (2017) Focal MRI-guided salvage high-dose-rate brachytherapy in patients with radiorecurrent prostate cancer. Technol Cancer Res Treat 16(6):1194–1201
96. Moman R, van den Berg C, Kruger A et al (2010) Focal salvage guided by T2-weighted and dynamic contrast-enhanced magnetic resonance imaging for prostate cancer recurrences. Int J Radiat Oncol Biol Phys 76(3):741–746
97. Kamrava M, Chung M, Kayode O et al (2013) Focal high-dose-rate brachytherapy: a dosimetric comparison of hemigland vs conventional whole-gland treatment. Brachytherapy 12(5):434–441