Brachytherapy

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Introduction

Prostate brachytherapy offers a convenient and cost-effective treatment option for patients with clinically localized prostate cancer. This minimally invasive technique carries a comparatively low risk of incontinence and impotence [1] while simultaneously avoiding the wider distribution of radiation dose to normal tissue and extended treatment course of conventional external beam radiation.

The implantation of radioactive sources, termed brachytherapy, is one of the earliest forms of radiotherapy. In 1898, only 3 years after Wilhelm Röntgen described the Röntgen Ray, Marie Curie discovered radium, the first known radioactive nucleotide [2, 3]. By 1911, the French physician Octave Pasteau reported the therapeutic effects of radium when used against carcinoma of the prostate, which at that time was considered a rare disease [4]. Hugh Hampton Young, the Johns Hopkins urologist and pioneer of the prostatectomy, revised the implantation of radium needles through 1917 [5]. This was a primitive procedure by today's standards and was performed without image guidance. With haphazard seed implantation, frequently involving the bladder or rectal wall, nearly every patient experienced significant toxicity and brachytherapy fell out of favor. In 1952, as the limitations of therapeutic castration were realized, the interest in brachytherapy was revitalized by Dr. Rubin Flocks at the University of Iowa [6]. Using an aqueous solution of ^{198}Gold, Dr. Flocks was able to show efficacy in otherwise unresectable cases. Between 1956 and 1971, at what is now Memorial Sloan-Kettering Cancer Center, Dr. Willet Whitmore experimented with various isotopes including ^{222}Radon, ^{192}Iridium, and ^{125}Iodine [7]. Dr. Whitmore ultimately described a well-tolerated technique in which ^{125}Iodine was sealed in titanium cylinders and implanted using a retropubic approach. However, the necessity for an open approach offered little advantage to the prostatectomy, and it was not until 1983 when Dr. Holm from Denmark described transrectal ultrasound (TRUS)-guided ^{125}I placement that the advantages to brachytherapy were realized [8].

Experience with brachytherapy has expanded rapidly since the introduction of TRUS and template guidance over 30 years ago, and now nearly a century after the first brachytherapy experiments, brachytherapy has become a simple, minimally invasive and well-tolerated option for the management of localized prostate cancer. Advantages to modern brachytherapy include rapid post-procedure

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recovery, relatively low morbidity, low cost, and excellent long-term control rates. Brachytherapy is a standard therapeutic option for patients with clinically localized disease and is recognized by various national and international organizations including NCCN, NCI, ACS, AUA, ASTRO, and EORTC among others. This chapter reviews the modern indications and techniques for the performance of brachytherapy.

Evaluation

The pre-procedure evaluation for a patient considered a candidate should be similar to those undergoing other definitive localized therapies such as surgery or external beam radiotherapy (EBRT). This includes a thorough history and physical focusing on previous genitourinary or pelvic surgeries (including transurethral resection of the prostate), previous radiotherapy, use of anticoagulants, medical conditions associated with increased risk with anesthesia, and radiation-related complications (i.e., active lupus, scleroderma, or inflammatory bowel disease). Special attention should be paid to urinary symptoms—practitioners may find the IPSS (International Prostate Symptom Score) to be a useful validated system to document pre-procedure function. Laboratory components of the workup should include a recent PSA (prostate-specific antigen) and pathologically confirmed prostatic carcinoma with Gleason scoring. For intermediate and particularly high-risk patients a metastatic workup including a bone scan and CT imaging of the abdomen and pelvis may be indicated. Preanesthesia evaluation typically includes complete blood count, complete metabolic profile, coagulation studies, and a urinalysis. Further advanced testing may be indicated to investigate any potential anesthesia risks identified during the standard evaluation.

Patient Selection

Patient selection is perhaps the most critical step to performing prostate brachytherapy. A number of organizations including the American Brachytherapy Society (ABS), American College of Radiology (ACR), and the American Society for Radiation Oncology (ASTRO) have published recommendations for the selection of brachytherapy candidates [9, 10], though institutional practices in experienced centers may allow for selection both within and beyond these fundamental guidelines.

Patient-related factors to consider include a patient's age, medical comorbidities and associated life expectancy, pelvic anatomy, surgical history, and pre-implant urinary symptoms. Age and comorbidities should be considered as in any therapy for prostate cancer whereby those at low risk of prostate cancer mortality during their expected lifetime should strongly consider active surveillance. Patients who are obese may be comparatively best suited for brachytherapy, as prostatectomy may be complicated and they are at increased operative and perioperative risk, while their body habitus may challenge external beam image guidance, dosimetry, and table limits.

Care should be taken in patients who may be at high risk for post-implant toxicity. These include a high IPSS score or a post-void residual of more than 100 cm^3 [9]. ABS guidelines define "high" IPSS score as greater than 20 although recent Radiation Therapy Oncology Group (RTOG) trials exclude scores persisting above 15 [11] despite the use of alpha-blockers. Such patients may benefit from prostatectomy as this may relieve obstructive or irritative symptoms, whereas radiation (and in particular brachytherapy) may elicit at least short-term exacerbation of these symptoms [1]. If such patients are adequately counseled regarding the risk of exacerbation, the potential for dependence upon intermittent straight catheterization, and a future TURP, the procedure may be performed.

Relative contraindications to brachytherapy such as a previous history of TURP and a large prostate are also manageable with experience. A prior history of TURP may make the procedure more technically challenging as it limits some positions that could be used for source placement. Additionally it may predict for urinary incontinence after brachytherapy based on

the initial experience in Seattle, Washington [12], though this has been challenged in the recent literature [13]. TURP also poses technical challenges for other treatment options such as prostatectomy by potentially making the surgical anastomosis more challenging. Patients with history of TURP should be considered on a case-by-case basis as the size and anatomy of the TURP can vary significantly and counseled for potential risk of incontinence when proceeding with brachytherapy.

The ABS guidelines consider prostate size greater than 60 cm^3 to be a potential contraindication [14]. With the implantation of larger prostates one might encounter pubic arch interference during an implant; however, with patient positioning and needle technique this can typically be overcome in our experience. Flexion of the patient's hips (to open the pubic arch), flattening of the probe angle, and needle insertion at a medial and inferior grid coordinate with a lateral and upward needle angle all help overcome arch interference. Likewise, the number of sources required increases linearly with prostate volume although there is no known maximum threshold. In our experience, biochemical outcomes are significantly improved with larger glands, though some series do suggest slightly higher acute urinary retention rates [15, 16].

Hesitation may be necessary when a patient presents with a history of prior pelvic irradiation although after consideration, brachytherapy may be the ideal option provided the patient and disease factors support the risk of treatment, given that pelvic adhesions may inhibit the surgical approach and external beam radiation may expose significantly more tissue to reirradiation and the associated potential for toxicity.

Disease-related factors are generally grouped according to the NCCN risk stratification. Low-risk patients, those with a Gleason score of 6, PSA less than 10 ng/mL, and T1-T2a clinical stage, are ideal candidates for brachytherapy with biochemical outcomes at least equal to other available treatment modalities [17, 18]. Intermediate-risk patients, those with a Gleason score of 7, PSA 10–20 ng/mL, or T2b-T2c clinical stage, also appear to be good candidates for implant alone. ABS guidelines have recommended caution in approaching these patients with brachytherapy as monotherapy as intermediate-risk (and high-risk) patients may have a higher prevalence of extraprostatic extension (EPE), seminal vesicle invasion (SVI), or nodal spread, all of which may place the patient at risk of failure with brachytherapy implant alone. Despite this, an increasing volume of data supports the notion that brachytherapy alone can achieve equivalent outcomes to other modalities for intermediate-risk prostate cancer and in our center this is a routine treatment option (Fig. 8.1) [17, 19, 20]. The use of brachytherapy monotherapy in high-risk patients, those with a Gleason of ≥8, PSA above 20 ng/mL, or T3 disease, is investigational as these patients have historically not been considered candidates for brachytherapy alone. Select experiences have shown encouraging results with HDR or LDR brachytherapy [21, 22] though this is not a standard treatment option for high-risk disease. Many institutions combine EBRT with androgen deprivation, with or without brachytherapy boost in these patients [23]. This has been associated with favorable outcomes in some series; however it needs to be approached with caution due to increased risk of toxicity in this group [17, 19]. Of particular concern, RTOG 00-19 examined the role of EBRT to 45 Gy in 25 fractions followed 2–6 weeks later by an ^{125}I boost of 108 Gy in 183 intermediate-risk prostate cancer patients [24]. The 8-year estimated rate of grade 3 and higher GU and GI toxicity was 15 %, including two patients with grade 4 bladder necrosis. This reported toxicity is significantly higher than that seen in other similar select single-institution studies and emphasizes that caution should be taken in considering patients for combined EBRT and brachytherapy. The presence of confirmed lymph node metastasis or other metastatic disease is a contraindication to brachytherapy.

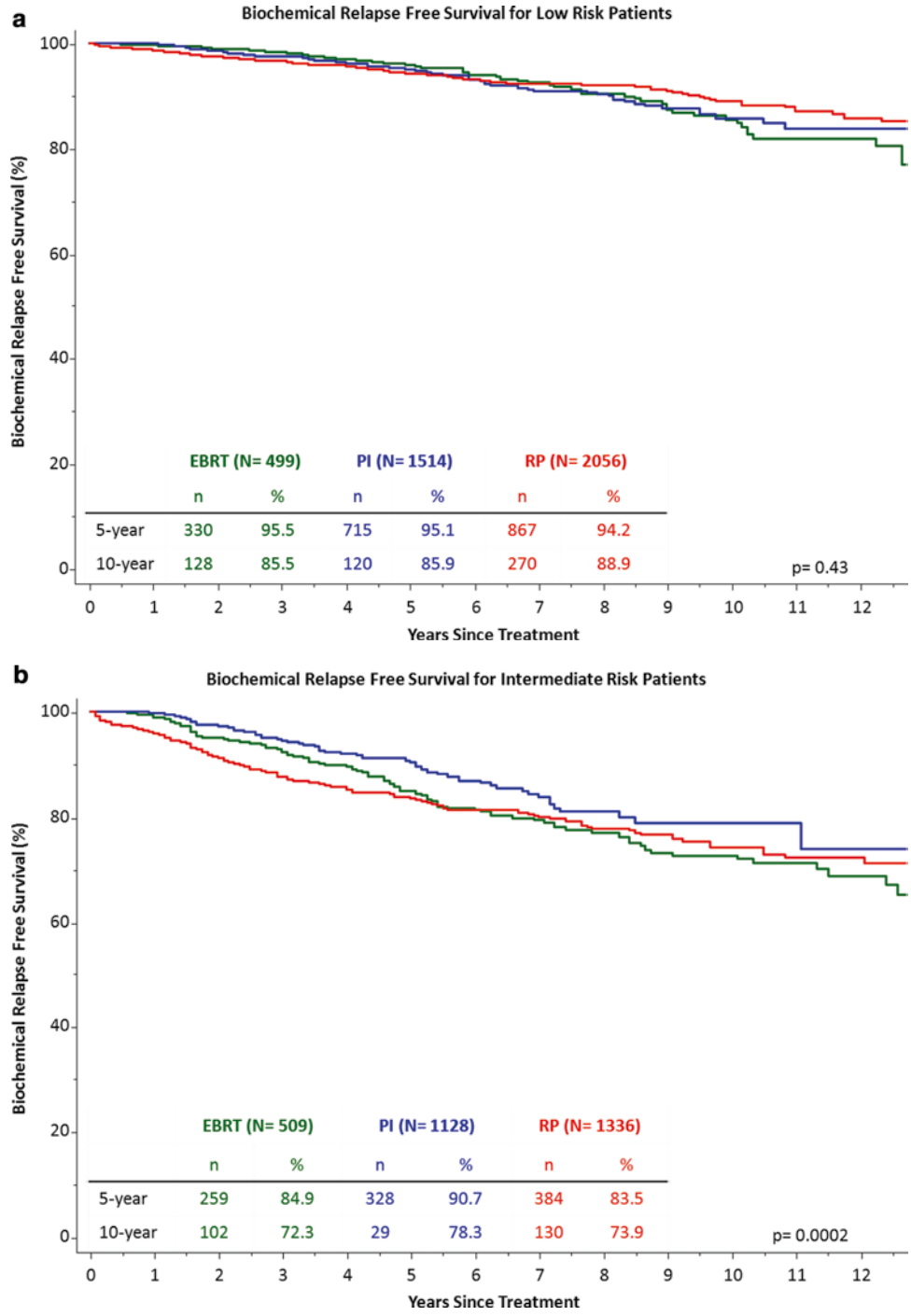

Fig. 8.1 Cleveland Clinic institutional outcomes by NCCN risk category between 1996–2014. Part (**a**) is low-risk, part (**b**) intermediate-risk and part (**c**) high risk. The number at-risk at 5 and 10 years along with the biochemical relapse free survival is listed in each table. Radical prostatectomy (RP) is shown in read, permanent implant (PI) listed in blue and external beam radiotherapy (EBRT) listed in green

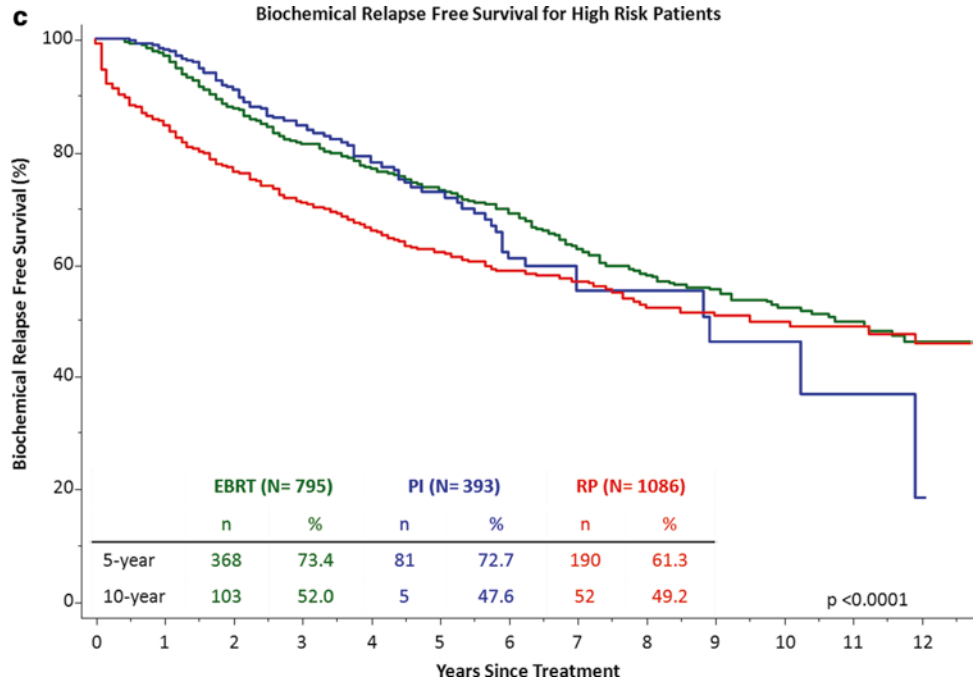

Fig. 8.1 (continued)

Personnel and Roles

To perform brachytherapy safely and efficiently a multidisciplinary team is necessary which may include the urologist, radiation oncologist, medical physicist, radiation therapist, anesthesiologist, and perhaps a medical dosimetrist. Furthermore, prostate brachytherapy has been shown to have a significant learning curve and therefore referral to a team experienced in prostate brachytherapy is recommended [25–27].

If brachytherapy is the recommended procedure, involvement of a medical physicist is necessary. Medical physicists are trained and certified in the planning, calibration, delivery, and quality control of radiotherapy. Their role is critical to the appropriate calculations required to deliver the radiation dose prescribed by the physician. A radiation therapist qualified in the handling and delivery of radiotherapy can aid in the logistical challenges inherent to radioactive sources as well as catheter loading during the procedure.

Anesthesia is recommended in the performance of brachytherapy although the type and delivery are institution specific. General anesthesia is most often used although some institutions prefer spinal anesthesia and obtain excellent outcomes. Local anesthesia with or without sedation is also possible although it requires an experienced physician and, while generally well tolerated, is occasionally more uncomfortable for the patient [28].

Radiation Biology and Physics

A basic understanding of radiation biology and physics can be useful when participating in the planning and the delivery of brachytherapy. Two broad categories of dose delivery can be identified: low dose rate (LDR) and high dose rate (HDR). LDR implants typically deliver dose at a rate of 0.01–2 Gy per hour and require weeks to months to reach full dose. HDR implants may deliver dose at a rate greater than 12 Gy per hour and require only minutes to deliver full dose to the target. LDR brachytherapy for prostate cancer is typically given via permanent seed implants using isotopes of ^{103}Palladium, ^{125}Iodine, or ^{131}Cesium elements. HDR implants in the modern era typically employ ^{192}Iridium via a remote

Table 8.1 Physical properties of various elements used in prostate brachytherapy

Element	Avg. photon energy (keV)	Method of decay	Half-life (days)	Initial Estimated dose rate (cGy/h)
^{103}Palladium	21	EC	17	21.2
^{125}Iodine	28	EC	59	7.0
^{131}Cesium	29	EC	9.7	34.2
^{192}Iridium	398	β^- (95 %) and EC	73.8	>1,200
^{198}Gold	412	β^-	2.7	107

afterloader. HDR brachytherapy as monotherapy is considered investigational by many investigators [29]. Table 8.1 lists various elements used in prostate brachytherapy for comparison.

Measurement of Dose

Various methods for quantification of ionizing radiation dose are available and a general familiarity is necessary for the clinician comparing various techniques in radiotherapy, particularly between EBRT and prostate brachytherapy. The most clinically relevant measure of radiation dose today is the Gray (Gy) which is the SI unit of absorbed dose and defined as 1 Joule (J) of energy deposited per kilogram of tissue (J/kg). The rad, previously the standard, is equivalent to 0.01 Gy, or 1 cGy. Gray is a measure of energy deposited in tissue and has various biological effects dependent on a myriad of other factors. The sievert (Sv) is a unit defined as the human biologic equivalent or effective dose and is most relevant in radiation safety applications. For photons, 1 Gy is approximately equal to 1 Sv. Protons, having an increased mass and an increased relative biologic effectiveness, deliver approximately 2 Sv per 1 Gy absorbed. The rem (Röntgen equivalent in man), a previous standard, is equivalent to 1 rad or 1 cGy. It is important to remember that the biologic effective dose (BED) is a complex comparison particularly when made between brachytherapy and EBRT. The clinical BED is most related to the fraction size and number of fractions delivered but is also related to the quality of radiation (energy, photon vs particles such as protons), dose rate, the type of tissue in question, the rate of cellular repair, oxygenation, and the cell-cycle state of the tumor. The complexity of these comparisons explains the challenges encountered when attempting to identify the ideal radiotherapeutic approach to prostate cancer.

Dose Deposition: Energy and the Inverse Square Law

The energy of ionizing radiation is a key factor in determining the depth of tissue penetration. Higher energy photons travel further into tissue before attenuating as defined by the percent depth–dose (PDD) curve. Early kilovoltage units used for EBRT were ineffective in treating prostate cancer due to the inability to deposit dose deep into the pelvis. The key advantage of brachytherapy over EBRT is quantified by the "inverse square law" which states that the intensity of radiation emitted from a source is inversely proportional to the square of the distance from the source (8.1). This allows for relatively high doses to the tissue in contact with the source and a much lower dose to the normal tissue surrounding the target.

Inverse Square Law

$$\text{Dose}(r) \propto \frac{1}{r^2}, \tag{8.1}$$

where r = distance from source.

Treatment Planning and Dosimetry

Target Volume Delineation

Regardless of the technique used for delivering prostate brachytherapy, the target and the organs at risk (OARs) remain the same. The prostate, including the capsule and a margin surrounding the capsule, is the key target for localized disease.

For intermediate and high-risk disease the proximal 1–2 cm of the seminal vesicles may be included in the target volume. Key OARs include the urethra, bladder, rectum, and penile bulb. It is not possible to deliver sufficient dose to the pelvic lymph nodes with transperineal prostate brachytherapy.

Contouring

"Contouring," a common term in the field of radiation oncology, is the process by which targets and OARs are identified on imaging in order to calculate dose delivered to the structure. While automated algorithms exist, contours are always checked and edited by the physician. The urologist, radiation oncologist, and medical physicist vary in their degree of involvement in contouring based on institution and physician preference. The RTOG has assembled an expert panel to define an atlas of standardized references for contouring [30].

Generally the prostate should be contoured as the key target, sometimes coined the "gross tumor volume" (GTV) although it may be more appropriate to describe the prostate as the "clinical target volume" (CTV) as it is a volume concerning for disease which is not entirely composed of cancerous tissue. Some may describe a "planning target volume" (PTV) which, by strict definition, is an expansion on the CTV accounting for motion or set-up error. Given that brachytherapy is performed under real-time visualization of the target this standard definition of PTV is of debatable importance in the brachytherapy setting and is more applicable to EBRT. Many centers however do target an expansion of the prostate to account for risk of extracapsular extension which in surgical series appears to be within 4 mm in more than 90 % of cases [31, 32]. If an expansion is applied this may vary by NCCN risk group, but is typically approximately 5 mm at the apex and base, 2–3 mm anteriorly and laterally with no expansion on the posterior border. This could be considered part of the CTV, or otherwise PTV.

For ultrasound-based planning techniques commonly applied intraoperatively, images are sent from the ultrasound probe to the contouring software. The physician is then able to contour the edges of the prostate to define the CTV as well as the bladder or rectum as necessary. Any desired expansion can be easily performed at this time. After contouring, a plan can be generated which specifies a seed arrangement which best meets the targeted metrics (Table 8.2). For CT-based HDR plans or post-implant dosimetry verification scans the rectum is typically contoured from the rectosigmoid junction to the level of the anal verge. The peritoneal reflection and true rectosigmoid junction are difficult to delineate on imaging and therefore typically defined as the level where the colon begins to deviate laterally on axial imaging and begins to lose a circular shape. The bladder should be distended and the wall from the dome to the bladder neck should be included. The penile bulb, which is difficult to visualize on CT imaging without contrast, catheterization, or MRI fusion, begins inferiorly to the apex of the prostate and originates posterior to the urethra, having a circular shape in this region. Although debatable, some studies have related the dose delivered to the penile bulb to the risk of erectile dysfunction [42, 43]. The penile bulb contour should not extend to the pendulous portion of the penis. Small bowel and femoral heads are not typically of concern in brachytherapy and receive only background dose.

Table 8.2 Example of dosimetric goals for LDR and HDR brachytherapy

	Monotherapy prescription	Prescription with EBRT
^{125}I	144–160 Gy	110–125 Gy
^{103}Pd	108–110 Gy	90–100 Gy
^{192}Ir	6–7 Gy × 6 fractions [33–36]	9–15 Gy × 1 fraction [37, 38]
	12–13.5 Gy × 2 fractions [39]	5.5 Gy × 3 fractions [40, 41]

	Preplan	Post-plan
V100	100 %	90 % Ideal, acceptable 80 %
V150	<50 %	<50 %
V200	<20 %	<20 %
D90	115 % (110–130 %)	100 %
Urethra D_{max}	<150 % (ideally <120 %)	<150 %
Rectum D_{max}	<1 cm^3 receiving 100 %	<1 cm^3 receiving 100 %

Dose Prescription

After selecting and contouring the CTV and PTV, dose is prescribed to cover the intended target volume. For LDR monotherapy, common dose prescriptions include 144–160 Gy for ^{125}I and 110–125 Gy for ^{103}Pd. For a combined modality approach, the dose is typically 108–110 Gy for ^{125}I, 90–100 Gy for ^{103}Pd, and 10–22.5 Gy in 1–3 fractions for HDR (although no consensus in HDR dosing has been reached) [44]. Typical planning goals for ^{125}I monotherapy include a preplanned D90 (minimum dose to 90 % of the PTV) between 110 and 130 % of the prescribed dose to reach a post-plan goal of 100 %. The preplanned V100 (volume receiving 100 % of the prescribed dose) should approach 100 % (at least >99 %) to obtain a post-plan V100 of at least 80 %, though ideally greater than 90 %. Regarding OARs, the maximum urethral dose should be less than 150 % of the prescribed dose (our institution target is less than 120 %) and the volume of the rectum receiving the prescription dose should be less than one cubic centimeter [45–47]. These dosimetric goals are summarized in Table 8.2. Figure 8.2 shows an example of a TRUS-guided preplan and the resulting post-implant evaluation on CT.

Isotope Selection

As stated in Table 8.1, there are various properties inherent to each isotope. Selection between LDR isotopes is based primarily on institution preference and there is debate in the literature regarding any potential clinical benefit of palladium, iodine, or cesium [48]. Iodine may have a logistical and cost-saving benefit as the half-life is extended and excess seeds can be saved for future procedures. The low dose rate of iodine allows for very low radiation exposure to personnel performing the procedure but may lead to a longer duration of sequelae. The decreased half-life of palladium potentially reduces the duration of sequelae and allows the option of implantation prior to EBRT in the setting of combined therapy. A randomized trial comparing ^{125}I to ^{103}Pd found no difference in biochemical outcome or long-term toxicity while suggesting a greater peak but faster resolution of acute effects with ^{103}Pd as one might expect from the dose rate [49]. Theories of a low alpha/beta ratio for prostate cancer suggest that cesium may have a tumor control benefit due to increased rate of dose deposition although no clear clinical data support this [50]. Iridium is the element of choice for HDR brachytherapy.

Planning: Intraoperative vs. Preoperative

Planning of radiation dosimetry can be accomplished before, during, or after the implant procedure is performed. If the planning is accomplished days to weeks before the procedure, this is termed preplanning and has the logistical benefit of estimating the seed count although organ motion may be an issue. Intraoperative planning can be performed before the implant (intraoperative preplanning) or simultaneous with the implant (interactive intraoperative planning). With HDR brachytherapy treatment planning is performed postoperatively via CT performed with the implant in place and radiation is delivered via remote afterloader. Advantages to the preoperative technique include logistical flexibility and decreased time under anesthesia. The intraoperative preplanning technique, preferred by our institution, allows for accurate planning of the sources without significant interference of organ motion or deformation and improves dosimetric parameters compared to a preplanning technique [51]. If performed efficiently the increase in time under anesthesia is minimal. Post-planning with HDR brachytherapy has the potential advantage of optimization of source dwell times, allowing for some adjustment of the dose distribution after the implant. Despite this, implant (needle or catheter) position is critical and cannot be completely overcome by source optimization alone. If preoperative or intraoperative planning is performed, a postoperative verification scan is necessary.

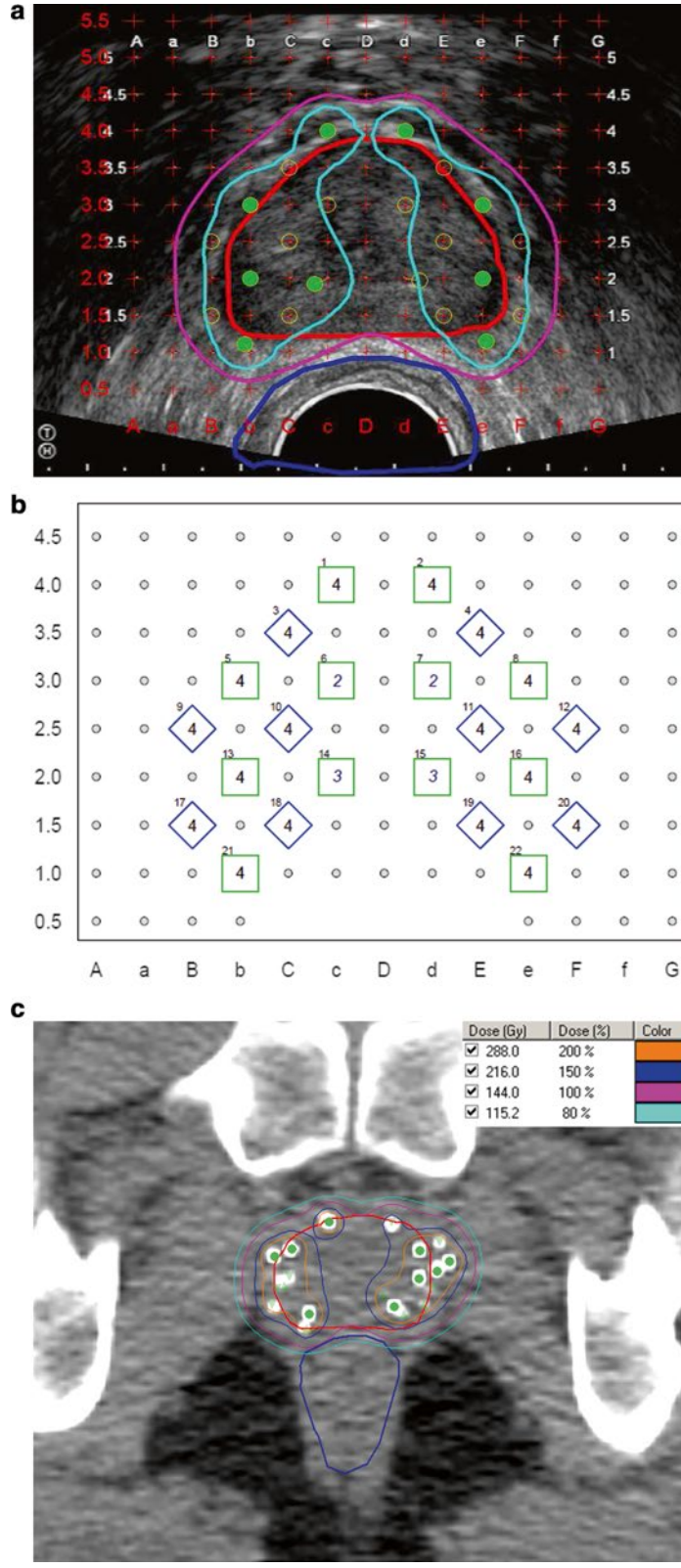

Fig. 8.2 TRUS-guided preplan and the resulting post-plan evaluation by CT. Isodose lines represent varying levels of radiation deposition. (**a**) TRUS-guided preplan showing the prostate CTV (*red*) with the 100 % isodose line (*purple*) and 150 % isodose line (*light blue*) with seed locations superimposed on the template grid (*green*). Note the urethral and rectal sparing. (**b**) TRUS-guided template showing needle spacing. (**c**) Axial post-plan by CT. (**d**) Coronal post-plan by CT. (**e**) Sagittal post-plan by CT. (**f**) 3D reconstruction depicting seeds within the prostate in comparison to the contoured bladder and rectal volumes

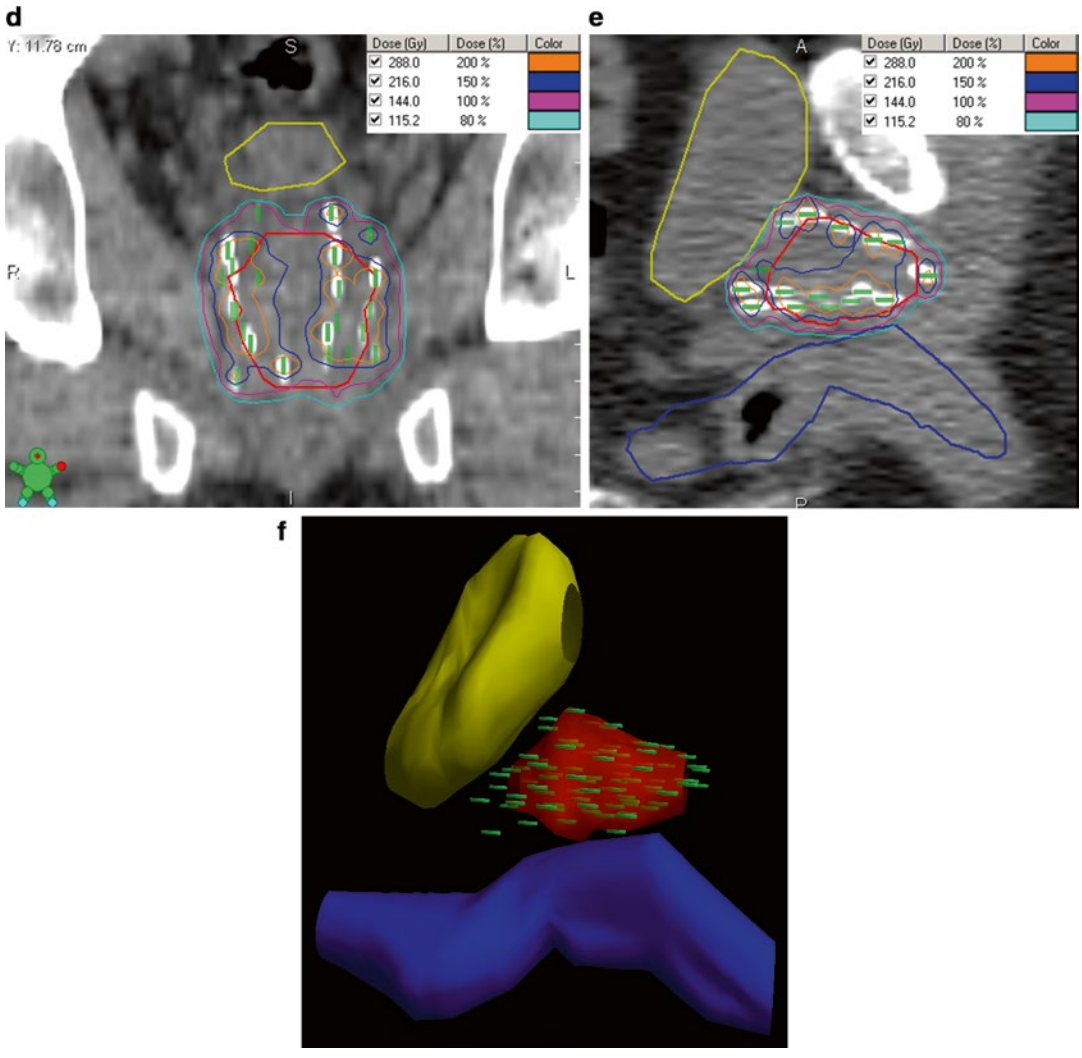

Fig. 8.2 (continued)

Dosimetry and Planning: LDR vs. HDR Brachytherapy

HDR brachytherapy varies slightly in dosimetry and technique from LDR brachytherapy. During LDR brachytherapy permanent seeds are implanted whereas during HDR brachytherapy temporary catheters are placed (via the same TRUS-guidance technique) before the radioactive source is administered via remote afterloader. This technique eliminates the potential for seed migration or embolization and eliminates dose to treating staff. Another advantage is the ability to confirm the quality of the implant after the catheters have been placed but prior to radiation delivery. HDR can potentially deliver a more homogeneous dose profile due to post-planning and a higher energy of ^{192}Ir is compared to the LDR isotopes (Table 8.2) [52]. A third potential radiobiologic advantage includes the hypofractionated schedule which may have a disease-control benefit based on the theories of a low alpha/beta ratio as mentioned above. Despite these advantages, careful technique is still required to ensure a high-quality implant. One potential disadvantage is the increased volume of normal tissue receiving low doses of radiation. The major disadvantage, however, is that most current schedules call for multiple implantation procedures

(or for the implant to remain in place for an extended period of time over multiple fractions) as the use of single-fraction HDR monotherapy or boost remains investigational [53]. Ultimately, while there are multiple potential advantages to HDR brachytherapy, long-term randomized trials with patient-reported outcomes are yet to be conducted; therefore, brachytherapy technique remains the physician and institution's choice.

Implantation Technique

LDR Technique

Procedural techniques will vary according to institution and type of implant required. Here a typical LDR implant using an intraoperative preplanning technique is described.

Prior to the procedure patients are encouraged to undergo routine preparation including avoidance of aspirin and anticoagulants for 5 days and abstaining from eating the night before. A bowel preparation using a Fleet enema or comparable can be helpful and is routinely administered 1 h prior to the procedure in our practice. Perioperative antibiotics are routine and typically include a cephalosporin or fluoroquinolone as indicated.

In the operating room the patient is placed in the exaggerated dorsal lithotomy position. Routine clean-contaminated surgical preparation is indicated. A complete surgical drape is institution specific but in our opinion is unnecessary. Ultrasound jelly placed into the rectum following rectal irrigation can be helpful prior to ultrasound placement. The TRUS unit should be capable of providing axial as well as sagittal images and include a stabilization device with template guidance. A template is attached to the TRUS unit to allow for accurate catheter insertion. Urethral visualization is usually possible with ultrasound and it is unnecessary to use a Foley catheter in the majority of cases. The use of a Foley can obstruct the view of the anterior prostate. If the urethra is unable to be visualized, consider injection of a small amount of either lubricant jelly or air if clinically necessary.

The entire prostate from 1 cm proximal to the base to 1 cm distal to the apex is imaged with 5 mm axial slices and images are sent to the planning software. The length, width, and height of the prostate are measured and volume is calculated both by the ultrasound unit and by the planning software. Correlation with the length of the prostate on sagittal view and the number of axial slices should be ensured to avoid error (e.g., a 4 cm prostate length should yield approximately 8–9 slices of prostate, 12–13 total captured slices).

Following image acquisition, commercially available planning software is then used to contour the CTV and OARs as detailed above. After calculation of the seed distribution, a final plan will display the number of sources and needles necessary and the correlated insertion location on the grid attached to the TRUS unit. At this point, ensure that the preplanned isodose lines are appropriate and that the preplan dosimetric goals have been met. Linked seeds ensure accurate separation and have been shown to decrease the rate of migration and embolization [54, 55]. Linked seeds should be used in the periphery with loose seeds inserted centrally near the urethra to allow for spontaneous or cystoscopic removal of a single source should such a situation arise. Likewise, we routinely use loose seeds for the inferior medial perirectal seeds as a precaution. Brachytherapy plans should typically be symmetrical and follow a modified peripheral loading technique [56].

During implantation under axial guidance (Fig. 8.3a), insert the needle through the template and firmly into the perineum. Begin with the needle in the axial coordinate farthest from the TRUS probe as image distortion may increase if the seeds are first delivered near the probe. An increased speed of needle insertion will minimize deflection of the needle. The deflection of the needle is related to the direction of the bevel and can be used to adjust for error. Once the needle is within the target coordinate, switch to a sagittal view to guide the depth as necessary. This use of sagittal ultrasound imaging eliminates the need for fluoroscopy in guiding the depth of needle insertion. Next, visualize the bladder wall and insert the needle in to the prostate base (Fig. 8.3b). At this point you will feel the increased resistance of the prostate capsule and also visually see increased deflection of the prostate on ultrasound. Once depth of insertion has been confirmed,

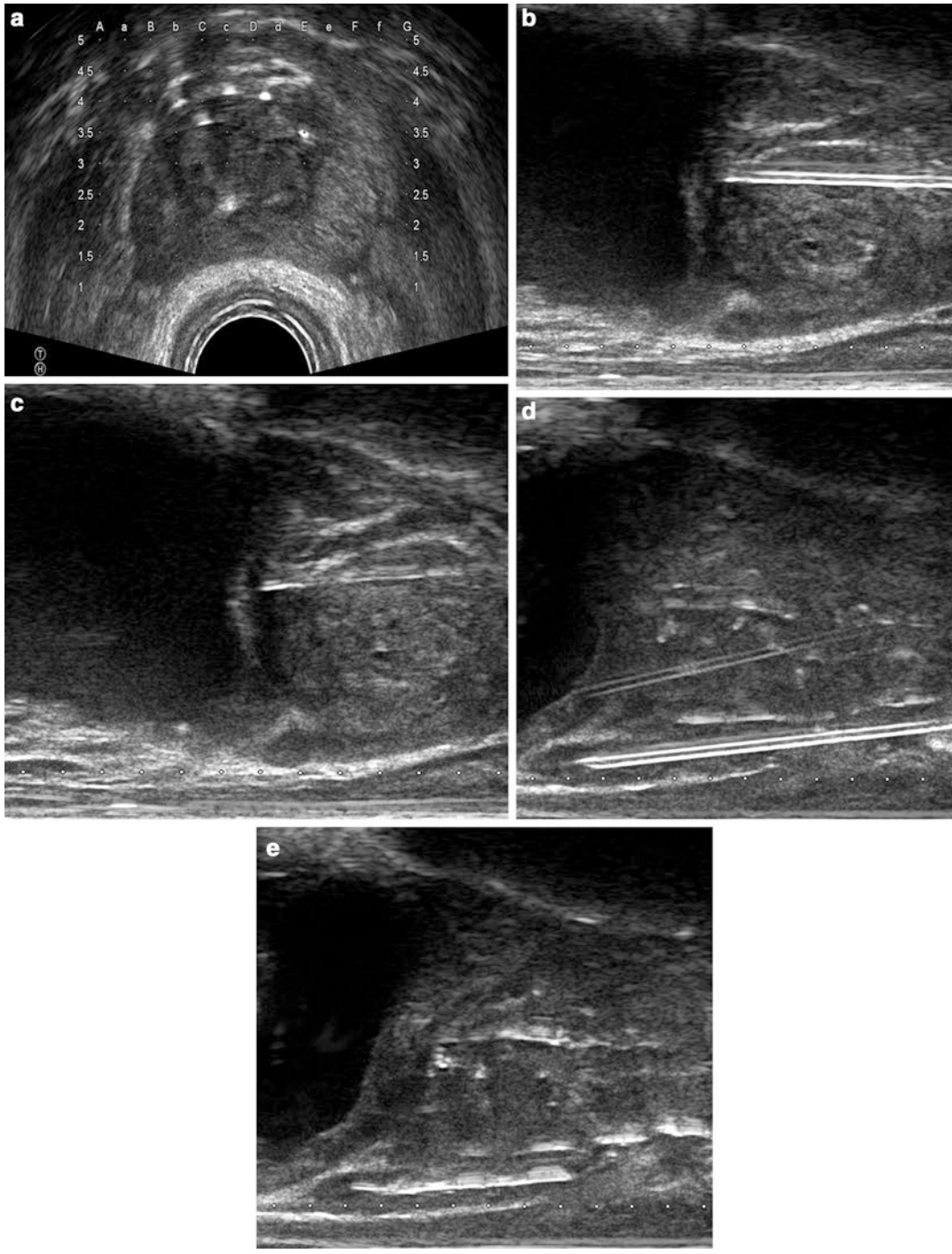

Fig. 8.3 Intraoperative ultrasound images. (**a**) Template grid superimposed on the prostate on axial TRUS with needle insertion at coordinate E, 3.5. (**b**) Needle inserted in to the base of the prostate abutting the bladder wall as visualized on sagittal ultrasound imaging. (**c**) After removal of the needle in (**b**) the strand of seeds remains in place. (**d**) Sagittal image showing a needle tangential to the rectal wall. This technique is acceptable provided the seeds are implanted deep enough not to be deployed into the wall itself. (**e**) After the stranded seeds are deployed they rest in the prostate and seminal vesicle volume with a clear margin on the rectal wall

deploy the seeds by holding the stylet in place and removing the needle (Fig. 8.3c). Ensure that the needle is not inserted further during the process of deploying the seeds as the bladder wall may be implanted. When inserting the inferior, perirectal needles extreme caution must be used to avoid deploying a source in, or immediately adjacent to the rectum. While it is occasionally necessary to pass a needle through the rectum for some patients, this can typically be avoided by inserting the needle into a higher than intended grid location and then guiding the needle inferiorly during insertion to avoid the rectal wall (Fig. 8.3d, e). A careful understanding of how this effects dosimetry is important and should be considered during planning. During placement we routinely use this technique for patients with steep rectal angles.

HDR Technique

The technique used for the implantation of HDR catheters is similar to the technique used when implanting permanent LDR sources. The catheters are inserted via the same TRUS-guided template technique described above although the catheters are left in place and the spacing may be wider due to the increased energy of ^{192}Ir. Following implantation of the catheters, the placement is confirmed via either TRUS, CT, or MRI. This scan is then used for planning purposes and the typical OARs are contoured. It is critical that the catheters remain in place once the planning has begun, as any displacement may result in dosimetric error. Once structures are contoured, inverse planning may be applied to optimize the dwell times of the ^{192}Ir source. Once the plan is complete, it is sent to the remote afterloader which is connected to the catheters. The treatment time varies by implant but is approximately 10 min.

Difficult Cases

Occasionally the delivery of the prescribed plan may be technically challenging. With proper technique and experience, almost no case need be aborted. Pubic arch interference, one of the most common challenges, can typically be avoided via an exaggerated lithotomy position as increasing hip flexion removes the pubic arch from the path of the needle and allows for direct access to the prostate from the perineum. If pubic arch interference remains an issue a more medial and inferior insertion position is selected and the needle's bevel adjusted to track superior and laterally. If needed a finger or other tool can be placed between the perineum and the template to further guide and deflect the needle. A slower insertion speed will increase the degree of deflection. Attempts at insertion should be kept to a minimum as the risk of prostatic hematoma increases as more attempts are made.

Post-procedure Management and Acute Toxicity

After completion of the implant cystoscopy may play a role in evaluating the urethra and bladder wall for improperly placed seeds. Some institutions choose to perform cystoscopy routinely while others choose only to pursue cystoscopy if blood is present at the urethral meatus and does not clear with irrigation. In coordination with the institution's radiation safety guidelines, a survey meter is used to screen any fluid leaving the patient. Measurements necessary may vary; however, exposure 1 m from the patient after implant must be less than one millirem per hour for discharge. Exposure is negligible to routine contacts who may come near a patient in the first weeks although it is recommended that small children do not spend extended time in the lap of a patient in the first 2–3 months following LDR implant (no more than 20 min out of a 3 h period repetitively). Implant activity is considered negligible after a period of five half-lives has passed (approximately 85 days for ^{103}Pd and 295 days for ^{125}I).

Acute toxicity from brachytherapy is typically modest. Acute toxicity is dominated by temporary urinary irritative and obstructive symptoms as well as fatigue, though may also include prostatitis, dysuria, urinary obstruction, or proctitis. Upon discharge it is recommended to provide an antibiotic regimen for 7–10 days. An α-blocker

such as tamsulosin is recommended for 2–6 months or until urinary symptoms resolve to ameliorate urinary obstruction due to radiation-induced edema. Rarely catheterization may be necessary for patients experiencing urinary obstruction. We strongly recommend self-catheterization with a straight catheter rather than an indwelling Foley in order to minimize discomfort and risk of infection. Pain is usually minimal with a mild analgesic rarely necessary. Four weeks after LDR implant the patient should return for a CT scan to evaluate the quality of the implant. Commercially available software is used to identify the seeds and estimates the dose distribution. The prostate and OARs are delineated as above. If areas with insufficient dose are identified one should consider their clinical significance, and if needed they may be reimplanted with supplemental seeds at this time.

Quality of Life, Late Toxicity, and Management

The severity and frequency of late toxicity from brachytherapy is a frequent topic of debate in the literature. The variance in the incidence of erectile dysfunction, dysuria, cystitis, and radiation proctitis among physician-reported cohorts highlights the role for patient-reported outcomes in future studies. The largest study of patient-reported outcomes comparing quality of life between EBRT, prostatectomy, and brachytherapy is the 2008 ProstQA study reported in the *New England Journal of Medicine* [1]. In this study prostatectomy was associated with a relative detriment in sexual function and incontinence scores. EBRT and brachytherapy were associated with better preservation of continence and sexual function while causing more significant acute urinary obstruction (which ultimately returned towards baseline), as well as mild bowel irritation. Factors which independently predicted changes in quality of life and satisfaction for brachytherapy patients included increased age, increased initial PSA, hormonal therapy, EBRT boost, Gleason score less than 7, and prostate size.

The management of late complications from brachytherapy including dysuria, urinary obstruction, urethral stricture, cystitis, or proctitis typically requires a multidisciplinary approach. Dysuria may relate to prostatitis, cystitis, or urethritis. Infectious etiologies should be excluded. For supportive care mild symptoms of dysuria, urgency, or frequency, medical management is possible with medications such as tamsulosin, pyridium, oxybutynin, tolterodine, pentosan, hyoscyamine, or belladonna/opium suppositories. A transient flare in obstructive symptoms is common but the majority return to baseline IPSS score and greater than 90 % of patients return to baseline within 1 year [57]. Urethral stricture or chronic obstruction is uncommon and can be managed endoscopically. Chronic radiation cystitis presenting as hematuria is rare after brachytherapy and may require bladder irrigation and cystoscopy with coagulation. Radiation proctitis presents as rectal urgency or bleeding and on colonoscopy appears as erythema or friability localized to the anterior rectal wall. Medical management may include sucralfate, steroid enemas, or 5-ASA compounds such as sulfasalazine. Endoscopic management of rectal bleeding with 4 % formalin or argon plasma coagulation appears equivalent [58]. Randomized evidence also exists for the benefit of hyperbaric oxygen to accelerate the healing process inhibited by radiation-induced injury to the microvasculature [59]. Biopsy of the irradiated rectum should be judicious to avoid possible fistula formation. If necessary to exclude second malignancy or inflammatory bowel disease, biopsy should be directed towards the lateral or posterior rectal wall. The incidence of Grade 3 late toxicity after brachytherapy is variable in the literature but in the modern era is expected to be on the order of 5–10 % for any genitourinary toxicity and 1–5 % for any gastrointestinal toxicity [57, 60–63]. Less than one percent of patients will require formalin for rectal bleeding and 0.3 % will develop a fistula [62]. With experienced users extremely low rates of toxicity are reported with 10 year grade 2 or higher GU and GI toxicity in only 4.3 and 1.7 % percent of patients treated at the Cleveland Clinic, respectively (Fig. 8.4) [60].

The development of a radiation-induced second malignancy of the pelvis is a theoretical

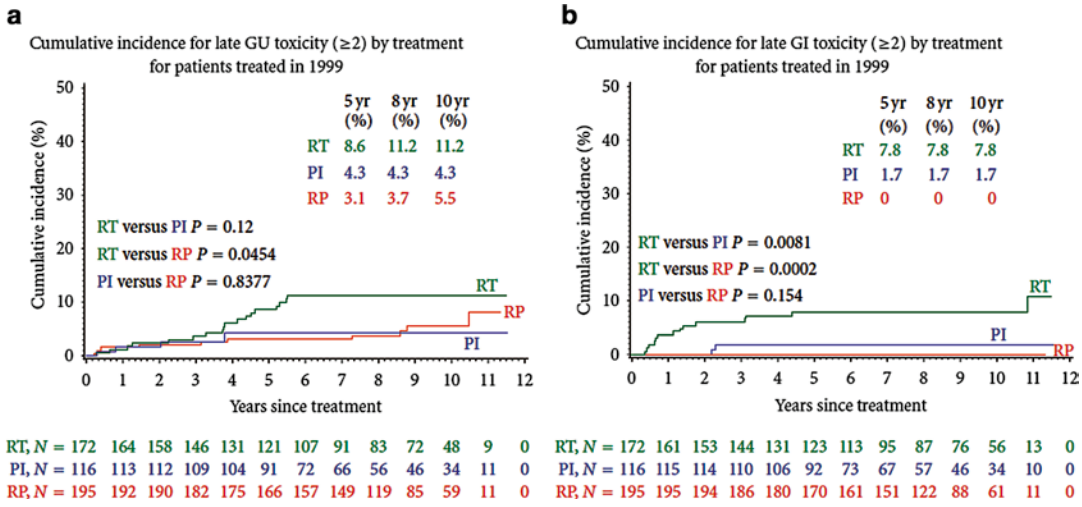

Fig. 8.4 Long-term Grade 2 or higher toxicity comparisons between radical prostatectomy, permanent seed implant, and external beam radiotherapy at the Cleveland Clinic Foundation in 1999 [59]. Reprinted from Hunter GK, Reddy CA, Klein EA, et al. Long-term (10-year) gastrointestinal and genitourinary toxicity after treatment with external beam radiotherapy, radical prostatectomy, or brachytherapy for prostate cancer. Prostate Cancer. 2012;2012:853487

concern of radiotherapy although incidence is likely very small. SEER data for all patients receiving radiotherapy estimated the risk of radiation-induced second malignancy to be roughly 0.5 % [64]. One series found age and smoking to be independent predictors of second malignancy after prostate radiotherapy while the use of radiotherapy over surgery was not [65].

Posttreatment Surveillance, Biochemical Recurrence, and the PSA Bounce

Recent NCCN guidelines for routine prostate cancer surveillance include a PSA every 6–12 months for 5 years then annually with a digital rectal examination every year which may be omitted if the PSA is undetectable [66]. A PSA measured every 6 months appears optimal in the detection and surveillance of brachytherapy patients [67]. The upper age limit when surveillance becomes unnecessary is not specified and left to clinical judgment.

Biochemical recurrence after radiotherapy has been a topic of debate in the past decades. The original RTOG consensus defined recurrence as three consecutive rises in PSA above the post-treatment nadir [68]. However, this definition is very dependent upon the number and timing of PSAs taken, and the 2006 RTOG "Phoenix" definition of a rise in PSA by more than 2 ng/mL is more widely accepted today [69]. Androgen recovery should be considered in patients after discontinuing antiandrogen therapy.

The "PSA bounce," defined as an increase in PSA greater than 0.2 ng/mL than the nadir followed by a decrease to or below the initial nadir, is a known phenomenon following prostate brachytherapy and occurs in roughly 46 % of patients [70]. This can occur despite androgen deprivation therapy and is more common in younger patients. PSA bounce most commonly occurs within the first 3 years of implant (median 15 months), and close PSA follow-up should be considered for patients with a PSA rise within this timeframe without other clinical evidence of recurrent disease.

Conclusion

Brachytherapy is a straightforward outpatient procedure and is an option for patients with clinically localized prostate cancer offering cure rates comparable to other treatment options. Treatment results primarily in acute GU irritation and obstruction, with a very low long-term toxicity profile. There is debate in the literature regarding the optimal techniques in patient selection and treatment delivery although experience is critical to minimize complications. Ultimately, patient selection is driven by clinical risk and the toxicity profile of each modality, whereas brachytherapy technique is driven by physician preference and institutional experience. Future directions in prostate brachytherapy include optimization of treatment planning, measurement of patient reported outcomes, and healthcare value analyses.

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