

American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy

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ABSTRACT

PURPOSE: A well-established body of literature supports the use of high-dose-rate (HDR) brachytherapy as definitive treatment for localized prostate cancer. Most of the articles describe HDR as a boost with adjuvant external beam radiation, but there is a growing experience with HDR monotherapy.

METHODS AND MATERIALS: The American Brachytherapy Society has convened a group of expert practitioners and physicists to develop guidelines for the use of HDR in the management of prostate cancer. This involved an extensive literature review and input from an expert panel.

RESULTS: Despite a wide variation in doses and fractionation reported, HDR brachytherapy provides biochemical control rates of 85–100%, 81–100%, and 43–93% for low-, intermediate-, and high-risk prostate cancers, respectively. Severe toxicity is rare, with most authors reporting less than 5% Grade 3 or higher toxicity. Careful attention to patient evaluation for appropriate patient selection, meticulous technique, treatment planning, and delivery are essential for successful treatment.

CONCLUSION: The clinical outcomes for HDR are excellent, with high rates of biochemical control, even for high-risk disease, with low morbidity. HDR monotherapy, both for primary treatment and salvage, are promising treatment modalities. © 2012 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords:

High-dose-rate brachytherapy; Prostate cancer; American Brachytherapy Society; Guidelines

Introduction

There is mounting evidence that the outcome of patients with localized prostate cancer is related directly to local tumor control, even for patients with high-risk features (1). For example, the risk of distant metastasis is closely tied to

local control (2). Dose-escalation strategies, particularly with intermediate- and high-risk prostate cancer, have improved local control, and higher doses of radiation, whether with brachytherapy, external beam radiation, or a combination, have consistently demonstrated improved outcomes (2–11).

High-dose-rate (HDR) brachytherapy is a vehicle for absolute and radiobiologic dose escalation that has resulted in high tumor control and low toxicity rates. As with all advanced technology, meticulous treatment planning and carefully executed methods are essential to the accurate delivery of high-dose radiation to complex volumes such as the prostate and seminal vesicles while avoiding excessive dose to the rectum, bladder, and urethra. The following

Received 1 April 2011; received in revised form 23 September 2011; accepted 23 September 2011.

Continuing Medical Education Institute Speakers Bureau.

No other disclosures for any of the other authors.

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guidelines have been developed to assist practitioners in achieving consistently high levels of tumor control while minimizing toxicity.

In 2010, the American Brachytherapy Society (ABS) Board of Directors appointed a group of practitioners having extensive clinical and research experience in prostate brachytherapy to provide guidelines for the current practice of HDR brachytherapy. Sources of recommendations include current guidelines published by medical societies, clinical trials of prostate brachytherapy, published medical literature, and the clinical experience of the committee. Specific recommendations for therapy and for further investigations were made when there was a consensus. Where major controversy or lack of evidence persists, the ABS declines to make specific recommendations. In formulating guidelines, it should be noted that there are commonplace, accepted and appropriate variations in approaches to the management and treatment of HDR patients. The guidelines presented here are meant to aid practitioners but are not to be viewed as rigid practice requirements by which to establish a legal standard of care. This report was reviewed and approved by the Board of Directors of the ABS.

We have categorized these guidelines into four areas: (1) Patient evaluation, (2) Patient selection and contraindications, (3) Planning and postimplant management, and (4) Continuing areas of controversy where accepted practice is evolving and specific guideline recommendations are not established. The term “relative contraindication” refers to the situation in which a patient may be at a higher risk of complications but the risk may be outweighed by other considerations or mitigated by other measures. Such relative contraindications do not preclude patients from undergoing HDR brachytherapy. Indeed, there are often substantial published studies from experienced groups, which demonstrate that patients with such supposed relative contraindications can be managed with HDR with little or no appreciable difference in outcome.

Background

HDR brachytherapy delivers radiation at a dose rate of >12 Gy/h (12), and usually significantly higher. It requires remote afterloading of physically small high-activity sources. Modern HDR prostate brachytherapy, taking advantage of the latest advances in imaging and computer technology, is able to provide high levels of local tumor and biochemical control, even for high-risk disease (13–15).

As the HDR literature has matured, series with extended followup (6, 16, 17) have consistently reported excellent rates of tumor control and low toxicity. Nonetheless, a survey of the literature reveals that the most of the evidence is single institution or pooled data. Patients have also been treated heterogeneously, most commonly receiving an HDR boost with external beam radiation. The HDR boost schedules vary

from 9–15 Gy in a single fraction to 26 Gy in four fractions, with numerous intermediary dose fractionation protocols. In addition, HDR brachytherapy without external beam radiotherapy (EBRT, i.e., HDR monotherapy) has been used successfully to treat early and intermediate-risk prostate cancer. The wide variance in dose schedules, however, makes systematic evaluation of HDR outcomes complex.

In general, excellent 5-year biochemical disease control with HDR has been reported for patients with low- (85–100%), intermediate- (83–98%), and high-risk (51–96%) localized prostate cancer, using both combination and monotherapy, and a variety of definitions of risk (see Table 1).

Patient evaluation

Patients being considered for HDR should be evaluated for suitability for treatment in the following domains: (1) Tumor factors to assess the extent of disease and clinical risk category and (2) Patient factors that may impact the toxicity and safety of treatment.

Medical history

A detailed medical history is essential. Patient factors including pretreatment urinary and gastrointestinal (especially rectal) symptoms and their severity, and baseline sexual function should be assessed. A history of prior pelvic radiation, pelvic malignancy, or surgery including urologic procedures, should be documented. Comorbidities that will affect the anesthetic risk such as history of bleeding or thromboembolic disease, cardiovascular and pulmonary conditions, among others, should be documented. Medications and allergies should be accurately noted. Referrals to other specialty physicians should be made as needed in advance of the HDR procedure.

Extent/risk category of disease

The primary goal of HDR is local tumor control. Accurate and complete patient evaluation to assess the extent of disease and to categorize the disease into the appropriate risk category should be performed. Definitions of risk are defined by clinical stage, serum prostate-specific antigen (PSA), and Gleason grading according to the National Comprehensive Cancer Network (18).

Table 2 provides a summary of the components of the recommended initial evaluation. The importance of a detailed and complete medical history and examination cannot be overemphasized. Evaluation and description of the prostatic disease burden and of any extraprostatic extent can be accomplished with careful digital rectal examination and, when appropriate, ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). MRI may either use an endorectal coil or high Tesla imaging (19). Lymph nodes are typically evaluated with CT or MRI in cases of high-risk

Table 1
Literature summary

Author	N	Median Followup (mo)	HDR dose	Treatment type	Comments	Low risk	Intermediate risk	High risk
Boost								
Astrom (60)	214	48	10Gyx2	Boost	13 patients experienced urethral strictures	92%	88%	61%
Bachand (16)	153	44	9Gyx2–10Gyx2	Boost	PSA bounce in 10% of patients	96%	96%	96%
Valero (13)	134	37	4.75Gyx4	Boost	Phase 2 study. High-risk patients with ADT 7% Grade 3 GU and 3% GI Grade 3. No higher toxicity			
Chen (61)	85	49	5.5Gyx3	Boost	Whole pelvis EBRT increased GI toxicity	100%	91%	81%
Demanes (17)	209	86	5.5 Gy–6.0Gyx4	Boost	6.7% late Grade 3 and 1% Grade 4 GU toxicity (TUR related)	90%	87%	69%
Deutsch (3)/ Yamada (30)	160	47	7Gyx3	Boost	Benefit for intermediate-risk patients vs. IMRT 86 Gy	100%	98%	93%
Duchesne (56)	108	78	4Gyx4–5Gyx4	Boost	Toxicity did not increase with dose escalation			
Galalae (6)	324	64	5.5Gyx3–15Gyx2	Boost	Hormone-naïve patients only	85%	81%	69%
Hoskin (8)/ Chin (62)	109	30	8.5Gyx2	Boost	RCT EBRT alone vs. HDR boost. No late Grades 3–4 GU or GI toxicity. FACT-P scores favor HDR boost	100%	85%	80%
Hsu (7)	112	30	9.5Gyx2	Boost	Less than 3% Grade 3 toxicity at 18 mo: RTOG 0321 Phase 2			
Ishiyama (28)	100	36	6.3Gyx5	Boost + 3Gyx10 EBRT	Greater GU toxicity with higher urethral doses			
Kalkner (63)	154	73	10Gyx2	Boost	Risk analysis based on WHO grade, PSA, and stage	97%	83%	51%
Kaprealian (64)	165	105/43	6Gyx3/9.5Gyx2	Boost	No difference between fractionation schedules for bNED or toxicity			
Martinez (15)	1260	48–59	5.5Gyx3/15Gyx2	Boost	The addition of hormonal tx did no improve survival or bNED in high-risk patients			
Morton (65)	125	24	15Gyx1	Boost	Dose to 10% urethra was significant predictor of EPIC urinary QOL			
Niehoff (66)	35	27	15Gyx2	Boost	HDR boost with EBRT for recurrence after radical prostatectomy. 67% PSA recurrence post tx			
Pellizzon (67)	209	64	4 Gy–6Gx4	Boost	Risk grouping, higher HDR doses, 3D HDR planning predicted for better bNED	91%	90%	89%
Phan (49)	309	59	6Gyx4	Boost	4% late Grade 3 GU, 1 late Grade 4 GI	98%	90%	78%
Pistis (68)	114	32	9Gyx1	Boost	97% bNED at 4 yr for entire cohort	100% (T1–2)		43% (T3)
Sato (69)	53	61	7.5Gyx2	Boost				

Vargas (70)	197	59	11–26 Gy/2–4 fractions	Boost	High-risk patients benefited from more hypofractionated tx	86%	69%
Vargas (71)	755	48	5.5Gyx4–11.5Gyx2	Boost	The addition of pelvic RT did not improve bNED in patients with high risk of +pelvic LN	100%	93%
Wildner (72)	284	26	5.5Gyx4	Boost	No significant differences between risk groups	94%	76%
Zwahlen (73)	587	66	5Gyx4–6Gyx3	Boost	7% late Grade 3 GU toxicity, no late Grade 3 GI toxicity	97% (includes intermediate risk)	
Monotherapy							
Demanas (57)	298	62	7Gyx6	Mono	<1% GI toxicity		
Ghilizan (51)	173	17	9.5Gyx4	Mono	3% G3 GU toxicity		
Jabbari (74)	6	26	12–13.5Gyx2	Mono	16% GU Grade 2, 1% GU Grade 3		
Lee (23)	21	19	6Gyx6	Mono	Prior APR no Grade 3 toxicity		
Grills (22)	248	58	6Gyx6	Mono	Salvage tx after EBRT or LDR seed failure, 89% nBED at 2 yr		
Rogers (75)	284	35.1	9.5Gyx4/7Gyx6	Mono/Boost	Less urinary and GI toxicity compared with LDR boosts	97%	83%
			6.5Gyx6	Mono	Two sessions of 6.5 Gy × 3, over mean 19 d. No urethral strictures. 82.6% potency preservation. No GI toxicity >Grade 1.	94.4%	
Tharp (25)	7	58	6Gyx2/7Gyx3/9Gyx2	Mono	Salvage HDR after LDR or EBRT failure, 5 patients developed strictures, 71% bNED		
Yoshioka (76)	112	65	6Gyx9 (5 days)	Mono	No greater than Grade 3 toxicity	85%	79%

HDR = high dose rate; PSA = prostate-specific antigen; EBRT = external beam radiotherapy; ADT = androgen deprivation therapy; GU = genitourinary; GI = gastrointestinal; TUR = transurethral resection; IMRT = intensity modulated radiotherapy; RCT = randomized control trial; FACTP = Functional Assessment of Cancer Therapy Prostate; RTOG = Radiation Therapy Oncology Group; WHO = World Health Organization; PSA = prostate-specific antigen; bNED = biochemical no evidence of disease; EPIC = Expanded Prostate Cancer Index Composite; QOL = quality of life; RT = radiotherapy; LN = lymph node; APR = abdominal perineal resection; tx = treatment; LDR = low dose rate.

Table 2
Initial evaluation

Activity	Purpose	Comments
History and physical examination	Assess medical suitability, clinical stage, and anesthesia risk	Prior pelvic radiotherapy, rectal or prostatic surgery, inflammatory bowel disease, bladder tumors, history of cardiovascular disease, use of blood thinners, allergies should be documented.
Sexual function assessment	Document pretreatment sexual function status	Use of validated self-reporting instruments or toxicity scales recommended
Gastrointestinal/rectal function assessment	Document pretreatment rectal function	Use of validated self-reporting instruments or toxicity scales recommended
Urinary function assessment	Document degree of pretreatment urinary frequency, urgency, nocturia	Use of validated self-reporting instruments or toxicity scales recommended
Serum prostate-specific antigen	Risk assessment	Must have documented pathologic confirmation
Biopsy/pathology review	Risk assessment	
Magnetic resonance imaging (MRI)/computed tomography	Local and regional extent of disease, prostate volume	For selected intermediate- and all high-risk patients. Endorectal coil or MRI (1.5–3 T) is preferred to assess extracapsular extension
Bone scan	Rule out bone metastasis	For selected intermediate-risk and all high-risk patients

disease and bone scan should be considered for patients with higher risk features or symptoms suggestive of bone involvement. Practice patterns may vary from nation to nation.

Patient selection/contraindications

Appropriate patient selection is an important part of the treatment decision process for HDR prostate brachytherapy. HDR brachytherapy should be considered as a means of dose escalation for any patient receiving radiotherapy for prostate cancer. It is particularly valuable for use as a boost in combination with EBRT for intermediate- or high-risk disease. In this setting, it provides highly conformal and biologically efficient dose escalation within the prostate, with less radiation dose to other pelvic organs (20), and excellent local and biochemical control (3, 21, 22).

Special considerations

Prior rectal surgery

In cases with prior rectal surgery pretreatment CT imaging maybe helpful, especially in cases where surgical staples mark the proximity of the surgical anastomosis to the prostate. Colonoscopy or proctosigmoidoscopy may also be helpful to assess the rectal mucosa and confirm that there is no evidence of recurrent rectal cancer. Patients should be counseled regarding the risks of rectal complications in situations where significant dose may be delivered to the surgical anastomosis. Care should be taken during the procedure when placing the transrectal ultrasound probe and HDR catheters near an anastomosis.

In cases where patients have concurrent diagnoses of operable rectal cancer and prostate cancer requiring treatment, HDR can be given as a boost treatment after external

beam pelvic radiotherapy, when indicated (see prior pelvic radiotherapy).

Prior pelvic radiotherapy

The most common scenario for HDR after prior pelvic radiation is in the setting of prior rectal cancer. Because there is an extensive experience with combined modality therapy with external beam pelvic radiation and HDR boost, the same paradigm can be used effectively when external beam radiation doses are within the range of 50 Gy in conventional fractionation. In cases where the prior external beam dose exceeds this level, a careful evaluation of the potential risks and benefits must be performed. Alternatives to HDR brachytherapy should be considered, and referral to a center with special HDR expertise (23).

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is not an absolute contraindication for HDR brachytherapy, but patients need to be made aware of the potential risks of radiation in this setting. In general, it is recommended that patients with IBD avoid radiation (24). However, in cases where definitive treatment is indicated and the patient is not a suitable candidate for surgical intervention, prostate HDR can be considered. The best candidates will be those who are asymptomatic and have not required medical management of IBD for at least 6–60 months. A colonoscopy should be performed before treatment. HDR monotherapy may be preferable to EBRT alone or in combination with brachytherapy because the volume of rectum and/or bowel that is irradiated is less with brachytherapy compared with external beam radiation (20).

Prior prostate radiation

HDR monotherapy as a salvage treatment for local failure after external beam radiation or permanent seed brachytherapy has been recently reported (23, 25), and appears to be a promising option, particularly for patients who are not fit for salvage prostatectomy. In this setting, referral to a specialty center with salvage HDR experience is recommended.

Prior surgical urethral manipulation

Transurethral resection of the prostate (TURP) or transurethral incision are commonly performed to help alleviate urinary outlet obstruction. There is no definitive data suggesting that patients who have undergone such procedures are at increased risk of significant toxicity with HDR brachytherapy (26). Nonetheless, it is recommended that particular attention be given to urethral dosimetry in these patients, and that urethral maximum doses not exceed 110% of the prescription dose. The standard practice of using the outline of a catheter to represent the surface of urethra is not adequate because the contour of urethra is irregular after TURP. Using additional urethral contrast in the form of aerated gel will help outline the true shape of the urethra and avoid unintentional overdose. At least 90 days between the time of surgery and radiation is suggested for healing of the resection site.

Large prostate volume

HDR brachytherapy remotely delivers a radiation source into an array of catheters after treatment planning has been completed. 3D inverse treatment planning algorithms are used to produce optimized plans that provide excellent target coverage even in cases where the prostate volume is large. Traditionally, based on the low dose-rate experience, some brachytherapists have shied away from implanting large volume glands (>50 cc). However, there are a number of reports describing successful HDR brachytherapy of large prostates without significant increases in toxicity (27, 28). A large prostate volume is only a relative contraindication to HDR, but practitioners should still carefully consider factors such as pelvic arch width, applicator insertion technique (fixed template and stabilizer vs. freehand), and baseline urinary function. In a case with low-risk disease and median lobe protrusion into the bladder, consideration should be given to reducing proximal coverage of the median lobe to spare the bladder neck and avoid high proximal urethra doses. Alternatively, a limited TURP can be performed before brachytherapy, with a suitable interval for healing before radiation treatment. Androgen deprivation or 5- α reductase therapy may be considered for cytoreduction, but should be used with caution in cases of preexisting cardiovascular disease (29). Patients should be counseled about expected side effects including erectile

dysfunction and possible increased acute and chronic urinary morbidity (30).

Significant urinary symptoms

Urinary toxicity after HDR has a favorable profile, even in the setting of significant baseline urinary morbidity (International Prostate Symptom Score > 20) (31) and most patients do not experience permanent worsening of urinary symptoms (30). In patients with a high International Prostate Symptom Score, meticulous attention to urethral and bladder dosimetry is crucial for avoiding adverse effects. The dose coverage of the bladder base and neck, and even the anterior prostate, may be reduced because the likelihood of prostate cancer in this area is low (5). Significant urinary symptoms are only a relative contraindication to HDR brachytherapy, but patients should expect short-term and possibly long-term worsening of urinary function, and may require medications such as alpha-blockers or anticholinergics, or occasionally urinary catheterization.

High-risk prostate cancer

Dose escalation is important for high-risk localized prostate cancer (2, 32), and HDR brachytherapy is an excellent method of accomplishing this (4, 30, 33). Dose escalation can be achieved by an absolute increase in dose as with standard EBRT or by increasing the dose per fraction, known as hypofractionation. According to the linear quadratic formula, hypofractionation is a way to increase the biologic effective dose (BED), and is a strategy that has been clinically corroborated (34).

There is an additional advantage to large fraction sizes in brachytherapy. The inverse square relationship that governs dose distribution results in normal tissues adjacent to the target receiving significantly less than the prescribed dose (e.g., 80% to the bladder and rectum). At large fraction sizes, the exponential nature of the linear quadratic model creates a greater spread in the BED for normal vs. tumor tissue. A nominal difference of 20% is biologically more than this at large fractions sizes. For example, if the prostate were to receive 12 Gy but the bladder dose was constrained to receive 10 Gy (a 20% difference), the BED calculated difference is nearly 40%, assuming an α/β ratio of 3.

High local tumor control rates achieved with HDR brachytherapy in all risk groups strongly suggest that local control is an achievable goal. A review of the literature suggests that biochemical control can be achieved in 60–90% of high-risk patients at 5 years without undue side effects (see Table 1).

In selected cases, local control may be an appropriate therapeutic goal even in the setting where there is a high risk of subclinical metastatic prostate cancer. Hence, some patients with advanced disease, including T3b disease, Gleason score 9–10, or serum PSA in excess of 50 ng/mL may be potential candidates for HDR. In such cases, care

must be taken to ensure that the goals of treatment are clearly elucidated and weighed against the potential toxicity.

Adjuvant hormonal therapy is typically used in the setting of high-risk disease, but with HDR brachytherapy the indications and duration of hormonal therapy remain controversial.

Absolute contraindications

Absolute contraindications for HDR brachytherapy include the following conditions:

1. Preexisting rectal fistula,
2. Medically unsuited for anesthesia, and
3. No proof of malignancy.

Catheter insertion and treatment planning

Transperineal catheter insertion is usually performed under general or spinal anesthesia, with transrectal ultrasound guidance. Various catheter placement patterns have been described. A template is usually used to aid placement, and some method is used to fix catheters in position until treatment has been delivered. Many templates incorporate a locking mechanism for this purpose.

Iridium 192 (^{192}Ir) is the most commonly used isotope for HDR. ^{192}Ir has an average energy of 380 KeV, a half-life of 73.8 days and a half value layer of 2.5 mm of lead (12). ^{192}Ir HDR brachytherapy uses a stepping source. Dosimetry is based on 3D scanning images and the creation of a virtual volume for treatment planning purposes. The dose distribution is created, evaluated, and adjusted before the dose is delivered so as to reliably meet the requirements of the individual case. Source dwell times at each stopping point are optimized to achieve target coverage while limiting dose to critical organs at risk. Thus, postimplant dose calculation performed before dose delivery allows for adjustments in the treatment plan to allow for individual patient anatomy and catheter positioning to optimize dose coverage of the target volume while minimizing high doses to adjacent normal tissues.

When more than one insertion is performed as part of the prescribed course of treatment, care should be taken to provide uniform treatment with each insertion. This can be best accomplished by reproducing the same patient positioning for each subsequent insertion, and using a similar catheter array the same number of catheters and template to place brachytherapy catheters in the same position at each treatment. It is not uncommon for the prostate to have varying volumes between brachytherapy procedures, and this must, of course, be taken into account on an individualized basis. However, the same procedures should be used to identify and contour targets and normal tissue structures with each insertion. However, each new insertion should be replanned instead of relying on the initial plan for subsequent fractions.

Treatment planning must be performed on a commissioned system with source-specific documentation and quality assurance measures, as per recommendations put forward by American Association of Physicists in Medicine (AAPM) Task Group 53 (35). Three-dimensional dose calculations must be performed, and dose–volume analysis of target and normal tissues should be undertaken for every patient. Treatment planning is most commonly performed using either CT or transrectal ultrasound (TRUS) imaging after catheter placement. CT imaging usually involves transferring the patient to a CT scanner outside the operating room, and care must be taken to minimize catheter displacement. Ultrasound-based planning systems allow planning to be completed in the procedure suite or operating room, without moving the patient and risking catheter displacement. CT scanners and TRUS machines should undergo appropriate quality assurance testing (36, 37).

Image acquisition

Images for treatment planning can be ultrasound, CT, or MRI based. For CT-based planning, the images should be contiguous and no more than 3 mm thick in the axial plane. Imaging should extend at least 9 mm above and below the target volume, and should include the proximal tips of the implant catheters along with sufficient normal anatomy such as seminal vesicles, bladder, and bowel for meaningful normal tissue dosimetry. It is not necessary to include the patient's body contour for treatment planning purposes. Urethral identification is recommended using either a radio-opaque urinary catheter for CT or aerated gel for ultrasound.

Target volume and normal tissue

Treatment planning is typically performed with ultrasound-, CT-, or MRI-based imaging. Key ingredients to proper planning are accurate identification of the target volume (prostate \pm periprostatic tissues/seminal vesicles) and normal structures (bladder, urethra, and rectum). The bladder is typically readily identified on imaging, and can be aided via a urinary catheter with balloon inflated in the bladder, and, with CT planning, via contrast within the bladder itself. The urethra is also well imaged with a urinary catheter, and can be further assisted with a specially designed radio-opaque catheter or a standard catheter with contrast as needed. The rectum may be defined by its external and mucosal surfaces. The external surface is more difficult to define precisely but corresponds roughly to the posterior layer of Denonvillier's fascia, the fascia propria of the rectum. Recognition of the mucosal surface can be abetted on CT by the addition of contrast within the rectum. In full appreciation of anatomic distortion by the ultrasound probe, the rectal mucosa on ultrasound may be defined as the anterior probe surface. Additionally, the penile bulb, the portion of the bulbous spongiosum inferior to the urogenital

Table 3
Current dose fractionation schedules

Institution	Dose fractionation	Bladder	Urethra	Rectum
MSKCC	Boost 7Gyx3 Mono 9.5Gyx4 Salvage 8Gyx4		<120% prescription	$D_{2cc} < 70\%$
UCSF	Boost 15Gyx1 Mono 10.5Gyx3 Salvage 8Gyx4*	$V_{75} < 1cc$	$V_{125} < 1cc$, $V_{150} = 0cc$ *(dose tunnel whenever possible)	$V_{75} < 1cc$
WBH	Boost 10.5Gyx2 Mono 4 × 9.5 Gy (historical) 12–13.5Gyx2 (current) Salvage 7Gyx4 combined with hyperthermia	No constraint (intra-op TRUS-based dosi)	$V_{100} < 90\%$ of prescription $V_{115} < 1\%$ of prescription	$V_{75} < 1\%$ of prescription
TCC	Boost 6Gyx2 ×2 implants	<80% of Rx	<125% of prescription	<80% of Rx to outer wall
GW	Boost 6.5Gyx3 Mono two sessions of 6.5Gyx3	<100% prescription	<110% prescription	mucosa <60%, outer wall <100%
Toronto	Boost 15Gyx1	n/a	$D_{10} < 118\%$ Max < 125%	$V_{80} < 0.5cc$
UCLA-CET	Boost 6Gyx4 Mono 7.25Gyx6	90–100% wall 80% balloon	120% combo 105% any TUR 110% mono	Rectal wall 80% Rectal wall 80–85%

MSKCC = Memorial Sloan-Kettering Cancer Center; UCSF = University of California San Francisco; WBH = William Beaumont Hospital; TCC = Texas Cancer Center; GW = GammaWest Brachytherapy; Toronto = University of Toronto; UCLA-CET = University of California Los Angeles-California Endocurietherapy Cancer Center; V_{80} = fractional volume covered by 80% of the prescription dose; V_{100} = fractional volume covered by 100% of the prescription dose; V_{115} = fractional volume covered by 115% of the prescription dose; V_{125} = fractional volume covered by 125% of the prescription dose; V_{150} = fractional volume covered by 150% of the prescription dose; D_{10} = dose that covers the highest 10% of the organ; Rx = prescription; TUR = transurethral resection.

diaphragm, may be defined as an organ at risk, or may be avoided by careful identification of the prostatic apex, with planning that specifically limits dose into the penile bulb, and bulbomembranous urethra. The definition of volumes should follow the International Commission on Radiation Units and Measurements Report 58 (38). The planning target volume (PTV) for brachytherapy is generally the same as the clinical target volume, which is defined by the treating physician, and may include a customized treatment margin.

In cases with advanced disease, there may be large volume disease near the edge of the clinical target volume.

It is therefore especially important to review the biopsy and imaging data and know the precise location and extent of the tumor (extracapsular extension, seminal vesicle, etc) at the time of the procedure to ensure the tumor volume is adequately covered. In such cases, HDR brachytherapy treatment planning is ideally suited to customize dosimetry to give the required dose to the tumor while sparing normal tissue.

Although the number and array of brachytherapy catheters depend on prostate shape, volume, and regional anatomy, generally a minimum of 14 catheters should be

Table 4
Grade 3 late GU complications

Author	N	Followup (mo)	Dose	Type of treatment	Comments
Astrom (60)	214	48	10Gyx2	Boost	13 patients experienced urethral strictures
Demanis (17)	209	86	5.5 Gy–6.0Gyx4	Boost	6.7% late Grade 3 and 1% Grade 4 GU toxicity (TUR related)
Hsu (7)	112	30	9.5Gyx2	Boost	Less than 3% Grade 3 toxicity at 18 mo
Phan (49)	309	59	6Gyx4	Boost	4% late Grade 3 GU
Deger (50)	442	60	9–10 Gyx2	Boost	9% late Grade 3 GU toxicity
Martinez (77)	207	66	5.5–11Gyx2	Boost	8% late Grade 3 GU toxicity
Sullivan (52)	425	41	4–5Gyx46.5 Gyx3	Boost	8% late Grade 3 GU toxicity
Zwahlen (73)	587	66	5Gyx4–6Gyx3	Boost	7% late Grade 3 GU toxicity
Demanis (57)	298	62	7Gyx6 9.5Gyx4	Mono	3% late Grade 3 GU toxicity
Ghilizan (51)	173	17	12–13.5Gyx2	Mono	1% late GU Grade 3 toxicity
Hoskin (78)	197	37	8.5Gyx4 9Gyx4 10.5Gyx3 13Gyx2	Mono	3–7% strictures

GU = genitourinary; TUR = transurethral resection.

used to avoid unnecessary hot spots within the PTV (39). When a “boost within a boost” is intended, placing extra catheters in the boost volume is beneficial. Care should be taken to avoid piercing the urethra with HDR catheters (40).

Although the entire prostate is generally included in the target volume, periprostatic structures such as seminal vesicles or extracapsular tissue can also be considered for inclusion based on the clinical circumstance. Both the normal tissues and all the HDR catheters must be accurately identified for treatment planning. In cases of CT-based treatment planning, small metallic fiducial markers to identify the prostatic apex and/or base are useful, and help during planning to limit dose to the bulbomembranous urethra and penile bulb (41). Fiducial markers may also be helpful to assess catheter migration during treatment.

Dosimetry and dose calculation

The air kerma strength of each new ^{192}Ir source should be independently measured and compared with specifications supplied by the vendor. The comparison should be carried out using a National Institute of Standards and Technology (NIST) traceable ion well chamber (42). Dosimetry should be compliant with recommendations outlined by AAPM Task Group 43 (43). The prescribed dose will be the intended minimum dose delivered to the PTV. A computerized optimization program based on a geometric or inverse planning algorithm should be used, although manual optimization is also acceptable. For treatment planning systems that use sample dose points, a minimum of 5,000–10,000 sample points should be used for the calculation of each cumulative dose–volume histogram. The planner must ensure that calculation parameters for the dose–volume histogram are set to obtain accurate values. It would be unusual for the prescribed dose to cover less than 90% of the target volume ($V_{100} > 90\%$ [V_{100} = fractional volume receiving 100% of the prescribed dose]), with an expected $V_{100} > 95\%$. A range of isodose distributions of 50%, 100%, 110%, 120%, and 150% of the prescription dose relative to the PTV should be used for treatment plan evaluation.

The dose plan is typically prepared by a dosimetrist or physicist. It is then reviewed and approved by the treating physician. An independent check should be performed by a second physicist and (44, 45) should include patient’s identification, dates of treatment, total dwell time, prescription dose, catheter positions, dose coverage, and normal tissue doses.

Prescription doses

Given the heterogeneity of prescription doses described in the literature, all reporting similar excellent outcomes in terms of toxicity and disease control (see Table 1), no particular dose fractionation schedule can be recommended.

HDR brachytherapy has most frequently been used as a boost given in one to six fractions in conjunction with

external beam radiation given in standard fractionation to doses between 36 and 50 Gy. In the setting of HDR monotherapy, treatment has been administered in three to six fractions. The trend over the past decade has been to deliver fewer fractions with a larger dose per fraction. This is especially true because the advent of ultrasound-based planning where one fraction per implant is common.

Normal tissue constraints

Given the extreme heterogeneity in dose fractionation scheduled published in the literature, with corresponding excellent results, it is difficult to establish absolute dose guidelines for normal tissues. In lieu of such limits, Table 3 lists the dose fractionation schedules, and normal tissue constraints used by experienced HDR centers as a reference for readers to evaluate their own practice.

Treatment delivery

In cases where patients have HDR catheters in place and require hospital admission, appropriate pain management, such as oral, epidural, or intravenous patient-controlled analgesia is indicated. Routine precautions for deep venous thrombosis should be undertaken. If multiple HDR fractions are given using each implant, it is preferable to complete the sequence in less than 24 h to minimize risk of thrombosis, infection, and patient discomfort. It is better to repeat the implant rather than keep the patient in bed for multiple nights.

Catheter displacement during a course of several fractions has been reported as an important potential source of error (46–48). Visual inspection and measurement of the catheters before each fraction is important, but is not always indicative of internal catheter localization. Fluoroscopy or CT imaging is useful to verify the proper depth of each catheter before treatment. When fiducial markers are present, they can be used to help assess the degree of catheter displacement. The treating physician should reposition displaced catheters, and in cases where the catheters cannot be repositioned satisfactorily, replanning based on the new catheter positions is required. Treatment may need to be modified, postponed, or rescheduled if the new plan is unsatisfactory.

Before each HDR brachytherapy fraction, the patient’s identification, date of treatment, source activity, total treatment (dwell) time, and dose prescription must be confirmed via photo and/or direct questioning. Transfer tubes from the HDR afterloading apparatus must be correctly attached to each brachytherapy catheter and confirmed by the treating physician or physicist. Dose delivery should only begin after transfer tube and catheter patency, and linear dimension have been checked with a dummy source. Treatment should be observed with real-time camera visualization of the patient, and preferably the afterloader also. A medical physicist must be present at the treatment console throughout the entire fraction. A radiation oncologist must

supervise the treatment in accordance with Nuclear Regulatory Commission and State regulations. The treatment room and the patient must be surveyed after the procedure to ensure that the source has properly retracted.

Posttreatment management

After removal of the HDR catheters, the bladder may need to be irrigated with a sterile solution to remove blood clots before removal of the urinary catheter. Perineal pressure after catheter removal will minimize the risks of hematoma formation. Antibiotics, steroid medications, and alpha-blockers can be prescribed as clinically needed.

Toxicity

Acute urinary irritative symptoms such as urgency and frequency are common and usually resolve with time. Urinary retention occurs in less than 5% of cases (5, 37, 49–51), can be managed with catheterization. In the unusual case of prolonged retention, intermittent self-catheterization may be preferable to the prolonged use of an indwelling catheter. Urinary strictures are reported in up to 15% of patients, and most commonly seen in the bulbomembranous urethra (52, 53). Table 4 summarizes the rates of urethral strictures associated with HDR brachytherapy. TURP should be avoided after HDR prostate brachytherapy (54), but there is no absolute contraindication to a properly performed procedure (50, 55). Prolonged urinary incontinence after HDR brachytherapy is extremely rare, and seen in less than 2% of cases (53, 56).

Transient rectal irritation causing rectal urgency or frequency is more likely when HDR is used in conjunction with external beam radiation therapy. Late rectal bleeding may occur and is usually not clinically significant. Serious complications, such as a rectal fistula, are extremely rare, and seen in less than 1% of cases (49, 57).

Erectile dysfunction (5, 30) has been reported in up to 40% of men who were fully potent at baseline but approximately 80% will respond to pharmacologic agents such as phosphodiesterase-5 inhibitors (30).

Patients should be seen after the implant to assess acute problems and then subsequently to evaluate disease and side-effect status. The suggested followup schedule is twice a year for the first 2–3 years, and then at least annually. Assessment should include a PSA, digital rectal examination, and an evaluation of urinary and rectal toxicity, and sexual function. At present, the ABS recommends using the Phoenix definition of biochemical failure, but acknowledges that assessment of PSA requires individual case evaluation. Patients should be counseled that transient elevations of PSA after HDR brachytherapy (PSA bounce) are not uncommon (58). They should also be advised to avoid urinary instrumentation or rectal biopsy without careful consideration of the risks and benefits.

HDR safety considerations

Appropriate quality assurance programs should include daily tests of the HDR delivery equipment including source positioning as specified by the manufacturer. All team members should be credentialed and maintain appropriate licensure to practice their respective roles, particularly handling HDR radiation sources. These recommendations have been clearly stipulated by the American Society for Therapeutic Radiation and Oncology (ASTRO) and the American College of Radiology (59). All involved staff should be fully trained in emergency safety procedures and updated at least annually. These activities should be documented. Treatment should occur in fully shielded rooms in full compliance with regulatory standards.

Monotherapy

HDR monotherapy has been reported by several institutions (see Table 1), largely for low-risk, but also for intermediate-risk patients. The reported outcomes for disease control and toxicity are favorable. Monotherapy demands a higher degree of technical and planning expertise than boost HDR therapy. Institutions should take the requirements of HDR monotherapy into consideration before embarking on a monotherapy program. Monotherapy for high-risk patients should be considered investigational.

There is a promising data describing the use of HDR monotherapy as salvage for localized recurrence after prior external beam radiation or permanent seed brachytherapy. The ABS recommends that the use of HDR as salvage therapy be limited to Institutional Review Board-approved protocols or specialty centers with appropriate expertise.

Summary

HDR brachytherapy is an excellent option for the definitive treatment of localized prostate cancer in any risk category. Biochemical control is high across all risk groups, and severe toxicity is uncommon because of the precision and control with which conformal optimized treatment can be delivered. Performance of dosimetry after catheter insertion and before treatment delivery eliminates uncertainty in dose delivery. Lastly, HDR optimally exploits the radiobiologic advantage of large fraction sizes and partitioning of radiation between the target and normal tissue organs.

Careful selection of patients is based on evaluation of the extent of disease, risk assessment, medical history, and physical examination including preexisting urinary and rectal symptoms, sexual function, and appropriate radiographic studies. Patients must be made aware of the potential risks and complications of treatment, particularly in the urinary, rectal, and sexual function domains. Important considerations and precautions in recommending HDR brachytherapy include prior pelvic radiation or rectal surgery, IBD,

prostatic enlargement, and preexisting lower urinary tract symptoms.

Because the dose per fraction is high, meticulous attention to detail in all technical aspects of treatment, including catheter placement and drift, treatment planning, and delivery are of paramount importance. Despite a wide variation in prescribed doses, the outcomes are highly favorable; no one optimal dose fractionation schedule or normal tissue tolerance criteria can be recommended. Nonetheless, with a multitude of studies reporting long-term results with excellent tumor control and a favorable side-effect profile, HDR brachytherapy is now an established and important treatment for prostate cancer.

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