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State of the Art Review

High-dose-rate brachytherapy as monotherapy for prostate cancer

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ABSTRACT

PURPOSE: To review and analyze the published data on high-dose-rate brachytherapy as monotherapy in the treatment of prostate cancer.

METHODS: A literature search and a systematic review of the high-dose-rate (HDR) brachytherapy (monotherapy) prostate literature were performed on PubMed using ''high-dose-rate, brachytherapy, prostate, monotherapy'' as search terms. More than 80 articles and abstracts published between 1990 and 2013 were identified. Data tables were generated and summary descriptions created. Commentary and opinion was formulated through discussion and consensus based on the critical review of the literature and the author's combined personal experience and knowledge.

RESULTS: Thirteen articles reported clinical outcome and toxicity with followup ranging from 1.5 to 8.0 years. Results were available for all risk groups. A variety of dose and fractionation schedules were described. Prostate-specific antigen progression–free survival ranged from 79% to 100% and local control from 97% to 100%. The toxicity rates were low. Genitourinary toxicity, mainly frequency/urgency, was 0–16% (Grade 3). Gastrointestinal toxicity was 0–2% (Grade 3). Erectile function preservation was 67–89%. The radiobiological, clinical, and technical features of HDR brachytherapy were reviewed and discussed.

CONCLUSIONS: Consistently high local tumor control and low complications rates are reported with HDR monotherapy. It provides reproducible high-quality dosimetry, it has an advantage from a radiobiology perspective, and it has a good radiation safety profile. HDR brachytherapy is a safe and effective local treatment modality for prostate cancer.

Keywords: Prostate; Prostate cancer; High-dose-rate brachytherapy; Radiation therapy; Monotherapy

Introduction

A literature search and systematic review of the high-dose-rate (HDR) brachytherapy (monotherapy) prostate literature was performed on PubMed using ''high-dose-rate, brachytherapy, prostate, monotherapy'' as search terms. More than 80 articles and abstracts published between 1990 and 2013 were identified. Data tables were generated and summary descriptions created. Historical information was derived from the literature and the author's combined personal experiences and knowledge. Commentary and opinion was formulated through discussion and consensus.

HDR prostate brachytherapy began in 1986 at Kiel University in Germany and soon after in the United States, independently at the Seattle Prostate Institute in 1989 and in 1991 at the California Endocurietherapy Cancer Center (CET) in Oakland, California, and William Beaumont Hospital (WBH) in Royal Oak, Michigan (1–6). HDR was initially used only as a boost in conjunction with external beam radiation therapy (EBRT) because of concerns about the effect of large doses per fraction on normal tissues. Dose escalation studies by Martinez *et al.*, however, established the safety and efficacy range for HDR in the context of combined EBRT and HDR (7–9). During the 1990s, ultrasound image guidance and computer treatment planning technology evolved, clinical experience accumulated, and outcomes of HDR prostate brachytherapy began to be reported. The clinical rationale for HDR monotherapy for prostate cancer was derived from organ-specific treatments such as radical prostatectomy and permanent seed monotherapy. Recognition of the technical capabilities of HDR to reliably treat the prostate (and seminal vesicles) with a margin of surrounding tissue and to simultaneously control the dose to adjacent normal tissues led to the development

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of HDR prostate monotherapy clinical trials, which were initiated in the mid-1990s at WBH and CET for low- and intermediate-risk groups, and in Osaka, Japan for all risk groups (9–11).

Why HDR?

HDR brachytherapy and improvements in EBRT evolved simultaneously. Conformal EBRT and intensity modulated radiation therapy are two technologies, which allow physicians to deliver higher total doses and achieve better tumor control rates. However, three major drawbacks of conformal EBRT or intensity modulated radiation therapy are day-to-day variations in internal anatomy secondary to organ motion (interfraction motion), organ deformation and other variations in internal anatomy during radiation therapy delivery (intrafraction motion), and daily setup inaccuracies (setup errors). To overcome these limitations, HDR brachytherapy was identified as a potentially advantageous vehicle for dose-escalation.

HDR technology combines a number of favorable qualities of brachytherapy with the sophisticated treatment planning developed for EBRT. HDR brachytherapy procedures are performed under general or spinal anesthesia, are usually done through a perineal template guide, and use ultrasound guidance similar to low-dose-rate (LDR) permanent seed implants. Organ motion and setup inaccuracies are not an issue with HDR either because they do not occur, or because they can be corrected with interactive online dosimetry during the procedure, or modified during simulation and treatment planning before dose delivery. There is no need to add treatment volume (margins) beyond the intended target to account for patient motion or variations in beam delivery.

Common problems associated with permanent seeds implants such as discrepancy between planned and actual seeds distribution, inability to correct seeds position or to optimize the dose delivered once the seeds are in place, and operator dependency are relatively low in HDR brachytherapy, particularly with the introduction of intraoperative online HDR treatment planning and delivery (12, 13).

Important features of HDR brachytherapy

1. HDR catheters are relatively easy to visualize with transrectal ultrasound (TRUS), and they can be safely implanted outside the prostate capsule and into the seminal vesicles without the risk of seed migration.
2. HDR avoids uncertainties in dosimetry (target dose) associated with prostate volume changes that occur with permanent seed brachytherapy. Immediate swelling and subsequent gland shrinkage due to fibrosis are irrelevant.
3. Real-time dose modulation HDR planning software offers immediate feedback for the physician and physicist to achieve optimal implant catheter distributions.
4. HDR planning provides multiparametric dose optimization through modulation of catheter geometry, dwell position, and dwell time. HDR dosimetry is "high density" because there are approximately twice as many HDR dwell positions as seeds in the typical permanent seed prostate (LDR) implant.
5. The versatility of intratarget dose modulation inherent to brachytherapy can be controlled and directed with HDR to deliver high doses to gross disease (concomitant boost), or it can be used to selectively reduce the dose to parts of the prostate or organs-at-risk (OARs) as in partial prostate irradiation (focal therapy). This process is sometimes described as dose sculpting or dose painting.
6. HDR dosimetry is prospective (known and approved before treatment delivery), and it consistently provides good target coverage and normal organ sparing (14).
7. The low alpha/beta ratio (estimated 1.2–4) means that the large fraction sizes used in HDR have a relatively high biological effectiveness for prostate cancer (15–17).
8. HDR is applicable to a wide range of clinical circumstances in prostate cancer.
9. A single radioactive source may deliver treatment to large numbers of patients and it can be used for many disease sites. The modality can be deployed in a cost-effective manner.
10. HDR treatment courses are of short duration, and recovery from acute side effects is comparatively brief.
11. HDR radiation safety is good because patients are not radioactive after the procedure. As such, patients do not need to follow special precautions such as limiting distance or duration of contact with other adults, children, or pregnant women. Likewise, there are no issues in handling radioactive sources by pharmacy or medical personnel.
12. Because androgen deprivation therapy (ADT) has not been shown to enhance disease control with prostate HDR monotherapy, and as ADT is usually not required for downsizing of prostate volume with HDR brachytherapy, it can usually be omitted, at least in low- and intermediate-risk group cases.

Patient and case selection

Patients whose disease is confined to the prostate or immediate surrounding tissue are ideal candidates for locally directed treatments such as prostatectomy, EBRT, or brachytherapy alone. National Comprehensive Cancer Network defined low- and intermediate-risk cases are more likely to have disease confined to the prostate region and, therefore, are logically the best candidates for local treatment (National Comprehensive Cancer Network guidelines version 1.2014 at www.nccn.org/professionals/physician_gls/pdg/prostate.pdf).

Nonetheless, some centers have elected to use HDR monotherapy in high-risk group patients based on the idea that it provides a treatment margin greater than radical prostatectomy and that there is no convincing evidence showing an improvement in outcome by treating the pelvic lymph nodes. The use of HDR monotherapy in high-risk group disease is being tested because it can reliably distribute dose around the prostate and into the seminal vesicles. It creates a dose margin without the risk of seed migration, and the dose to the bladder and rectum remain significantly lower than when treating with EBRT.

HDR brachytherapy is technically feasible after transurethral resection of the prostate (TURP) because it uses a scaffolding of catheters rather than prostate tissue to hold the radiation source and the dose to the prostatic urethra can be controlled to limit toxicity (18). Careful urethral dosimetry (maximum dose not exceeding 110% of the prescribed dose) and waiting at least 3 months after TURP to allow wound healing are recommended. In the authors' experience, by following these measures, HDR brachytherapy can be safely administered after TURP.

HDR brachytherapy enables treatment of prostates across a wide range of gland sizes for a variety of reasons including, among other things, the use of a catheter matrix, dwell time modification, and the relatively high energy of the source. It has been shown that prostate glands larger than 50 cm^3 can be treated with HDR without the need of hormonal downsizing (19, 20). The authors have successfully treated prostate glands larger than 100 cm^3. Although prostate size does not always correlate with symptom scores, highly symptomatic patients can be expected to have more urinary outflow issues after brachytherapy than patients who are not symptomatic. However, HDR appears to be less likely to cause prolonged exacerbation of urination symptoms than LDR or EBRT because even patients with International Prostate Symptom Score (IPSS) of 20 or higher tend to have a relatively rapid return to pretreatment baseline urinary function status (20).

Prior pelvic radiation, inflammatory bowel disease, and prior pelvic surgery are not contraindications to prostate HDR brachytherapy, but the dosimetry must include carefully defined normal tissue constraints and there must be full disclosure to the patient of the additional potential risks. Normal tissue sparing is substantially better with HDR than with EBRT and the dose distribution more accurate and predictable than with LDR (21–23). Finally, HDR is one of the salvage treatment options for locally recurrent prostate cancer (24–28).

HDR planning and dosimetry: CT or MRI scan vs. TRUS-based

There are currently two common ways to perform dosimetry and treatment planning for prostate HDR brachytherapy, based on the image acquisition modality and its timing relative to the insertion of the brachytherapy catheters: CT-based and real-time TRUS based. Each method has advantages and disadvantages; choosing one or the other is a matter of departmental resources, site-specific logistics, experience, and personal preferences.

CT scan–based simulation and dosimetry

TRUS-guided HDR catheter insertion is the first of four steps using this method. The catheter insertion is performed under anesthesia in an operating or procedure room. After postoperative recovery, the patient is transferred to a CT scanner for Step 2 where simulation images are obtained and refinements of the catheter positions can be made. CT is most often used for this purpose because they are much more available and practical, although MRI scanners provide better anatomic detail of the prostate and surrounding anatomy. Once approved, the CT image data set is transferred to a treatment planning computer for Step 3 where contours of the target and OARs are generated. Implant catheter distributions are registered and dose calculations are made to produce isodose clouds, dose volume histograms, and virtual dosimetry images. After dosimetry is reviewed and approved by the physician, the plan is uploaded to the treatment console, which transfers the source delivery instructions to the robotic afterloader and where data about the final step, HDR treatment, are monitored.

CT-based dosimetry offers excellent visualization of the brachytherapy catheters and OARs (rectum, urethra, and bladder) and it allows time for careful assessment of the dosimetry (Fig. 1). Although the prostate is more accurately contoured on TRUS, the CT scans can be fused with MRI to gather even more detailed information on key anatomic relationships. Except where dosimetry is performed in a room shielded for HDR brachytherapy, CT simulation in its current form often involves moving the patient. Therefore, the potential disadvantages of CT dosimetry are the need to move the patient and the time it takes to go from one location to another to perform serial functions.

Moreover, changes in catheter positions that occur between simulation and treatment delivery must be identified and corrected.

TRUS-based dosimetry

This method uses the ultrasound images and computer planning in "real-time" to simultaneously guide brachytherapy catheter placement and to perform the dosimetry calculations. It has the advantages that the ultrasound clearly delineates; the prostate capsule and treatment can be delivered immediately afterward without moving the patient, if the implant procedure is performed in a properly shielded venue (i.e., a shielded operating room or brachytherapy suite). TRUS-based planning, however, presents some technical challenges. The image distortions ("shadows") produced by the posterior (dorsal) catheters

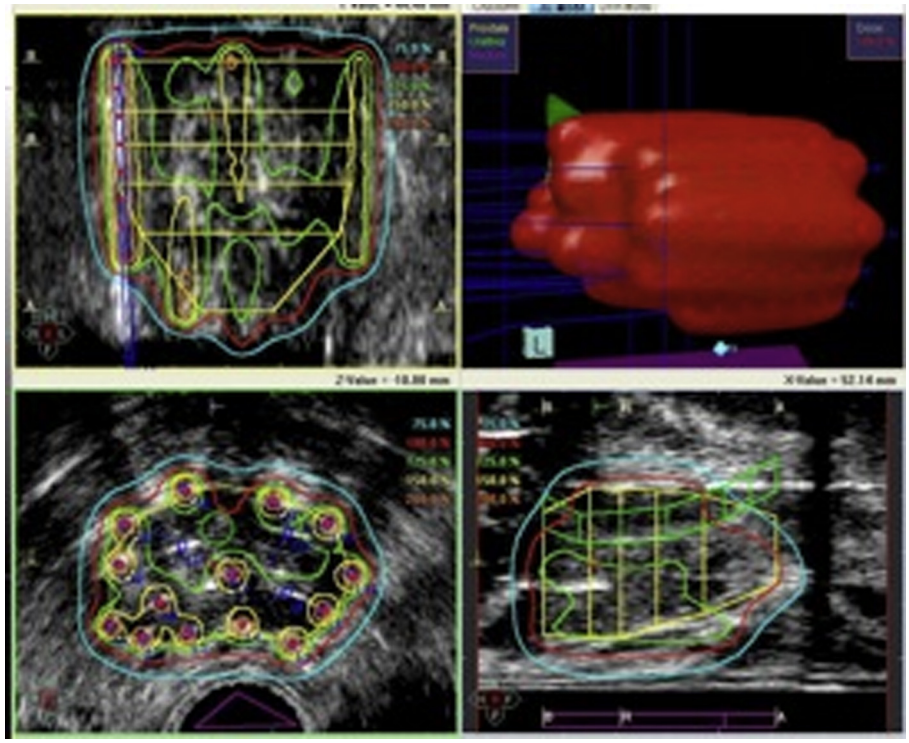

Fig. 1. CT-based dosimetry. Transverse, sagittal, coronal, and three-dimensional views.

can obscure the view of more anterior (ventral) catheters during treatment planning, and the catheters themselves can obscure the prostate contour especially near the apex. Schmid *et al.* (29) compared needle reconstruction accuracy with ultrasound to CT using a phantom. The two main problems were spurious echoes on TRUS and difficulty with craniocaudal needle tip identification (up to 6 mm). In addition, definition of contours of the rectum and to a lesser extent the bladder may be less accurately rendered with real time TRUS planning than with CT-based planning. Newer 3D ultrasound probes will likely reduce some of these technical difficulties (Fig. 2).

Patient motion and multifractioned HDR

Monitoring and adjustment of catheters is not unique to CT dosimetry or TRUS, but rather it is a key element of multifraction HDR brachytherapy. Most of the catheter displacement studies are based on the CT dosimetry process, which involves moving the patient between simulation and treatment delivery. Kovalchuk *et al.* (30) at the Mayo Clinic did a dosimetry study of catheter displacement by comparing initial dosimetry with doses that would be delivered with displaced catheters. They noted a mean needle displacement of 3.5 mm between fractions. The $D_{90} \geq 95\%$ was 100% vs. 82% (initial vs. displaced), $V_{100} \geq 95\%$ was 87% vs. 53%, and urethra $V_{115} \leq 10\%$ was 78% vs. 69%. Replanning improved the dosimetry. Huang *et al.* (31) at Henry Ford Hospital performed CT scans before every HDR fraction in 13 patients and made catheter adjustments when there was >3 mm catheter displacement. Adjustments were made on 30% catheters by an average of 5.8 mm. Without adjustments, the D_{90} would have been 10–32% less than the originally planned and after making adjustments, the D_{90} was within 10% of the original plan. Holly *et al.* (32) from Ontario Canada performed cone-beam CT to assess catheter displacement between planning and the first treatment in 20 consecutive patients and evaluated the ability to improve dosimetry by catheter readjustment. A mean catheter displacement of 11 mm was noted, and it would have resulted in a decrease in mean V_{100} from 98% to 77% ($p < 0.001$), mean D_{90} from 111% to 73% ($p < 0.001$), and an increase in urethra D_{10} from 118% to 125% ($p = 0.0094$) had it not been corrected. Catheter readjustments were helpful (V_{100} 90%, D_{90} 97%, and urethra D_{10} 126%) but did not completely restore the original dosimetry. These and other studies demonstrate that catheter displacement can be a source of discrepancy between the calculated and delivered dose (33–35). The clinical significance of small (e.g., <3 mm) changes in catheter position has not been demonstrated.

There are two TRUS treatment planning interfraction motion studies. Seppenwoolde *et al.* (36) in Holland studied dosimetry of 3 patients to determine if a TRUS ultrasound treatment plan (dwell positions and times) used for the first HDR fraction could be used for subsequent fractions based

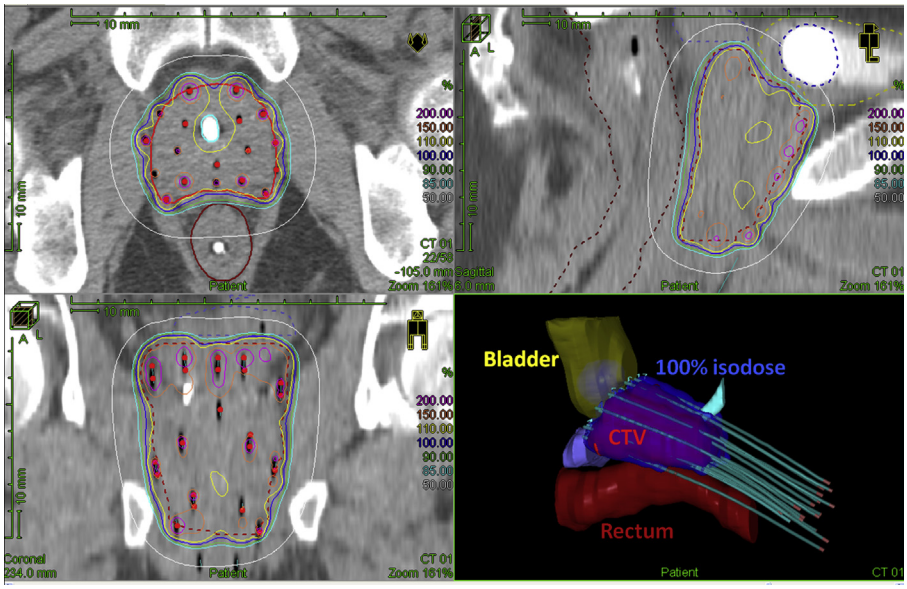

Fig. 2. Ultrasound-based dosimetry. Coronal, transverse, sagittal, and 3D views with 100% isodose lines and 3D cloud (red). 3D = three-dimensional. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

on CT images. They found that the changes in ''posture'' (i.e., leg position) resulted in significant decreases in planning target volume (PTV) coverage (6–28%) and increases in urethra dose. Martinez *et al.* (9) at WBH studied their first 23 patients treated with TRUS-based (four fraction, one implant) HDR monotherapy. Serial TRUS prostate volume measurements were made before each treatment and CT was obtained before the first and after the last treatment. They observed an increase in mean prostate volume from pretreatment 31–37 cm^3 by the first fraction. There was little additional change by the end of treatment (38 cm^3). The corresponding dosimetry between fractions was stable (D_{90} 104–100% and D_{10} urethra 122–132%). The main difference was that the leg position was maintained stable at WBH.

All these studies that address applicator and patient position during the course of HDR treatment highlight the importance of applicator fixation, consistent positioning (or not moving the patient at all), and the need to check and, if necessary, adjust catheters before treatment. The method of catheter and template fixation is another important variable, which has not been addressed in these studies.

Regardless of the technical differences, there is no outcome evidence that one treatment planning method (TRUS vs. CT) is more or less effective than the other. In an effort to improve patient comfort and work flow, the current trend is toward delivering fewer treatments with larger fractions. For example, one treatment per implant in 1–3 separate procedures eliminates interfraction displacement or need for replanning, reduces patient immobilization time, and eliminates an overnight hospital stay. In this regard, portable CT scanners have recently been developed that can be used to obtain the image data set necessary for HDR brachytherapy dosimetry. In terms of patient stability and motion avoidance, the portable CT process and workflow will be very similar to TRUS treatment planning. The real time dosimetry during needle placement will remain a distinct advantage of the TRUS approach and the image quality an advantage of the CT. It is interesting to speculate that technology development might lead to MRI-guided applicator insertion and dosimetry with the dual advantages of real time planning and high image quality.

Target definition and normal tissue dosimetry

Standardization of prostate target is complicated by differences in imaging techniques and variances in image interpretation. There is no consensus whether to contour the prostate at the capsule or with a margin. Although we include the proximal seminal vesicles in the target, it is not clear from the literature whether it is standard practice to do so or not. OAR contouring is similarly subject to variability; particularly because the distinction between the rectoprostate (Denonvillier's) fascia, and the bladder wall from the prostate can be difficult.

HDR prostate monotherapy dose and fractionation schedules have in common a high biological effective dose (BED; 237–354 Gy range at alpha/beta ratio 1.5) and a 1.8–2.0 Gy equivalent dose of ~100–120 Gy. As a general rule, the prostate target volume with or without the seminal vesicles should be covered by at least 95% of the prescription dose (i.e., V_{100} prostate >95%). Maintenance of dose constraints to OARs is equally important. The urethra maximum dose should be below 110% (ideally V_{100} urethra <90%). We recommend further reduction to 105% for patients who have had a TURP; and it is advisable to wait for

wound healing at least 3 months between TURP and prostate brachytherapy. The rectal dose constraints should be 75–80% (e.g., V_{75} rectum <1%). Bladder dosimetry should be considered in terms of minimum and maximum so the dose to bladder wall (surrogate for the peripheral base of the prostate) does not receive <80% nor the bladder neck and trigone >80% (V_{80} bladder neck <1%). Updated European and American guidelines for HDR prostate brachytherapy that include normal tissue dose constraints have been recently published (37, 38).

Clinical experience with HDR monotherapy

A summary of the clinical experience with HDR monotherapy can be found in Table 1 (the treatment protocols), Table 2 (late toxicity), and Table 3 (clinical outcomes).

In May 1995, the first trial of prostate cancer HDR brachytherapy as monotherapy was opened at the University of Osaka, Japan and reported by Yoshioka *et al.* in 2000 (11). The original treatment regimen was 48 Gy in eight fractions and five consecutive days delivered with a single implant. In November 1996, the radiation dose was increased to 54 Gy in nine fractions over 5 days. The treatments were delivered twice daily with an interfraction time of 6 h. Interestingly, 19/22 patients had high-risk features, either T3–4 disease or prostate-specific antigen (PSA) >20 ng/mL, and they received hormonal therapy.

They reported their results in 112 patients (68 high-risk) in 2011 (39). Intermediate-risk patients and those patients with prostate volumes >40 cm^3 received 6–12 months of neoadjuvant ADT, and high-risk patients were treated adjuvant ADT for 3 years to life. The 5-year PSA disease–free survival was 83% (low 85%, intermediate 93%, and high 79%), local control 97%, disease–free survival 87%, and overall survival 96%. Initial PSA and younger age were the only significant prognostic variables. Most toxicity was genitourinary (GU). Acute Grade 3 "Common Toxicity Criteria for Adverse Events" (CTCAE) toxicity was observed in 6 patients. There were thirteen Grade 2 and three Grade 3 toxicities reported.

A detailed dosimetry analysis of late toxicity in 83 patients treated with 54 Gy in nine fractions (median followup 3 years) was reported in 2009 (40). Toxicity correlations with dose volume histogram parameters revealed greatest difference for rectal toxicity were the V_{40} (volume of rectum that receives 40% of the prescription dose) and the D_5 (the dose to 5 cm^3 of the rectum). Rectal toxicity ($V_{40} \geq 8$ cm^3 vs. $V_{40} < 8$ cm^3) was 42% vs. 8%, respectively; $p < 0.001$ and ($D_{5cc} \geq 27$ Gy vs. $D_{5cc} < 27$ Gy) was 50% vs. 11%, respectively; $p < 0.001$. Dosimetry parameters of the urethra of 15 patients with late urinary toxicity were not significantly different from the 68 patients without toxicity. This higher dose regimen was changed to 45.5 Gy in seven fractions over 4 days and it is now the one widely used in Japan.

Komyia *et al.* (41) evaluated the quality of life 51 patients in various risk groups who were treated with a single implant of 45.5 Gy in seven fractions. Long term adjuvant ADT was used for high-risk cases. Quality of life outcomes were measured with the IPSS, the Functional Assessment of Cancer Therapy-Prostate—FACT-P, and the International Index of Erectile Function questionnaire. The FACT-P scores decreased for several months after HDR but subsequently recovered to baseline. In the physical and well-being domain, the score recovered baseline status by 12 weeks. In the social/family well-being domain, baseline status was achieved by 1 year. The total and components of IPSS increased and sexual function decreased at 2 weeks after treatment, but returned to baseline after 12 weeks. There were few severe complications.

Table 1
High-dose-rate monotherapy published dose, fractionation, and dosimetry

Author (reference)	Year	*N*	Risk group	Dose × fractions	Total dose (Gy)	Implant number	Implant interval (wk)	Dosimetry
Barkati *et al.* (50)	2012	79	Low–interm.	10–11.5 Gy × 3	30–34.5	1	n/a	CT
Demanes *et al.* (42)	2011	157	Low–interm.	7 Gy × 6	42	2	1	X-ray/CT
Ghadjar *et al.* (48)	2009	36	Low–interm.	9.5 Gy × 4	38	1	n/a	CT
Ghilezan *et al.* (52)	2012	50	Low–interm.	12 Gy × 2	24	1	n/a	TRUS
		44		13.5 Gy × 2	27	1		
Hoskins *et al.* (49)	2012	55	Interm.–high	8.5–9 Gy × 4	34–36	1	n/a	CT
		109		10.5 Gy × 3	31.5	1		
		33		13 Gy × 2	26	1		
Komiya *et al.* (41)	2013	51	Low–high	6.5 Gy × 7	45.5	1	n/a	
Mark *et al.* (46)	2010	317	Low–high	7.5 Gy × 6	45	2	4	CT
Martinez *et al.* (45)	2010	141	Low–interm.	9.5 Gy × 4	38	1	n/a	TRUS
Prada *et al.* (53)	2012	40	Low–interm.	19 Gy × 1	19	1	n/a	TRUS
Rogers *et al.* (47)	2012	284	Interm.	6.5 Gy × 6	39	2	1–5	CT
Yoshioka *et al.* (39)	2011	111	Interm.–high	6 Gy × 9	54	1	n/a	X-ray/CT
				6.5 Gy × 7	45.5	1		
Zamboglou *et al.* (51)	2013	141	Low–high	9.5 Gy × 4	38	1	n/a	CT
		351		9.5 Gy × 4	38	2	2	TRUS
		225		11.5 Gy × 3	38	3	3	TRUS

Interm. = intermediate; n/a = not applicable; TRUS = transrectal ultrasound.

Table 2
Late toxicity

Author (reference)	Year	*N*	Risk groups	GU Grade 2 (%)	GU Grade 3 (%)	GI Grade 2 (%)	GI Grade 3 (%)	ED (%)
Barkati *et al.* (50)	2012	79	Low–interm.	2–6	2–4	0–3	0	43
Demanes *et al.* (42)	2011	157	Low–interm.	10	3	1	0	n/a
Ghadjar *et al.* (48)	2009	36	Low–interm.	25	11	6	0	25
Ghilezan *et al.* (52)	2012	50	Low–interm.	16	1	1	1	n/a
		44						
Hoskins *et al.* (49)	2012	55	Interm.–high	33–40*	3–16,*	4–13*	0–1*	n/a
		109			3–6 strictures			
		33						
Komiya *et al.* (41)	2013	51	Low–high	QoL (IPSS, FACT-P & IIEF) at baseline after 12 wk				
Mark *et al.* (46)	2010	317	Low–high	3.2	0	1.3	1%	n/a
							0.6% (Grade 4)	
Martinez *et al.* (45)	2010	141	Low–interm.	Grade 1–3, 15–43	0	6.5	0	20
Prada *et al.* (53)	2012	40	Low–interm.	0	0	0	0	NR
Rogers *et al.* (47)	2012	284	Interm.	1.5	0.6	0	0	17.4
Yoshioka *et al.* (39)	2011	112	Low–high	7	1	6	2	NR
Zamboglou	2013	141	Low–high	15.6	9.2	0	0.7	11.1
et al. (51)		351		16.5	4.8	1.7	0	
		225		17.6	3.8	3.5	0	

GU = genitourinary; GI = gastrointestinal; ED = erectile dysfunction; interm. = intermediate; n/a = not applicable; RTOG = Radiation Therapy Oncology Group; QoL = quality of life; IPSS = International Prostate Symptom score; FACT-P = Functional Assessment of Cancer Therapy-Prostate; IIEF = International Index of Erectile Function; NR = not reported.

* RTOG toxicity scale.

Demanes *et al.* (6) at CET in the United States began treating low- and intermediate-risk group patients with HDR monotherapy in 1996 with 7 Gy × 6 fractions in two implants, 1 week apart. In 1997, Martinez *et al.* (9) at WBH initiated an even more hypofractionated program of 9.5 Gy × 4 fractions in one implant over 2 days using a TRUS real time planning system. Given the similarity of the selection criteria, dosimetry, and radiobiology used at CET and WBH, the two centers reported their results in 298 (CET 157 and WBH 141) patients together in 2011 (42). Eligibility criteria were T1c–T2a, Gleason ≤7 (3 + 4, no perineural invasion), and pretreatment PSA <15 ng/mL. Most of the patients had low- or intermediate-risk prostate cancer. The median followup was 5.2 years during which a mean of 10 PSA tests were performed. Twenty-four percent of patients received a median of 4 months ADT for downsizing the gland volume or other reasons by referring physicians. The dosimetry parameters are shown in Table 4. The 5-year (n = 158) and 8-year (n = 39) results were 99% local control, 97% biochemical disease–free survival at 5 years (nadir +2), 99% distant metastasis–free survival, 99% cause-specific survival, and 95% overall survival. GU toxicity was 10% transient Grade 2 urinary frequency or urgency and 3% Grade 3 urinary retention. Gastrointestinal (GI) toxicity was <1%. The low morbidity rates were not demonstrably different between protocols. There was no demonstrable impact from the short course of ADT.

During these early years of HDR monotherapy, there were concerns about normal tissues toxicities and long-term complications that might be associated with large

Table 3
High-dose-rate monotherapy disease control

First author	Year	*N*	Dose × fractions	Years median fu	Local control (%)	PSA-PFS low (%)	PSA-PFS interm. (%)	PSA-PFS high (%)	DMFS (%)	CSS (%)	OS (%)
Barkati	2012	79	10–11.5 Gy × 3	3.3	99		88	n/a	n/a	n/a	n/a
Demanes	2010	157	7 Gy × 6	5.2	99		97	n/a	99	99	95
Ghadjar	2009	36	9.5 Gy × 4	3	n/a	100	100	n/a	n/a	n/a	n/a
Hoskins	2012	55	8.5–9 Gy × 4	4.5	n/a	n/a	95	87	n/a	n/a	n/a
		109	10.5 Gy × 3	3							
Komiya	2013	51	6.5 Gy × 7	1.5	n/a		96		n/a	n/a	n/a
Mark	2010	317	7.5 Gy × 6	8	n/a		88		n/a	n/a	n/a
Martinez	2010	141	9.5 Gy × 4	5.2	99	97		n/a	99	99	95
Prada	2012	40	19 Gy × 1	1.6	100	100	88	n/a	98	98	98
Rogers	2012	284	6 Gy × 6	3	100	n/a	94	n/a	99	100	98
Yoshioka	2011	111	6 Gy × 9	5.4	97	85	93	79	n/a	87	96
Zamboglou	2013	492	9.5 Gy × 4	4.4	n/a	95	93	93	n/a	n/a	97.5
		225	11.5 Gy × 3								

fu = followup; PSA = prostate-specific antigen; PSA-PFS = PSA progression-free survival, biochemical control (ASTRO or nadir +2); interm. = intermediate; n/a = not applicable; DMFS = distant metastases-free survival; CSS = cause-specific survival; OS = overall survival.

Table 4
High-dose-rate monotherapy prescription doses and normal tissue doses

Institution	Dose (Gy × fx)	BED (α/β 1.8)	EBRT (1.8 Gy/fx)	Bladder (%)	Rectum (%)	Urethra (%)	D_{90} (%)	V_{100} (%)
CET	7 Gy × 6	205 Gy	103 Gy	80	80	110	>100	>97
WBH	9.5 Gy × 4	239 Gy	119 Gy	80	75	120	>100	>96

fx = fraction; BED = biological effective dose; EBRT = external beam radiation therapy; CET = California Endocurietherapy Cancer Center; WBH = William Beaumont Hospital.

Maximum normal tissue doses (as percent of prescription).

doses per fraction. However, the rationale for proceeding with HDR monotherapy was the precision dosimetry and ability of HDR to reliably partition the dose between the prostate target and adjacent normal organs, and ultimately in retrospect, the low alpha/beta ratio of prostate that makes large fraction radiobiologically advantageous. Assuming a prostate alpha/beta ratio of 1.5, these programs provided BED in the range of 237–354 Gy, considerably higher than the BED of 178 Gy achieved with EBRT to a total dose of 81 Gy in 1.8 Gy/fraction (43).

As a result of these favorable initial clinical experience with HDR monotherapy, several radiation oncologists around the world started HDR monotherapy programs of their own (Tables 1–3). Most of the centers providing HDR monotherapy follow, or started by following, programs similar to the Osaka, CET, or WBH.

HDR toxicity and comparisons with LDR (permanent seed) brachytherapy

Grills *et al.* (44) in the United States were the first to report the toxicity profile of HDR monotherapy. They assessed comparably match HDR and permanent seed implant, mostly low risk group, followed a median of 35 months (65 patients HDR 9.5 Gy × 4 vs. 84 patients Palladium^{103} 120 Gy). ASTRO definition PSA control disease–free survival was equally high for both treatments (97% and 98%). The majority of toxicities were Grade 1. Acute side effects were significantly lower with HDR (dysuria 36% vs. 67%, frequency/urgency 54% vs. 92%, and rectal pain 6% vs. 20%). Chronic frequency/urgency was also less with HDR 32% vs. 56%. Urethral stricture rates were not statistically different (8% vs. 3% $p = 0.17$). Potency preservation was better for HDR 83% vs. 55%.

WBH and CET did a comprehensive toxicity comparison between 248 HDR monotherapy patients and 206 ^{103}Pd permanent seeds patients (45). A short course (<6 months) of neoadjuvant ADT was used in 30% of patients. The 5-year actuarial biochemical control for monotherapy was 88% for HDR and 89% for seeds. There was no difference in cancer mortality or overall survival.

Acute toxicity

HDR brachytherapy was associated with statistically significant reductions in acute rates of dysuria (seeds 60% vs. HDR 39%) and urgency/frequency (seeds 91% vs. HDR 58%). HDR was also associated with lower rates of rectal pain (seeds 17% vs. HDR 7%). *Chronic toxicity:* HDR brachytherapy was associated with significantly less Grade 1–2 chronic dysuria (seeds 22% vs. HDR 15%) and urinary frequency and urgency (seeds 54% vs. HDR 43%). The occurrence of hematuria was slightly greater for HDR than seeds (11% vs. 7%). The rate of urethral stricture was equal (seeds 2.5% seeds vs. HDR 3%) with the median time to diagnosis of 17 months. Chronic Grade 3 GU toxicity was low in both groups. Approximately 75% of the HDR toxicities were self-limited and required little or no intervention (Grade 1), 23% responded to therapy (Grade 2), and about 2% had more prolong or more severe (Grade 3) symptoms (mostly urinary frequency/urgency). No HDR patient had Grade 4 toxicity. Erectile dysfunction data were available for study in 58% of the cases. The 5-year potency preservation rate was 80% for HDR of 80% and 70% for seeds ($p = 0.23$).

Toxicity and outcome of other CET/Osaka-like regimens (6–7 fractions, 1–2 implants)

Mark *et al.* (46) reported in abstract form the results of 301 patients with T1–2, Gleason 4–10, median PSA 9.3 (2.7–39.8) treated with HDR monotherapy. They administered 7.5 Gy in six fractions in two implants performed 1 month apart. Urethral dose points (12–16) limited to <105% of the prescription dose. Acute urinary retention occurred in 5%. Late Radiation Therapy Oncology Group (RTOG) urinary toxicity was 3% Grade 2 and Grade 3–4 (urethral stricture requiring dilation 6%). Late RTOG rectal toxicity was Grade 1–2 (2.3%) and Grade 3–4 (0.3%). The PSA progression–free survival was 88% at 8 years.

Rogers *et al.* (47) reported their experience on 284 patients with intermediate-risk group patients treated with two HDR implants to deliver six fractions of 6.5 Gy. The 5-year actuarial biochemical survival was 94.4%, local control and cause-specific survival 100%, and distant metastasis–free survival 99%. Percent of core positive over 75% and Stage T2c predicted for worse biochemical control. Patients without these adverse risk factors had a 5-year biochemical control of 97.5%. The incidence of side effects was low. Unlike other reports, there were no urethral strictures. Transient Grade 1 incontinence was found in 7.7% of cases after treatment, but exclusive of patients with prior transurethral resection or neurologic illness it was 2.5%. Grade 1 RTOG rectal toxicity occurred in 4.2%. Potency was maintained in 83% of patients 2 years after therapy.

Toxicity and outcome of WBH-like regimens (four fractions, single implant)

Ghadjar *et al.* (48) reported on 36 patients with low- (28) and intermediate- (8) risk prostate cancer treated with HDR monotherapy in a single implant and four fractions of 9.5 Gy over 2 days. Acute Grade 3 GU toxicity rate was 3% and late GU toxicity 11%. There was no Grade 3 GI toxicity. The 3-year PSA progression–free survival rate was 100%. The sexual preservation rate in patients without ADT was 75%. Late Grade 3 GU toxicity was associated with higher PTV doses as represented by the V_{100} (percent target coverage by 100% isodose) and D_{90} (dose to 90% of the PTV), and the urethral V_{120} (volume urethra receiving ≥120% of the prescription dose).

Hoskin *et al.* (49), in the United Kingdom, conducted a dose escalation trial for mostly intermediate- (52%) and high-risk (44%) patients. A total of 197 patients were treated with 34 Gy in four fractions, 36 Gy in four fractions, 31.5 Gy in three fractions, or 26 Gy in two fractions. Median followup times were 60, 54, 36, and 6 months. Incidence of *early* Grade ≥3 GU morbidity was 3–7%, and Grade 4 0–4%. Grade 3 or 4 *early* GI morbidity was not observed. Late GU toxicity (3 year actuarial) Grade 3 was 3–16%. The 4-year stricture (requiring surgery) rate was 3–7%. Late GI toxicity Grade 3 was 1%. There was no late Grade 4 GI or GU toxicity. At 3 years, 99% of patients with intermediate-risk and 91% with high-risk disease were free of biochemical relapse ($p = 0.02$).

Researchers at Peter McCallum Cancer Center in Australia reported the results of a Phase II prospective dose escalation study of 79 low- and intermediate-risk prostate cancer patients (50). Half of the patients had T2 and half had Gleason 7 prostate cancer. They administered HDR in a single implant over 2 days in three fractions; four different dose schedules were evaluated (10, 10.5, 11, or 11.5 Gy). The 3- and 5-year biochemical control rates (nadir + 2) were 88% and 85%. There were no differences in toxicity between doses. Acute rectal toxicity was nearly all Grade 1 and acute Grade 3 urinary toxicity occurred in only 1 patient. Chronic Grade 3 urinary toxicity was <10% and no Grade 4 toxicities were recorded.

The group from Offenbach Germany, lead by Zamboglou and Baltas, obtained excellent results in 718 patients using intraoperative TRUS treatment planning. The dose and fractionation schedule evolved over time (51). Protocol A (9.5 Gy × 4 in one implant), protocol B (9.5 Gy × 4 in two implants), and finally the current protocol C (11.5 Gy × 3 in three implants). The authors progressively included higher risk group cases so that for protocol C 57% of cases were intermediate- or high-risk compared with 27% in protocol A and 44% in protocol B. The median followup by protocol was 7.7 years for 141 patients (protocol A), 4.9 years for 351 patients (protocol B), and 2.1 years for 226 patients (protocol C). The 3-year biochemical control for all patients was 95% and distant metastasis–free survival was 98%. The 5-year results were available for protocols A and B (9.5 Gy × 4). Biochemical control was 97% and 94%. There were no significant differences correlated with T score, PSA, Gleason score, or risk group. Late Grade 3 GU and GI toxicities were 3.5% and 1.6%. Urinary strictures that required urethrotomy (Grade 3 GU toxicity) occurred in 1.8% and 2 patients required urinary diversion to manage urinary incontinence (Grade 4 GU toxicity). Although the followup is significantly less in protocol C, there were no apparent differences in tumor control or morbidity between the three protocols.

Toxicity and outcome of ultra-hypofractionation (1–2 fractions)

Ghilezan *et al.* (52) reported on an ultra-hypofractionated HDR monotherapy trial for low- and intermediate-risk prostate cancer that accrued 100 patients. The total dose was 24 Gy for the first 50 patients (one implant, two fractions, and 6 h interfraction interval) and 27 Gy in the next 50 patients. The median followup was 17 months. There were no differences in acute or chronic toxicities between the two doses. The maximum chronic GU and GI toxicities Grade 2 or higher were ≤5% with the exception of urinary frequency/urgency, which was 16%. These symptoms resolved by 6 months in most cases (0% for the 24 Gy and 4.8% for the 27 Gy). The program was changed to two implants 2–3 weeks apart to increase the time for normal tissue repair and to shorten the time of the procedure per day by removing the same day waiting between fractions. It also eliminated the need for epidural anesthesia and also improved patient tolerance and satisfaction. Encouraged by this favorable tolerance and toxicity profile, a new protocol of 19 Gy in one fraction was implemented. There has been no Grade 3 or 4 GI or GU toxicity with this protocol, during the first 3 months followup. Patients ineligible for single fraction HDR received the two fraction protocol. Patients with T1c disease, PSA <10 ng/mL, Gleason score 6, up to 3/12 cores positive, none >50% tumor involvement, and patients' age of 65 years or older, are offered 12 Gy × 2 fractions. All other cases are treated with 13.5 Gy × 2 fractions.

Prada *et al.* (53) from Spain published preliminary outcomes in 29 low-risk and 11 intermediate-risk group patients treated with one fraction of 19 Gy. Hyaluronic acid was injected in the rectoprostatic fascia to displace the rectum posterior and away from the prostate. Although the incidence of rectal complications with HDR monotherapy is low with fractionated HDR brachytherapy, the authors were concerned about the effect on the rectum of giving treatment as a single large HDR dose. The hyaluronic acid is injected after catheter placement so it does not interfere with TRUS imaging and then is slowly absorbed by the body over many weeks to months. The median followup was 19 (8–32) months. Thirty-five percent of patients received ADT before brachytherapy. Actuarial

biochemical control at 32 months was 100% in low-risk and 88% in intermediate-risk group patients. The CTCAE Version 4 was used, which, parenthetically, is a system that grades outlet obstruction requiring a catheter as Grade 1. The procedures were well tolerated (one case of postoperative urinary outlet obstruction) and the all the reported acute and chronic toxicity was ≤ Grade 1.

Hoskin *et al.* (54) compared acute GU and GI morbidity in patients with intermediate- and high-risk prostate cancer. They compared 13 Gy × 2 (n = 115), 19 Gy × 1 (n = 24), and 20 Gy × 1 (n = 20) using the RTOG scoring system and IPSS at 2, 4, and 12 weeks. The early (2 week) effect on IPSS was greater for 20 Gy × 1 fraction, but by 12 weeks "all groups were at pretreatment levels or less". Grade 3 GU toxicity was noted in 9% at 20 Gy × 1, 2% for 13 Gy × 2 fractions, and 0% for 19 Gy × 1 fraction. The numbers of patients were too small to demonstrate statistical significance. There were no Grade 4 complications. The single fraction programs were associated with a significant increase in the need for urinary catheters (19 Gy 21% and 20 Gy 29% compared with 13 Gy × 2 7%). The authors suggest that tolerance to single fraction HDR monotherapy may have been reached at 20 Gy × 1.

A randomized Phase II trial sponsored by Sunnybrook Health Science Center in Toronto (principal investigator Dr. Gerard Morton) was opened in 2013 in Canada (ClinicalTrials.gov identifier NCT01890096). Low- and intermediate-risk prostate cancer patients with a gland size up to 60 cm^3 are randomized to either two fractions of 13.5 Gy delivered in two separate implants 7–13 days apart or a single implant with one fraction of 19 Gy. CT and TRUS-based dosimetry are allowed. The primary end point is patient-reported toxicity and health-related quality of life at 1 year.

Focal prostate brachytherapy and organ at risk dose de-escalation

At the University of California Los Angeles research efforts have been directed toward focal prostate brachytherapy using HDR. Kamrava *et al.* (55) published a dosimetric analysis assessing the impact on target coverage and dose to OARs with hemi-gland compared with whole-gland treatment. As expected, the dose to OARs was significantly lower with hemi-gland treatments. Focal HDR treatment planning using interactive multimodality image combination such as multiparametric MRI and spectroscopy along with sophisticated image registration alogorithms are currently being investigated (56).

HDR monotherapy as salvage treatment

HDR monotherapy has been used for treatment of recurrent prostate cancer. Lee *et al.* (25) at the University of California San Francisco reviewed 21 cases they treated with 6 Gy × 6 fractions HDR monotherapy using TRUS-guided and CT treatment–planned HDR brachytherapy. Approximately half of the cases received neoadjuvant ADT. The median followup was 19 (6–84) months. CTCAE Version 3 Grade 1 or 2 GU morbidity was reported in 18 patients by 3 months after HDR salvage. Three patients developed Grade 3 GU toxicity. Three patients had transient (<3 months) Grade 1 or 2 GI toxicity. The 2-year biochemical control was 89%. Failure to achieve a PSA nadir of ≤1.0 ng/mL was associated with biochemical recurrence and the development of distant metastasis.

Tharp *et al.* (26) reported the 5-year results on 7 patients treated with HDR salvage after either external beam radiation (n = 5) or permanent seed implant (n = 2). Median followup was 58 (27–63) months. The disease-free survival was 71% (median not reached). Two patients died of metastatic disease but there were no local failures. One patient developed Grade 2 rectal bleeding attributed to radiation therapy. Although disease control was good and GI toxicity was low, the GU morbidity rate was high. Five patients (71%) developed symptomatic urethral strictures; 2 of these patients had prior TURP and 2 of them (prior seed brachytherapy) required artificial sphincters.

Yamada *et al.* (57) reported the results of a Phase II study of 40 patients treated with HDR brachytherapy (8 Gy × 4 in one implant) after prior EBRT (range 68.4–86.4 Gy). The median pretreatment PSA was 3.45 ng/mL. Twelve patients had neoadjuvant ADT. The median followup was 38 months and time from EBRT to recurrence was 73 months. PSA (nadir + 2) 5 year disease-free survival was 70% and cause-specific survival was 94%. Three patients developed distant metastasis. IPSS returned to baseline in 65% cases by 4.5 months. Patients with higher levels of GU symptoms at baseline were more likely to have Grade 2 urinary morbidity (but not so for Grade 3). Approximately 20% of cases had Grade 2 GI morbidity.

Discussion

HDR monotherapy is the logical extension of HDR used with EBRT as dose escalation and it builds on the large worldwide experience of permanent seed implants without EBRT. There is good evidence in the literature that HDR monotherapy is a safe and effective treatment for prostate cancer. The large doses per fraction take advantage of the radiobiology (low alpha/beta ratio) to potentially render HDR the most efficient and convenient form of radiation therapy. Although patients with early- and intermediate-risk groups are optimal candidates, patients with high-risk group disease also have reported excellent outcomes with HDR monotherapy when compared with other treatment methods. HDR delivers a therapeutic margin of safety for patients with periprostatic or seminal vesicle extension. Prostate HDR brachytherapy is versatile; it can be used as monotherapy, monotherapy salvage, combined with

EBRT, or it can be used as an adjunct to systemic treatment to reduce disease burden to improve remission rates.

HDR dosimetry is prospective (done before source delivery), consistent, and reliable because it is not impacted by setup errors, interfraction and intrafraction organ motion, prostate swelling, or shrinkage during treatment delivery. Furthermore, target coverage is verifiable through pretreatment image guidance designed to avoid unrecognized ''dwell position displacement''. Dose modulation of the stepping source can compensate for catheter spacing and volume discrepancies by using ''optimization'' programs so that dose painting and dose sculpting can be done for dose adjustments within the target boundaries. Such capacities make HDR an excellent choice for monotherapy or for EBRT boost; and in properly selected cases, it can be used to reduce or eliminate radiation to parts of the prostate (focal therapy or dose de-escalation). These measures may enhance the therapeutic index by delivery of dose in proportion to the extent and severity of the disease, and it can reduce morbidity by limiting dose to normal structures.

The excellent results of HDR prostate brachytherapy coupled with the radiobiological advantage of higher doses per fraction especially in tumors with low alpha/beta have prompted clinical trials of stereotactic body radiation therapy (SBRT) to deliver the full course of external beam therapy in 4–6 fractions like HDR (58–65). Fuller *et al.* (66) performed an analysis to determine if SBRT could reproduce the dosimetry achieved with HDR brachytherapy in what was termed ''virtual HDR''. The real stereotactic plans were compared with ''simulated'' HDR plans in which the theoretical brachytherapy trajectories were inserted on the same contours used for SBRT planning. Although the V_{125} and V_{150} were significantly higher with HDR, the urethral doses were lower with the SBRT plans suggesting to the authors that SBRT may limit urethra doses more effectively than HDR. Although such plan comparisons are valuable, they are highly dependent on the treatment planning process. In a more recent dosimetric analysis comparing virtual SBRT with actual HDR monotherapy plans from treated patients have demonstrated HDR achieves significantly higher intraprostatic doses while achieving similar urethral dose and lower maximum rectal dose compared with virtual SBRT treatment planning (67). There are no direct clinical comparison outcome studies of HDR, permanent seeds, or SBRT.

Because ADT has not been shown to enhance disease control with HDR prostate brachytherapy and ADT is usually not required for downsizing of prostate volume with HDR brachytherapy, it can usually be omitted for favorable risk group cases.

Conclusions

Most centers in the United States have used HDR monotherapy to treat low- and intermediate-risk group disease whereas those in Asia and Europe treat patients in all risk groups. HDR brachytherapy can be used to deliver the dose to a definable margin around the prostate and into the seminal vesicles; thus it effectively treats patients with local extension beyond the prostate. Whether higher risk group patients should have HDR monotherapy or HDR combined therapy with EBRT remains to be determined. There is no consensus on the optimal dose and fractionation schedule for HDR brachytherapy. The longest followup for outcomes is with moderate-hypofractionation (4–9 fractions), but excellent results are being reported with ultra-hypofractionation (1–3 fractions). The emergence of ultra-hypofractionation with only 1–2 treatments makes HDR logistically comparable to seed implant and adds a high degree of dosimetry control and accuracy in brachytherapy. There are two simulation and dosimetry methods (TRUS and CT). The advantages of TRUS are its use of real-time imaging and interactive dosimetry whereas CT dosimetry provides the clearest images of catheters and the relationship of the implant to adjacent organs. The TRUS approach is most time efficient. Regardless of the imaging modality and treatment planning system, HDR monotherapy is an excellent treatment modality for the management of prostate cancer.

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