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Review

The emerging role of high-dose-rate (HDR) brachytherapy as monotherapy for prostate cancer

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High-dose-rate (HDR) brachytherapy as monotherapy is a comparatively new brachytherapy procedure for prostate cancer. In addition to the intrinsic advantages of brachytherapy, including radiation dose concentration to the tumor and rapid dose fall-off at the surrounding normal tissue, HDR brachytherapy can yield a more homogeneous and conformal dose distribution through image-based decisions for source dwell positions and by optimization of individual source dwell times. Indication can be extended even to T3a/b or a part of T4 tumors because the applicators can be positioned at the extracapsular lesion, into the seminal vesicles, and/or into the bladder, without any risk of source migration or dropping out. Unlike external beam radiotherapy, with HDR brachytherapy inter-/intra-fraction organ motion is not problematic. However, HDR monotherapy requires patients to stay in bed for 1–4 days during hospitalization, even though the actual overall treatment time is short. Recent findings that the α/β value for prostate cancer is less than that for the surrounding late-responding normal tissue has made hypofractionation attractive, and HDR monotherapy can maximize this advantage of hypofractionation. Research on HDR monotherapy is accelerating, with a growing number of publications reporting excellent preliminary clinical results due to the high 'biologically effective dose (BED)' of >200 Gy. Moreover, the findings obtained for HDR monotherapy as an early model of extreme hypofractionation tend to be applied to other radiotherapy techniques such as stereotactic radiotherapy. All these developments point to the emerging role of HDR brachytherapy as monotherapy for prostate cancer.

Keywords: prostate cancer; high-dose-rate (HDR); brachytherapy; monotherapy; hypofractionation

INTRODUCTION

Multiple treatment options are available for clinically localized prostate cancer, including radical prostatectomy, external beam radiotherapy (EBRT), brachytherapy, and a combination of EBRT and brachytherapy. Brachytherapy in the form of a permanent low-dose-rate (LDR) seed implant, or as high-dose-rate (HDR) afterloading, can deliver a highly localized radiation dose to the tumor. While LDR brachytherapy has been examined and assessed the most and become a standard treatment option, HDR brachytherapy is recently gaining momentum as an alternative. Several features of HDR brachytherapy, including uniformly accurate, precise, and reproducible dosimetry resulting from its advanced optimization capabilities, radiobiological and radioprotective advantages, and reduced costs, have made HDR attractive for the treatment of prostate cancer. These advantages avoid the dosimetric uncertainties of LDR related to postimplant volume changes due to needle trauma and subsequent edema during the several months of overall treatment time. HDR significantly improves the radiation dose distribution because it can

modulate and accurately control both the spatial source position and dwell time during treatment.

Historically, HDR brachytherapy was introduced to boost EBRT [1, 2]. Accumulation of clinical results for EBRT and HDR brachytherapy combination therapy culminated in recommendations by the Groupe Européen de Curiethérapie (GEC)/European Society for Radiotherapy and Oncology (ESTRO)-European Association of Urology (EAU) [3], and consensus guidelines by the American Brachytherapy Society (ABS) [4]. However, this combination typically adds 4–5 weeks to the time needed for completion of EBRT, in addition to hospitalization for HDR brachytherapy. HDR brachytherapy as monotherapy, on the other hand, would definitely be the most efficient method of achieving a high degree of conformity and dose escalation. The aim of this paper is to review the literature to date for HDR brachytherapy as monotherapy and to discuss its function and future direction.

HISTORY AND INDICATION

Tables 1 and 2 list as many data on dose fractionation and its clinical results as we could collect from the literature on HDR brachytherapy as monotherapy for prostate cancer [5–22]. Our search resulted in a total of approximately 20 articles from only 11 institutions worldwide. The number of dose-fractionation schedules used was larger than the number of institutions because some institutions adopted several dose-fractionation schedules, mostly involving dose escalation. Since very few institutions were using HDR monotherapy in the 1990s, relevant articles published in the 2000s were also very few. In the 2000s, however, a growing number of institutions started to use HDR monotherapy, so that the number of germane papers published in the 2010s has also been increasing.

In the first article on HDR monotherapy from Osaka University, Japan, published in 2000, the authors reported they had initiated HDR monotherapy in 1995, with indications for low- to high-risk prostate cancer [5]. Two subsequent articles, however, one from the William Beaumont Hospital in the USA (2001) [6] and the other from Klinikum Offenbach in Germany (2004) [7], reported that indications were limited to low- or low-to-intermediate-risk patients. As a result, some investigators maintained that HDR monotherapy was suitable only for low or low-to-intermediate risk, and a combination of EBRT and HDR brachytherapy for intermediate- to high-risk patients, thus emulating the scheme for LDR brachytherapy. On the other hand, a subsequent report from Mount Vernon Cancer Centre in the UK published in 2008 [8] mentioned the inclusion of high-risk patients, and in their second report (2012) [9], the authors clearly stated that they had indicated HDR monotherapy mainly for intermediate- and high-risk groups. Similarly, radiation oncologists at Osaka University have been limiting their indications to intermediate- and high-risk groups since 2005 (and LDR brachytherapy to low-risk patients) (Y. Yoshioka *et al.*, submitted for publication). According to the second report from Klinikum Offenbach published in 2013 [10], indications had been extended to high-risk patients. Of their 226 patients, who were treated with their latest protocol using 34.5 Gy in three fractions with three implants, 42% were low-, 32% intermediate-, and 25% high-risk patients. A report from the GammaWest Cancer Services in Salt Lake City, UT published in 2012 listed the clinical results of HDR monotherapy for 284 intermediate-risk patients [11]. All these recent studies clearly indicate that limiting indications for HDR monotherapy to low-risk patients is no longer viable, and such indications now tend to be extended to high-risk patients.

However, one should be aware of the possibility of micrometastases to pelvic lymph nodes, especially in high-risk patients. The Radiation Therapy Oncology Group (RTOG) 9413 study showed superiority of whole-pelvic RT to prostate-only RT on progression-free survival [23, 24]. This may imply that whole-pelvic RT plus HDR brachytherapy boost, or simultaneous integrated boost intensity-modulated RT (SIB-IMRT), e.g., is more suitable for such high-risk patients. In contrast, some authors have denied the benefit of pelvic RT in high-risk patients of positive pelvic lymph nodes treated with high-dose radiation [25]. On the other hand, local dose escalation has been questioned many times concerning whether it is associated with decreasing disease-specific mortality [26]. Overall, the benefit of whole-pelvic RT or local dose escalation to overall survival is still in debate [27, 28], and investigators of HDR monotherapy, an ideal tool for local dose escalation which avoids whole-pelvic RT, are recommended to take this issue into consideration when they apply such a treatment to intermediate- to high-risk patients.

EQUIPMENT AND RADIATION PHYSICS

(i) Because the dose-rate of the radioactive source is high, a remote afterloading system (RALS) or an HDR unit, which is now commonly used for intracavitary brachytherapy for uterine cervix cancer, is essential. A typical HDR unit involves one ^{192}Ir stepping source, 4.5 mm in length and 0.9 mm in diameter, which has a radioactivity of 370 GBq at the time of certification. ^{192}Ir has an average energy of 370 keV and a half-life of 73.8 days.

(ii) Under lumbar or epidural anesthesia, plastic or metallic needle applicators are inserted via the perineum into the prostate gland with the aid of real-time transrectal ultrasound (TRUS) guidance. TRUS is usually equipped with a template that is used to determine placement of the needles. The

Table 1. Dose fractionation and BED of prostate HDR brachytherapy as monotherapy

Author [ref.]	Institution	Country	Start (year)	Publication (year)	HDR physical dose			BED (Gy)		EQD_{2Gy} (Gy)	
					Dose/ fraction	No. of fractions	Total dose	α/β = 1.5 Gy	α/β = 3.0 Gy	α/β = 1.5 Gy	α/β = 3.0 Gy
Yoshioka [5, submitted for publication, 19–21]	Osaka University	Japan	1995	2000	6 Gy	8	48 Gy	240	144	103	86
			1996	2011	6 Gy	9	54 Gy	270	162	116	97
			2005	in submission	6.5 Gy	7	45.5 Gy	243	144	104	86
Demanes [12]	California Endocurietherapy	USA	1996	2011	7 Gy	6 (2 implants)	42 Gy	238	140	102	84
Martinez [6, 18, 22]	William Beaumont Hospital	USA	1999	2010	9.5 Gy	4	38 Gy	279	158	119	95
			2005	2012	12 Gy	2	24 Gy	216	120	93	72
					13.5 Gy	2	27 Gy	270	149	116	89
Rogers [11]	Salt Lake City	USA	2001	2012	6.5 Gy	6 (2 implants)	39 Gy	208	124	89	74
Zamboglou [7, 10]	Klinikum Offenbach	Germany	2002	2004	9.5 Gy	4	38 Gy	279	158	119	95
				2013	9.5 Gy	4 (2 implants)	38 Gy	279	158	119	95
					11.5 Gy	3 (3 implants)	34.5 Gy	299	167	128	100
Hoskin [8, 9]	Mount Vernon Hospital	UK	2003	2008	8.5 Gy	4	34 Gy	227	130	97	78
					9 Gy	4	36 Gy	252	144	108	86
					10.5 Gy	3	31.5 Gy	252	142	108	85
				2012	13 Gy	2	26 Gy	251	139	108	83
Ghadjar [13]	University of Bern	Switzerland	2003	2009	9.5 Gy	4	38 Gy	279	158	119	95
Barkati [14]	Melbourne	Australia	2003	2012	10 Gy	3	30 Gy	230	130	99	78
					10.5 Gy	3	31.5 Gy	252	142	108	85
					11 Gy	3	33 Gy	275	154	118	92
					11.5 Gy	3	34.5 Gy	299	167	128	100
Yoshida [15]	Osaka National Hospital	Japan	2004	2010	7 Gy	7	49 Gy	278	163	119	98
					6 Gy	9	54 Gy	270	162	116	97
					9.5 Gy	4	38 Gy	279	158	119	95
Komiya [16]	University of Toyama	Japan	2007	2013	6.5 Gy	7	45.5 Gy	243	144	104	86
Prada [17]	Asturias	Spain	2008	2012	19 Gy	1	19 Gy	260	139	111	84

BED = biologically effective dose, HDR = high-dose-rate, EQD_{2Gy} = biologically equivalent dose in 2-Gy fractions.

template has many holes for the needles to pass through, and their positions are superimposed on the TRUS monitor in advance. The tips of these needles tip are closed, unlike the ones used for LDR permanent seed implants.

(iii) Treatment planning is based on the computed tomography (CT) images obtained after needle insertion, or on the TRUS images obtained at the time of needle insertion. The dwell positions of the stepping source are determined in terms of real anatomy, that is, of the actual condition with the needles inserted. The dwell time for each dwell position is then calculated with an optimization algorithm.

(iv) Medical staff are never exposed to radiation, and patients can stay in a regular ward since there is no need for a shielded room. Patients only need to go to a RALS room for irradiation, which takes approximately 10 minutes per fraction.

(v) Radiation dose from the source obeys the inverse square law. This means that the dose to the region outside the planning target volume (PTV) decreases rapidly, thus sparing the surrounding normal tissue. This process is visible as a rapid dose fall-off on a dose distribution plot.

(vi) Unlike for EBRT, inter-/intra-fraction organ motion is not a problem with HDR brachytherapy. In the case of EBRT, several factors including daily set-up errors, retention of feces, gas, or urine, respiratory motion, or peristaltic motion result in discrepancies between the coordinates of the tumor and the radiation beam. With brachytherapy, on the other hand, these two coordinates are always concordant because the tumor and the radioactive sources move in unison, so that PTV is normally identical to the clinical target volume (CTV). However, needle displacement is problematic with HDR brachytherapy (see (viii) below). The overall treatment time for HDR monotherapy typically ranges from 1–4 days, which is significantly shorter than for EBRT.

(vii) Unlike for LDR brachytherapy, HDR brachytherapy needles can be placed at the extracapsular lesion, and even into the seminal vesicles and/or into the bladder pouch, if necessary. The cable-connected stepping source simply moves back and forth within the closed space without any risk of source migration or dropping out. Therefore, the indication for HDR monotherapy can potentially be extended to even T3a/b or some T4 tumors. The above-mentioned dwell time optimization makes a significant urethral dose reduction possible for HDR compared to that for LDR.

(viii) One of the drawbacks of HDR brachytherapy is the problem of needle applicator displacement during treatment [6, 15, 29–34]. To overcome this problem, some radiation oncologists use daily CT scans to adjust needle positions or source dwell positions or use roentgenography to readjust the relative locations of the implanted fiducial markers and the needles. Another drawback of HDR is the requirement of hospitalization and patients having to stay in bed during the treatment period. As for the latter problem, treatment periods tend to become shorter with an increase in the fraction size (see the next section). Some practitioners have even adopted a multiple-implant schedule with a single fraction irradiation for each implant, which avoids the disadvantages of both needle displacement and hospitalization [10].

RADIATION BIOLOGY AND DOSE FRACTIONATION

The α/β value of prostate cancer is considered to be significantly lower than that of other cancers such as of the lung, or of the head and neck. In 1999, Brenner and Hall published a groundbreaking paper on this issue, in which they asserted that the α/β value of prostate cancer was 1.5 Gy [35]. This has been followed by a significant number of publications reporting α/β values mostly in the range of 1.2 – 3.1 Gy [36–39]. For the rest of this paper we will use $\alpha/\beta = 1.5$ Gy because we consider it to be closest to the standard value. On the other hand, the α/β value for late-responding normal tissue has been reported as 2.0 – 5.4 Gy, and recently a value of around 5.0 Gy has been gaining wider acceptance [40, 41]. However, the traditional value of 3.0 Gy is often still used, and this value is indeed safer when dealing with a hypofractionated dose-fractionation model such as HDR, so that $\alpha/\beta = 3.0$ Gy will be used hereafter. In addition, we will use the traditional linear-quadratic (LQ) formula [42]:

$$BED = nd(1 + d/(\alpha/\beta)),$$

where BED = biologically effective dose, n = number of fractions, and d = dose per fraction.

However, we note that for an extremely hypofractionated dose range such as ≥ 6.0 Gy/fraction, compatibility of the LQ formula is not entirely assured. To understand by intuition, we also calculated EQD_{2Gy} as the biologically equivalent dose in 2-Gy fractions.

Until the publication of the previously mentioned paper by Brenner and Hall in 1999, HDR for prostate cancer had

Table 2. Clinical results of prostate HDR brachytherapy as monotherapy

Author [ref.]	Dose fractionation	No. of Patients	Follow-up (year)	PSA control rate/ Risk group	Late toxicity ≥ Grade 2[a]	
					Genitourinary	Gastrointestinal
Yoshioka [submitted for publication, 21]	54 Gy/9 Fr.	112	5.4	85% (5y)/Low 93% (5y)/Intermediate 79% (5y)/High	7.1%	7.1%
	45.5 Gy/7 Fr.	63	3.5	96% (3y)/Intermediate 90% (3y)/High	6.3%	1.6%
Demanes [12]	42 Gy/6 Fr.	157	5.2	97% (5y)/Low–intermediate	28.9%	<1.0%
Martinez [18, 22]	38 Gy/4 Fr.	171	4.6	91% (5y)/Low–intermediate	40.5%	2.0%
	24 Gy/2 Fr.	50	1.4	Not available	25.5%	5.3%
	27 Gy/2 Fr.	44				
Rogers [11]	39 Gy/6 Fr.	284	2.7	94% (5y)/Intermediate	7.7%	0.0%
Zamboglou [10]	38 Gy/4 Fr.	141	4.4	95% (5y)/Low	27.5%	2.6%
	38 Gy/4 Fr.	351		93% (5y)/Intermediate		
	34.5 Gy/3 Fr.	226		93% (5y)/High		
Hoskin [9]	34 Gy/4 Fr.	34	3.5	95% (3y)/Intermediate 87% (3y)/High	33.0%	13.0%
	36 Gy/4 Fr.	25			40.0%	4.0%
	31.5 Gy/3 Fr.	55			34.0%	7.0%
Ghadjar [13]	38 Gy/4 Fr.	36	3	100% (3y)/Low–intermediate	36.1%	5.6%
Barkati [14]	30 Gy/3 Fr.	19	3.3	88% (3y)/Low–intermediate	59.0%	5.1%
	31.5 Gy/3Fr.	19				
	33 Gy/3 Fr.	19				
	34.5 Gy/3 Fr.	22				
Komiya [16]	45.5 Gy/7 Fr.	51	1.4	100% (2y)/Low–high	11.8%	2.0%
Prada [17]	19 Gy/1 Fr.	40	1.6	100% (2.7y)/Low 88% (2.7y)/Intermediate	0.0%	0.0%

HDR = high-dose-rate, PSA = prostate-specific antigen, Fr. = fraction(s). [a]Scored per event not per patient.

been considered disadvantageous in terms of radiation biology because its large fraction size had been associated with more late-tissue damage, as in the case of other cancers, although it was seen as more effective in terms of radiation physics. However, Brenner and Hall's paper resulted in a drastic change due to its astounding assertion that the α/β value of prostate cancer was smaller than that of normal tissue, implying that a hypofractionated dose fractionation regimen such as HDR could be considered advantageous in terms of radiation biology as well. HDR, especially as monotherapy, thus gained recognition as, at least in theory, an excellent method in terms of both radiation biology and physics. As seen in Table 1, only three institutions were using HDR monotherapy in the 1990s [5, 6, 12], whereas eight additional new institutions initiated it in the 2000s [7, 8, 11, 13–17].

Table 1 lists dose fractionations and associated BEDs of monotherapeutic HDR brachytherapy from the literature. The BED for prostate cancer ranges from 208–299 Gy, with a median of 256 Gy. In comparison with LDR brachytherapy, where some practitioners attempted to attain BED > 200 Gy by adding EBRT for a better outcome [43], HDR monotherapy has already achieved BEDs far higher than 200 Gy. The values for EQD_{2Gy} range from 89–128 Gy, with a median of 110 Gy, which may be impossible to administer with EBRT, even when using the most up-to-date IMRT technique. As for late toxicity, EQD_{2Gy} ranges from 72–110 Gy, with a median of 86 Gy, which can be considered the equivalent of the maximum dose of 86.4 Gy administered with the current IMRT [44]. This means that, theoretically, hypofractionation with a large fraction size can enhance BED for prostate cancer without increasing BED for late-responding tissue.

Recent trends are toward a smaller number of fractions and shorter treatment. In the 1990s and the early 2000s, many institutions started using a 4-fraction regimen, for example, 38 Gy/4 fractions [6–8, 13]. However, 3-, 2-, or even 1-fraction regimens have been adopted recently.

Zamboglou *et al.* [10], Hoskin *et al.* [9], and Barkati *et al.* [14] used 30–34.5 Gy/3 fractions (10–11.5 Gy per fraction), and Hoskin *et al.* [9] and Ghilezan *et al.* [18] used 26–27 Gy/2 fractions (13–13.5 Gy per fraction). Prada *et al.* [17] reported their findings for a 19 Gy/1 fraction regimen. Such a single-fraction regimen would maximize the therapeutic ratio, and at the same time would avoid the drawbacks of HDR brachytherapy (hospitalization and needle displacement during the treatment period). However, a single-fraction regimen might, by its very nature, diminish the advantages of fractionation, that is, reoxygenation and redistribution (reassortment). Careful watching thus seems to be essential for such an intriguing new regimen.

Multiple implants constitute an alternative approach. For this procedure, as performed at the California Endocurietherapy [12] and the GammaWest Cancer Services [11], each implant consists of three fractions over two days, after which this set is repeated. A total of 6 fractions are delivered with a moderate fraction size of 6.5–7.0 Gy. At Klinikum Offenbach [10], three implants are used with 11.5 Gy for each implant with a single fraction. At this institution, multi-fraction HDR monotherapy is reportedly completed without hospitalization.

At Osaka University, dose fractionation was changed from 54 Gy/9 fractions to 45.5 Gy/7 fractions in 2005, in conjunction with an increase in fraction size from 6 Gy to 6.5 Gy (Y. Yoshioka *et al.*, submitted for publication). The new schedule involves not only a reduction in the bed confinement period from 5 to 4 days, but also a reduction in BED. The stated reason for reducing the dose was that many clinical results with high biochemical control rates had proven the BED of HDR monotherapy to be high enough, and that the next step should be dose reduction to diminish the toxicity rate without compromising the high control rate.

REPORTED CLINICAL RESULTS

Table 2 lists clinical results of monotherapeutic HDR brachytherapy from the literature. Only 10 institutions worldwide have reported clinical results for prostate HDR monotherapy. The longest median follow-up was 5.4 years, while the median follow-up of most of the studies was only 1–3 years.

The reported 5-year prostate-specific antigen (PSA) control rate for low-risk groups ranged from 85–97%, mostly >90%. For intermediate-risk groups, some authors reported a PSA control rate of 93–94%, and for high-risk groups, it was reported between 79 and 93%, mostly >80%. Although none of these studies have reported a follow-up period much beyond 5 years, the overall PSA control rates reported thus far have been excellent, which may be attributed to the high BED of >200 Gy mentioned above.

The reported toxicity levels were generally acceptable. However, some authors have reported Grade 3 toxicity. Frequency of late genitourinary (GU) toxicity ≥ Grade 2 ranged from 0–59.0%, and for late gastrointestinal (GI) toxicity the rate was 0–13.0%. While late GI toxicity was ≤ 5% in most cases, several authors reported late GU toxicity as high as 20–40%. It should be noted, however, that these values were obtained per event, not per patient; that is, multiple events may have been counted for one patient. Because of the short follow-up period for most of the studies, very little actuarial toxicity data per patient has been available. A comparison with IMRT, for example, would be difficult at present and has to await the availability of more mature clinical data for HDR monotherapy.

HDR AS A PRECEDENT MODEL OF EXTREME HYPOFRACTIONATION FOR STEREOTACTIC RADIOTHERAPY AND PARTICLE THERAPY

A discussion of hypofractionation for prostate cancer would entail a typical fraction size of 2.5–3.0 Gy when a linear accelerator is used. Because HDR monotherapy adopts a much larger fraction size, such as 6–10 Gy or more, some authors refer to it as ‘extreme hypofractionation’ [21, 45]. Some groups, including Stanford University [46] and a multi-institutional trial in the USA [47], have introduced stereotactic body radiotherapy (SBRT) using e.g. CyberKnife with extreme hypofractionation, with reference to the dose fractionations and clinical results of HDR monotherapy. Some investigators at the CyberKnife Center in San Diego, CA, tested the ability of CyberKnife plans to approximate the dose distribution of HDR brachytherapy and concluded that this was indeed possible, naming the procedure the ‘virtual HDR’ CyberKnife treatment [48].

Particle therapy, which can be considered a kind of EBRT in terms of extracorporeal administration of ionizing radiation, can yield a better dose distribution as with SBRT. If an excellent dose concentration to the tumor, or a dose that sufficiently spares the adjacent normal tissue can be assured, we would be inclined to proceed to hypofractionation because of patient convenience and medical resource efficiency. Brachytherapy is generally deemed the most appropriate method for testing an unprecedentedly high dose of irradiation, because the dose invariably falls off rapidly due to the inverse square law. In addition, it is not affected by any organ motion either intra- or inter-fractionally. In other words, brachytherapy seems to be the least likely to entail unexpected pitfalls such as the uncertainty of dose distribution caused by the interplay effect when segmented or spotted beams are used in EBRT. It therefore seems reasonable to test an inexperienced BED or dose fractionation with HDR monotherapy first, and then to replace it with SBRT or particle therapy using the findings obtained by

HDR monotherapy, but also moving on to less invasive radiotherapy.

CONCLUSION

HDR monotherapy is a comparatively new brachytherapy method for prostate cancer with a dose distribution that is superior in terms of radiation physics. Furthermore, it can maximize the advantages of hypofractionation in terms of radiation biology. Research on HDR monotherapy is accelerating, with a growing number of publications reporting excellent preliminary clinical results due to the high BED. These findings, obtained by HDR monotherapy as a precedent-setting model of extreme hypofractionation, have recently tended to be used for other radiotherapy techniques, such as SBRT. All of these facts point to the emerging role of HDR brachytherapy as monotherapy for prostate cancer.

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REFERENCES

1. Galalae RM, Kovacs G, Schultze J *et al*. Long-term outcome after elective irradiation of the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;**52**:81–90.
2. Mate TP, Gottesman JE, Hatton J *et al*. High dose-rate afterloading Ir-192 prostate brachytherapy: feasibility report. *Int J Radiat Oncol Biol Phys* 1998;**41**:525–33.
3. Kovács G, Pötter R, Loch T *et al*. GEC/ESTRO-EAU recommendations on temporary brachytherapy using stepping sources for localised prostate cancer. *Radiother Oncol* 2005;**74**:137–48.
4. Yamada Y, Rogers L, Demanes DJ *et al*. American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy. *Brachytherapy* 2012;**11**:20–32.
5. Yoshioka Y, Nose T, Yoshida K *et al*. High-dose-rate interstitial brachytherapy as a monotherapy for localized prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. *Int J Radiat Oncol Biol Phys* 2000;**48**:675–81.
6. Martinez A, Pataki I, Edmundson G *et al*. Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: a feasibility report. *Int J Radiat Oncol Biol Phys* 2001;**49**:61–9.
7. Martin T, Baltas D, Kurek R *et al*. 3-D conformal HDR brachytherapy as monotherapy for localized prostate cancer. A pilot study. *Strahlenther Onkol* 2004;**180**:225–32.
8. Corner C, Rojas AM, Bryant L *et al*. A Phase II study of high-dose-rate afterloading brachytherapy as monotherapy for the treatment of localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;**72**:441–6.
9. Hoskin P, Rojas A, Lowe G *et al*. High-dose-rate brachytherapy alone for localized prostate cancer in patients at moderate or high risk of biochemical recurrence. *Int J Radiat Oncol Biol Phys* 2012;**82**:1376–84.
10. Zamboglou N, Tselis N, Baltas D *et al*. High-dose-rate interstitial brachytherapy as monotherapy for clinically localized prostate cancer: treatment evolution and mature results. *Int J Radiat Oncol Biol Phys* 2013;**85**:672–8.
11. Rogers CL, Alder SC, Rogers RL *et al*. High dose brachytherapy as monotherapy for intermediate risk prostate cancer. *J Urol* 2012;**187**:109–16.
12. Demanes DJ, Martinez AA, Ghilezan M *et al*. High-dose-rate monotherapy: safe and effective brachytherapy for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;**81**:1286–92.
13. Ghadjar P, Keller T, Rentsch CA *et al*. Toxicity and early treatment outcomes in low- and intermediate-risk prostate cancer managed by high-dose-rate brachytherapy as a monotherapy. *Brachytherapy* 2009;**8**:45–51.
14. Barkati M, Williams SG, Foroudi F *et al*. High-dose-rate brachytherapy as a monotherapy for favorable-risk prostate cancer: a Phase II trial. *Int J Radiat Oncol Biol Phys* 2012;**82**:1889–96.
15. Yoshida K, Yamazaki H, Nose T *et al*. Needle applicator displacement during high-dose-rate interstitial brachytherapy for prostate cancer. *Brachytherapy* 2010;**9**:36–41.
16. Komiya A, Fujiuchi Y, Ito T *et al*. Early quality of life outcomes in patients with prostate cancer managed by high-dose-rate brachytherapy as monotherapy. *Int J Urol* 2013;**20**:185–92.
17. Prada PJ, Jimenez I, González-Suárez H *et al*. High-dose-rate interstitial brachytherapy as monotherapy in one fraction and transperineal hyaluronic acid injection into the perirectal fat for the treatment of favorable stage prostate cancer: treatment description and preliminary results. *Brachytherapy* 2012;**11**:105–10.
18. Ghilezan M, Martinez A, Gustason G *et al*. High-dose-rate brachytherapy as monotherapy delivered in two fractions within one day for favorable/intermediate-risk prostate cancer: preliminary toxicity data. *Int J Radiat Oncol Biol Phys* 2012;**83**:927–32.
19. Yoshioka Y, Nose T, Yoshida K *et al*. High-dose-rate brachytherapy as monotherapy for localized prostate cancer: a retrospective analysis with special focus on tolerance and chronic toxicity. *Int J Radiat Oncol Biol Phys* 2003;**56**:213–20.
20. Yoshioka Y, Konishi K, Oh RJ *et al*. High-dose-rate brachytherapy without external beam irradiation for locally advanced prostate cancer. *Radiother Oncol* 2006;**80**:62–8.
21. Yoshioka Y, Konishi K, Sumida I *et al*. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: five-year results of an extreme hypofractionation regimen with 54 Gy in nine fractions. *Int J Radiat Oncol Biol Phys* 2011;**80**:469–75.
22. Martinez AA, Demanes J, Vargas C *et al*. High-dose-rate prostate brachytherapy: an excellent accelerated-hypofractionated

treatment for favorable prostate cancer. *Am J Clin Oncol* 2010;**33**:481–8.
23. Roach M, 3rd, DeSilvio M, Lawton C *et al*. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol* 2003;**21**:1904–11.
24. Lawton CA, DeSilvio M, Roach M, III *et al*. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys* 2007;**69**:646–55.
25. Vargas CE, Galalae R, Demanes J *et al*. Lack of benefit of pelvic radiation in prostate cancer patients with a high risk of positive pelvic lymph nodes treated with high-dose radiation. *Int J Radiat Oncol Biol Phys* 2005;**63**:1474–82.
26. Schulz RJ, Kagan AR. Dose escalation in the radiation therapy of prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;**80**:1289–91.
27. Morikawa LK, Roach M, III. Pelvic nodal radiotherapy in patients with unfavorable intermediate and high-risk prostate cancer: evidence, rationale, and future directions. *Int J Radiat Oncol Biol Phys* 2011;**80**:6–16.
28. Kim MM, Hoffman KE, Levy LB *et al*. Prostate cancer-specific mortality after definitive radiation therapy: who dies of disease? *Eur J Cancer* 2012;**48**:1664–71.
29. Damore SJ, Syed AM, Puthawala AA *et al*. Needle displacement during HDR brachytherapy in the treatment of prostate cancer. *Int J Radiat Oncol Biol Phys* 2000;**46**:1205–11.
30. Hoskin PJ, Bownes PJ, Ostler P *et al*. High dose rate afterloading brachytherapy for prostate cancer: catheter and gland movement between fractions. *Radiother Oncol* 2003;**68**: 285–8.
31. Mullokandov E, Gejerman G. Analysis of serial CT scans to assess template and catheter movement in prostate HDR brachytherapy. *Int J Radiat Oncol Biol Phys* 2004;**58**:1063–71.
32. Simnor T, Li S, Lowe G *et al*. Justification for inter-fraction correction of catheter movement in fractionated high dose-rate brachytherapy treatment of prostate cancer. *Radiother Oncol* 2009;**93**:253–8.
33. Foster W, Cunha JA, Hsu IC *et al*. Dosimetric impact of interfraction catheter movement in high-dose rate prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2011;**80**:85–90.
34. Kolkman-Deurloo IK, Roos MA, Aluwini S. HDR monotherapy for prostate cancer: a simulation study to determine the effect of catheter displacement on target coverage and normal tissue irradiation. *Radiother Oncol* 2011;**98**:192–7.
35. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999;**43**:1095–101.
36. Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? *Int J Radiat Oncol Biol Phys* 2001; **50**:1021–31.
37. Brenner DJ, Martinez AA, Edmundson GK *et al*. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. *Int J Radiat Oncol Biol Phys* 2002;**52**:6–13.
38. Wang JZ, Guerrero M, Li XA. How low is the alpha/beta ratio for prostate cancer? *Int J Radiat Oncol Biol Phys* 2003;**55**:194–203.
39. Miralbell R, Roberts SA, Zubizarreta E *et al*. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: α/β=1.4 (0.9–2.2) Gy. *Int J Radiat Oncol Biol Phys* 2012;**82**:e17–24.
40. Brenner DJ. Fractionation and late rectal toxicity. *Int J Radiat Oncol Biol Phys* 2004;**60**:1013–5.
41. Tucker SL, Thames HD, Michalski JM *et al*. Estimation of α/β for late rectal toxicity based on RTOG 94-06. *Int J Radiat Oncol Biol Phys* 2011;**81**:600–5.
42. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989;**62**:679–94.
43. Stone NN, Potters L, Davis BJ *et al*. Customized dose prescription for permanent prostate brachytherapy: insights from a multicenter analysis of dosimetry outcomes. *Int J Radiat Oncol Biol Phys* 2007;**69**:1472–7.
44. Spratt DE, Pei X, Yamada J *et al*. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2013;**85**:686–92.
45. Lee WR. Extreme hypofractionation for prostate cancer. *Expert Rev Anticancer Ther* 2009;**9**:61–5.
46. King CR, Brooks JD, Gill H *et al*. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;**82**:877–82.
47. McBride SM, Wong DS, Dombrowski JJ *et al*. Hypofractionated stereotactic body radiotherapy in low-risk prostate adenocarcinoma: preliminary results of a multi-institutional phase 1 feasibility trial. *Cancer* 2012;**118**: 3681–90.
48. Fuller DB, Naitoh J, Lee C *et al*. Virtual HDR CyberKnife treatment for localized prostatic carcinoma: dosimetry comparison with HDR brachytherapy and preliminary clinical observations. *Int J Radiat Oncol Biol Phys* 2008;**70**:1588–97.