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Original Article

High-dose-rate brachytherapy monotherapy versus low-dose-rate brachytherapy with or without external beam radiotherapy for clinically localized prostate cancer

Hideya Yamazaki [a,*], Koji Masui [a], Gen Suzuki [a], Satoaki Nakamura [a], Kei Yamada [a], Koji Okihara [b], Takumi Shiraishi [b], Ken Yoshida [c], Tadayuki Kotsuma [c], Eiichi Tanaka [c], Keisuke Otani [d], Yasuo Yoshioka [d], Kazuhiko Ogawa [d]

[a] Department of Radiology; [b] Department of Urology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Japan; [c] Department of Radiation Oncology, National Hospital Organization Osaka National Hospital; and [d] Department of Radiation Oncology, Osaka University Graduate School of Medicine, Japan

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ABSTRACT

Background: To compare the outcome of high-dose-rate interstitial brachytherapy (HDR-BT) monotherapy and low-dose-rate brachytherapy (LDR-BT) with or without external beam radiotherapy (EBRT) for localized prostate cancer.

Methods and materials: We compared 352 patients treated with HDR-BT as monotherapy (median follow-up time 84 months, NCCN risk classification; low: intermediate: high = 28:145:179) and 486 patients with LDR-BT with or without EBRT (90 months, 194:254:38). HDR-BT treated advanced disease with more hormonal therapy than LDR-BT. LDR-BT excluded patients with T3b–T4 tumor and initial PSA >50 ng/ml. Inverse probability of treatment weighting (IPTW) involving propensity scores was used to reduce background selection bias.

Results: The actuarial 5-year biochemical failure-free survival rates (bNED) were 92.9% and 95.6% ($p = 0.25$) in the HDR-BT and LDR-BT groups, respectively, and it was 100% and 97.3% ($p = 0.99$) in the low-risk, 95.6% and 94.3% ($p = 0.19$) in the intermediate, 89.6% and 94.9% ($p = 0.26$) in the high-risk groups, and 93.1% and 94.9% ($p = 0.98$) in selected high-risk group excluding T3b-4 and initial PSA $\geq$50. IPTW correction also indicated no difference in bNED between LDR-BT and HDR-BT groups. LDR-BT showed a higher incidence of genitourinary (GU) toxicity grade $\geq$2 than that of HDR-BT in the acute phase and grade 1 toxicity in late phase. Acute GU toxicity grade $\geq$1 predicted late GU toxicity grade $\geq$2. External beam radiotherapy plus LDR-BT elevated GI toxicity than LDR-BT only group. Accumulated incidence of late grade $\geq$2 GU and GU toxicity was equivalent between HDR-BT and LDR-BT. No grade 4 or 5 toxicities were detected in either modality.

Conclusion: HDR-BT monotherapy showed an equivalent outcome to that of LDR-BT with or without EBRT for low-, intermediate- and selected high-risk patients. LDR-BT showed equivalent incidence of grade $\geq$2 late GI and GU toxicities and higher grade $\geq$2 acute GU toxicity as that of HDR-BT as a monotherapy.

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Prostate cancer is one of the major malignancies in men in Western counties. The current common curative treatment options include radical prostatectomy, external beam radiotherapy (EBRT), and interstitial brachytherapy (BT), which can be divided into permanent implantation, low-dose-rate (LDR) and temporary implantation, high-dose-rate (HDR) [1]. BT can deliver a higher radiation dose to the prostate gland while avoiding surrounding normal tissue and is, therefore, considered an effective radiotherapy treatment option [2] and may improve outcome in long-term biochemical control.

LDR-BT monotherapy is an established treatment option for patients with low-risk prostate cancer, with excellent long-term outcome [3]. As an expansion of its application to intermediate- to high-risk patients, LDR-BT was used as a boost treatment addition to EBRT, which resulted in improved outcome [1–3].

HDR was also employed as a boost technique delivered concurrently with EBRT (HDR-BT plus EBRT) for patients with intermediate [1,3] and intermediate- and high-risk prostate cancer [1]. In

* Corresponding author at: Department of Radiology, Kyoto Prefectural University of Medicine, 465 Kajiicho Kawaramachi Hirokoji, Kamigyo-ku, Kyoto 602-8566 Japan.
E-mail address: hideya10@hotmail.com (H. Yamazaki).

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addition, several authors have administered HDR-BT as a monotherapy and reported excellent outcomes in all risk groups [4–6]. This method is the most efficient for achieving good dose distribution with a high degree of conformity even for adjacent tissue invasion (seminal vesicle or extracapsular extension) with a short overall treatment time. In addition, HDR-BT may reduce toxicity compared to that of LDR-BT because of the shorter irradiation periods [7].

However, direct comparison of LDR-BT and HDR-BT is difficult because few institutions employ both modalities equally, as there is a no consensus for the use of HDR-BT or LDR-BT and the efficacy equivalent to that of LDR brachytherapy has not been established in controlled clinical trials. Although retrospective studies have compared the treatment effectiveness and toxicity of these RT modalities [7–12], interpretation of retrospective evidence can be challenging partly because of background differences.

Propensity score matching is an analytical tool that has been demonstrated to reduce bias in observational studies by balancing known confounding variables in compared groups and is used in oncology research, including prostate cancer [10–12]. In the absence of randomized controlled trials, pairing patients with known and matching prognostic factors can be an alternative method to explore differences in patient outcome between treatments. Therefore, the aim of the present study was to compare the results of HDR-BT monotherapy versus LDR-BT with or without EBRT using propensity score matching analysis.

Patients and methods

Patients

The patient eligibility criteria included patients who had been treated with HDR-BT monotherapy or LDR-BT with or without EBRT with curative intent, clinical TNM stage T1-4 and N0M0 with histology-proven adenocarcinoma; availability and accessibility of data on pretreatment prostate-specific antigen (initial PSA = iPSA) level, Gleason's score sum (GS), and T classification; and a minimum one-year follow-up for surviving patients or until death. Of the 862 patients eligible for inclusion, 21 were excluded due to follow-up loss after less than one year or for missing data. Thus, 841 patients were included as the subjects of this study.

The 841 patients with stage T1–T4 N0M0 prostate cancer were treated using HDR-BT monotherapy (n = 352: treatment period = 1995–2013, 172 from Osaka University Graduate School of Medicine and 180 from Osaka National Hospital) or LDR-BT (n = 486: 2005–2013 from Kyoto Prefectural University of Medicine). The median patient age was 69 (range, 51–86) years. The patients' clinical characteristics are shown in Table 1. The patients were staged according to the National Comprehensive Cancer Network (NCCN) 2015 risk classification as follows: low: T1–T2a and GS 2–6 and iPSA <10 ng/mL; intermediate: T2b–T2c or GS 7 or PSA 10–20 ng/mL; and high: T3 or GS 8–10 or PSA >20 ng/mL [1]. A radiation oncologist and a urologist conducted the follow-up evaluations at least every 3 months for the first 2 years and every 6 months during subsequent years, including PSA determinations and queries about urinary and bowel symptoms. PSA failure was defined using the Phoenix definition (nadir, +2 ng/ml). Common Terminology Criteria for Adverse Events version 4.0 was used for toxicity analysis. All patients provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki and with institutional review board (IRB) permission from each institution.

Treatment planning

LDR-BT with or without EBRT

The implant technique was previously described in detail [13–15]. All the seeds were used with the strength of the sources (0.424 U). All patients underwent transrectal ultrasound (TRUS) preplanning 3–4 weeks before implantation to determine the number of seeds. Prostate contouring was performed by urologists and radiation oncologists blinded to each other. In the preplanning volume study, the clinical target volume was defined as the prostate plus a 3-mm margin. We performed permanent intraoperative I-125 implantation (OncoSeed model 6711; General Electric Healthcare, Barrington, IL) using a modified peripheral loading method. Inter-Plan version 3.4 (ELEKTA, Stockholm, Sweden) was used as the treatment planning system. The implant technique was previously described in detail (7). Briefly, loose 125I seeds (The OncoSeed model 6711; General Electric Healthcare, Barrington, IL) were implanted in all patients. Computed tomography examination was performed at 1 month after treatment and dosimetric parameters including D90 and V100 were analyzed. We used combination therapy for T3 $\leq$ or Gleason's score sum 8 $\leq$, or Gleason's score sum 7 (4 + 3) cases (not for Gleason's score sum 7 (3 + 4) cases). Our prescription dose for the clinical target volume (prostate) was 145 Gy (LDR-BT alone) or 110 Gy (LDR-BT with 40 Gy/20 fractions EBRT, 5 LDR-BT alone and 37 LDR-BT with EBRT in high-risk group). Hormonal therapy was administered for high-risk patients. Generally. hormonal therapy was applied for more than 6 months before and/or immediately after PB.

HDR-BT monotherapy

The detailed method of applicator implantation was described elsewhere [4,6,16]. From 1995 to 2007, a simple radiography-based treatment planning was used and the prescription dose point was positioned 5 mm away from one source in the central plane. This two-dimensional planning method was used for treating the initial patients. We then shifted from two- to three-dimensional (3D) planning to treat the remaining patients (that is, computed tomography [CT]-based planning, 3D vs. 2D = 238:114). For 3D planning, the D90 and D95 or more were used to evaluate the adequate coverage of the planning target volume. The CT-based planning with or without magnetic resonance imaging (MRI) assistance was performed by computer optimization (Nucletron an Elekta Company, Veenendaal, The Netherlands, PLATO® and Oncentra® brachy, Elekta AB, Stockholm, Sweden) with or without manual modification. The clinical target volume (CTV) included the whole prostate gland with a 5-mm margin except for the posterior (rectal) margin, which varied from 2 to 5 mm depending on the distance to the rectal wall. If extracapsular and/or seminal vesicle invasion had been observed or strongly suspected by the staging MRI, that area was included in the CTV and applicators were placed there. The planning target volume (PTV) was equal to the CTV, except in the cranial direction, where it was 1 cm larger and included the bladder base. The top 2 cm of the applicators were placed within the bladder lumen, such that the PTV included a 1-cm margin in the cranial direction from the CTV. Initial 114 patients underwent 2D planning The most commonly prescribed doses were 45.5 Gy per seven fractions, 54 Gy per nine fractions in five days, and 49 Gy per seven fractions, and other (36–38 Gy in four fractions). We began to implement HDR-BT monotherapy in the 1990 s and employed a 54-Gy arm as the initial, frequently used schedule [8,9,12–14]. We changed this schedule from nine (54 Gy/9 fractions, overall treatment time = 5–7 days) to seven (49 or 45.5 Gy/7 fractions, overall treatment time = 4 days) fractions to avoid treatment interruption due to holiday. Thereafter, the prescribed dose was changed to a 45.5 and 49-Gy arm [8,9,13,14]. The treatment machine used was a microSelectron-HDR® (Nucletron an Elekta Company, Veenendaal, The Netherlands, Elekta AB, Stockholm, Sweden).

Table 1
Characteristics and treatment factors of patients.

Variables	Strata	HDR			LDR		*p*-value
		n = 352			*n* = 486		
		No. or Median (range)	(%)		No. or Median (range)	(%)	
Age		71 (47–86)			69 (45–83)		**0.0029**
T category	1	94	(27%)		234	(48%)	**<0.0001**
	2	155	(44%)		240	(49%)	
	3	94	(27%)		12	(2%)	
	4	9	(3%)		0	(0%)	
iPSA	ng/ml	11.82 (1.97–378)			7.0 (1.4–46)		**<0.0001**
Gleason's score	-6	117	(33%)		278	(57%)	**<0.0001**
	7	146	(41%)		185	(38%)	
	8-	89	(25%)		23	(5%)	
NCCN risk classification	Low	28	(8%)		194	(40%)	**<0.0001**
	Intermediate	145	(41%)		250	(51%)	
	High	179	(51%)		42	(9%)	
Prescribed dose	45.5 Gy/7 fx	86	(24%)	110 Gy plus EBRT	68	(14%)	NA
	49 Gy/7 fr	148	(42%)	145 Gy	418	(86%)	
	54 Gy/9 fx	111	(32%)				
	others	6	(2%)				
Hormonal therapy	Yes	274	(78%)		155	(32%)	**<0.0001**
Neoadjuvant	months	7 (1–55)			6 (1–13)		
Adjuvant	months	24 (1–162)			2 (1–9)		
	No	78	(22%)		331	(68%)	
Follow-up	Months	84 (19–216)			90 (12–151)		0.114

Bold values indicate statistically significance, NA; not available.
HDR-BT = high-dose-rate brachytherapy, LDR-BT = low-dose-rate brachytherapy, EBRT = external beam radiotherapy (40 Gy/20 fractions).

Statistical analysis

StatView 5.0 statistical software and R stat package [17] were used for statistical analyses. R stat package was used only to calculate the propensity score and matched-pair analysis. Percentages were analyzed using chi-square tests and Student's *t*-tests were used for normally distributed data. Mann–Whitney's U-tests for skewed data were used to compare means or medians. The Kaplan–Meier method was used to analyze the biochemical control rate, survival, and accumulated toxicity and comparisons were made using log-rank tests. Cox's proportional hazard model was used for uni- and multivariate analyses. $P < 0.05$ was considered statistically significant. Because the included patients were not randomized, unbalanced baseline characteristics could have led to selection bias and influenced the decision to undergo HDR-BT monotherapy. The propensity score was defined as the probability of being assigned to the HDR-BT monotherapy or LDR-BT radiotherapy groups given the patient characteristics. In the calculation of the propensity scores, the logistic regression model was used based on the baseline covariates (all variables were categorized variables), as shown in Table 2 (age, T category, Gleason's score, pretreatment PSA level, hormonal therapy; all variables were categorized variables). IPTW recalculated the treatment effects with a Cox model. Weighted survival analysis was performed using the IPTW method, i.e., patients who received HDR-BT were weighted by 1/propensity score, whereas patients who received LDR-BT were weighted by 1/(1–propensity score).

Table 2
Univariate and multi-variate analysis for biochemical control rate using Cox proportional hazards model.

Variable	Strata	PSA control					
		Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*	HR	95% CI	*p*
Age, years	<75	1	(referent)	–	1	(referent)	
	75 ≤	0.559	0.269–1.162	0.1192	0.58	0.278–1.213	0.1481
T classification	T1-2	1	(referent)	–	1	(referent)	–
	T3-4	1.716	0.997–2.952	0.0512	1.128	0.582–2.184	0.7213
Gleason's score	≤7	1	(referent)	–	1	(referent)	
	8≤	1.207	0.651–2.236	0.55	0.963	0.501–1.849	0.9091
Pretreatment PSA (ng/mL)	<20	1	(referent)	–	1	(referent)	–
	20≤	2.643	1.649–4.238	**<0.0001**	2.803	1.528–5.141	**0.0009**
NCCN risk classification	Low	1	(referent)	–			
	Intermediate	1.561	0.821–2.967	0.1744			
	High	2.626	1.411–5.13	**0.0026**	NA		
Hormonal therapy	No	1	(referent)	–	1	(referent)	
	Yes	1.175	0.755–1.831	0.4748	0.804	0.443–1.459	0.4733
Treatment modalities	LDR-BT	1	(referent)	–	1	(referent)	–
	HDR-BT	1.297	0.832–2.022	0.2502	1.003	0.549–1.832	0.1182

Bold values indicate statistically significance.
Abbreviations: CI = confidence interval, HR = hazard ratio, NA = not available.
HDR-BT = high-dose-rate brachytherapy, LDR-BT = low-dose-rate brachytherapy.

Results

The median follow-up for the entire cohort was 87 (range: 12–216) months, with a minimum of one year for surviving patients or until death.

A comparison of the two schedule backgrounds is shown in Table 1. HDR-BT monotherapy was used to treat advanced disease. Hormonal therapy was used significantly more in the HDR-BT group compared with the LDR-BT group 78% vs. 32% ($p < 0.0001$). LDR-BT excluded T3b–T4 tumors from indication and no patients had an initial iPSA of 50 ng/mL or more.

As shown in Table 2, the predictors of biochemical control on univariate analysis included treatment (LDR-BT vs. HDR-BT), T classification (T1-2 vs. T3-4), Gleason's score sum (≤7 vs. 8≤), a higher baseline PSA level (<20 vs. 20 ≤ ng/mL), and age (<75 vs. 75 ≤ years). In multivariate Cox regression analysis, only a higher initial PSA level remained significant for improving biochemical control.

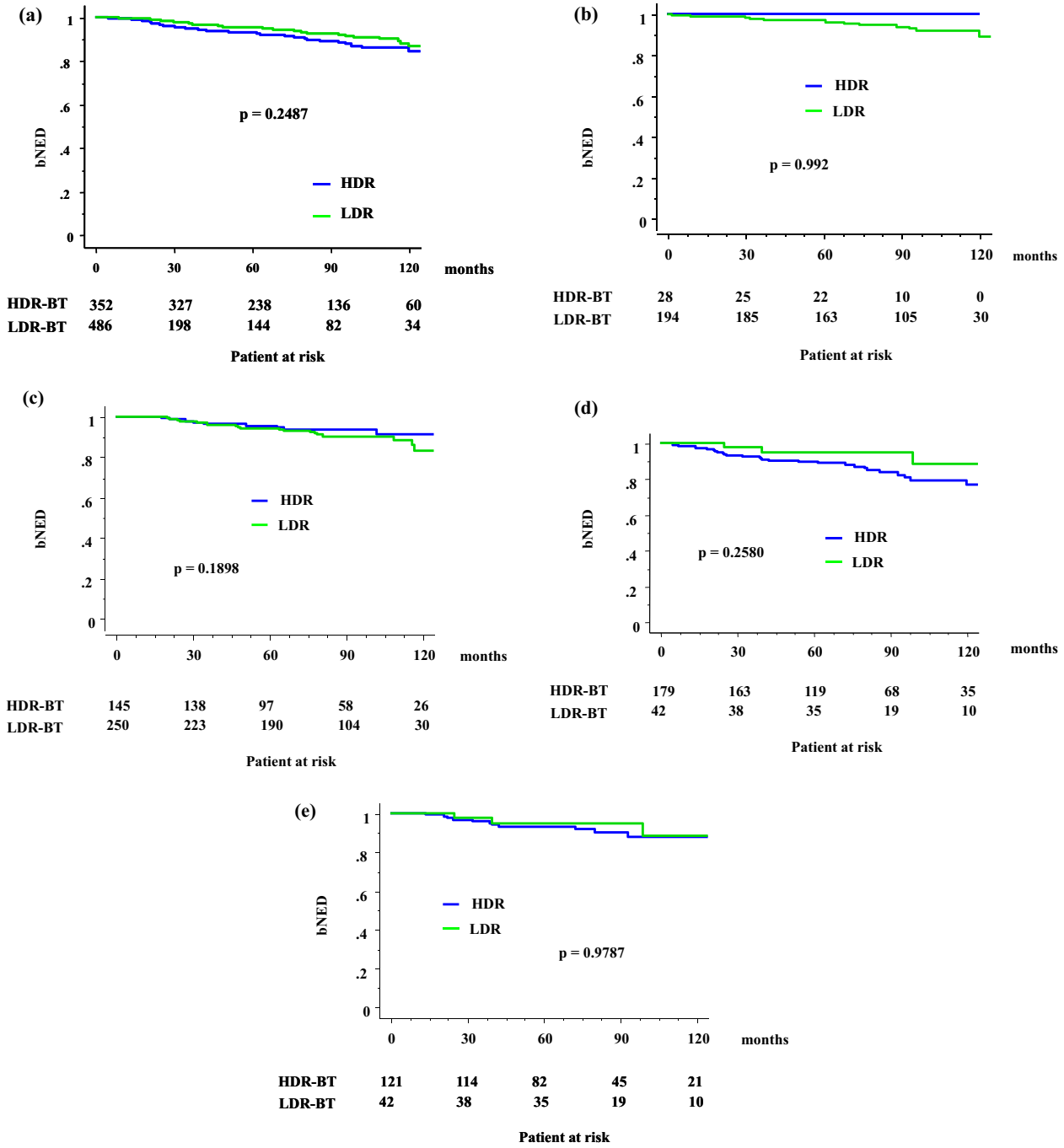

Fig. 1. Biochemical control rates between HDR-BT monotherapy and LDR-BT with or without EBRT. (a) Biochemical control rates between HDR-BT monotherapy and LDR-BT with or without EBRT in the total population. (b) Biochemical control rates between HDR-BT monotherapy and LDR-BT with or without EBRT in the low-risk group. (c) Biochemical control rates between HDR-BT monotherapy and LDR-BT with or without EBRT in intermediate-risk group. (d) Biochemical control rates between HDR-BT monotherapy and LDR-BT with or without EBRT in high-risk group. (e) Biochemical control rates between HDR-BT monotherapy and LDR-BT with or without EBRT in high-risk group excluding T3b-4 and/ or iPSA ≥50. bNED = no biochemical evidence of disease.

In the HDR-BT monotherapy group, 39 (11.0%) patients developed biochemical failure, compared to 41 (8.4%) in the LDR-BT group. The actuarial five-year biochemical failure-free survival rates (5y-bNED) were 92.9% (95% confidential interval [95% CI] 90.1–95.6%) and 95.6 92.9% (93.7–97.5%, $p = 0.2487$, $p = 1.0$ in IPTW, Fig. 1, Table 3) (Hazard risk 1.297, 95% CI = 0.832–2.022, $p = 0.2502$) in the HDR-BT and LDR-BT groups (95.8% in LDR-BT alone and 93.5% in LDR-BT + EBRT, Fig. 2), respectively, and 97.7% (100% for HDR-BT and 97.3% for LDR-BT, $p = 0.99$, $p = 0.8$ in IPTW) in the low-risk, 94.6% (95.6% and 94.3% [94.6% in LDR-BT and 89.1% in LDR + EBRT], $p = 0.19$, $p = 0.7$ in IPTW) in the intermediate, 90.9% (89.6% and 94.9% [100% in LDR-BT alone and 97.1% in LDR-BT + EBRT], $p = 0.26$, $p = 0.3$ in IPTW) in the high-risk groups, and 93.1% (93.1% and 94.9% [100% in LDR-BT alone and 97.1% in LDR-BT + EBRT], $p = 0.98$, $p = 0.8$ in IPTW) in selected high-risk group excluding T3b-4 and iPSA ≥50. There was a significant difference in the biochemical control rates among those three risk groups ($p = 0.0064$).

The overall 7-year survival rates were 93.7% (95% CI = 90.7%–96.8%) and 97.8% (95% CI = 96.4%–99.3%, $p = 0.0080$) in the HDR-BT and LDR-BT groups, respectively (HR = 2.279, 95% CI = 1.220–4.257, $p = 0.0098$), it was 98.2% (98.6% and 94.7%, $p = 0.0035$) in the low-risk groups, and 96.3% (93.8% and 97.8%, $p = 0.1162$) in the intermediate, 94.0% (93.5% and 95.2%, $p = 0.9881$) in the high-risk, and 93.5% (92.7% for HDR-BT and 95.2% for LDR-BT, $p = 0.8251$) in the selected high-risk group excluding Tb-4 and iPSA ≥50 ng/ml. There were no statistically significant differences in overall survival rate among these three risk groups ($p = 0.2873$).

As there were only three prostate-cancer-related deaths in this cohort (three high-risk patients who underwent HDR-BT monotherapy died of prostate cancer at 55, 75 and 157 months after treatment), the 7-year cause-specific survival rates were 99.7% (99.1% in HDR-BT and 100% in LDR-BT, $p = 0.075$).

Table 4a shows the incidence of maximal acute gastrointestinal (GI) and genitourinary (GU) toxicities. In GI toxicity, HDR-BT monotherapy and LDR-BT with or without EBRT showed similar frequency. LDR-BT showed higher ratio of grade ≥1 (92%) and grade ≥2 acute toxicity (43%) than HDR-BT (69.3% and 12.3%, both $p < 0.0001$). Elevated GI toxicity was observed in the EBRT (40 Gy/20 fractions) and LDR-BT than LDR-BT only group (24% versus 8% grade ≥1, $p < 0.0001$), although grade 3 toxicity was not observed. The detailed toxicity profile (per event) is shown in supplemental Table 1.

Table 4b shows the incidence of maximal late GI and GU toxicities. No grade ≥4 late complications were observed in either arm. Grades 1, 2, and 3 late GI toxicities occurred in 33 (9%), 10 (3%), and one (0.3%) patients in the HDR-BT group and in 35 (7%), eight (2%), and zero (0%) patients in the LDR-BT group, respectively ($p = 0.2526$). Grades 1, 2, and 3 late GU toxicities occurred in 100 (28%), 57 (16%), and 10 (3%) patients in the HDR-BT group and in 195 (40%), 75 (15%), and four (0.8%) patients in the LDR-BT group ($p = 0.0007$), respectively. Elevated GI toxicity was observed in the EBRT and LDR-BT than LDR-BT only group (6% versus 25% grade ≥1, $p < 0.0001$), although grade 3 toxicity was not observed. The accumulated rates for GU toxicity grade ≥2 were 17.6% at 7 years in the HDR-BT group and 15.8% in the LDR-BT group (Fig. 3a. $p = 0.3289$ [15.9% in LDR-BT alone and 17.8% in LDR-BT + EBRT, Fig. 3b]). The accumulated rates for GI toxicity were 2.8% at 7 years in the HDR-BT group and 1.9% in the LDR-BT group (Fig. 3c, $p = 0.1511$). The detailed toxicity profile (per event) is shown in supplemental Table 2.

Multivariate analyses revealed that acute GU toxicity predicted grade ≥2 late GU toxicity (Table 5). Grade ≥2 late GU toxicity showed correlation not only to grade ≥2 late GU toxicity (hazard ratio 3.855, $p < 0.0001$; Table 5) but also to grade 1 acute GU toxicity (hazard ratio 2.062, $p = 0.0016$; Table 5). Accumulated 7-year incidence of grade ≥2 late GU toxicity were 9.2%, 15.2%, and 23.2% for patients with acute GU toxicity grade 0, 1 and 2, respectively ($p = 0.0003$, Fig. 3d. EBRT with LDR-BT elevated grade ≥2 late GI toxicity than LDR-BT only group with a hazard ratio of 5.586 ($p = 0.0323$, Fg 3e). Accumulated 7-year incidence of grade ≥2 late GI toxicity were 2.6% 1.2%, and 6.3% for HDR-BT, LDR-BT, and EBRT + LDR-BT ($p = 0.0140$), respectively. Details of late toxicity (per event) are shown in supplemental Table 2.

Discussion

Our data showed equivalent excellent outcomes between HDR-BT monotherapy and LDR-BT with or without EBRT in low-, intermediate-, and selected high-risk prostate cancer patients by direct comparison of HDR-BT and LDR-BT performed with the best possible statistical methods.

HDR has several potential advantages over LDR-BT: (i) dose optimization by manipulation of dwell times and dwell positions of the "stepping source" even after implantation, which is impossible in LDR-BT resulting in better tumor coverage and avoidance of organ at risk [8]; (ii) fewer radioprotection issues for patients and staff. The patient selection criteria for HDR-BT as monotherapy remain a subject of debate, especially for intermediate- and high-risk groups. Several studies have suggested that HDR-BT monotherapy should only be used in low- to intermediate-risk groups, whereas a combination of EBRT and HDR-BT is suitable for intermediate- and high-risk patients and similar for LDR-BT. [1,2]. In contrast, several authors, including the present study, explored HDR-BT monotherapy not only for low-risk but also for intermediate- and high-risk patients because HDR-BT can provide adequate dose distributions even for extracapsular lesions without EBRT [4,5,6,16]. For example, Zamboglou et al. reported five-year biochemical control rates of 95%, 95% and 93% in low-, intermediate-, and high-risk groups (D'Amico) among 700 patients receiving HDR-BT monotherapy [5]. Therefore, HDR-BT is one option with high curative potential not only for low- and intermediate-risk patients but also for high-risk patients. Our HDR-BT monotherapy data included patients with more advanced

Table 3
The 5-year biochemical failure free survival rates between treatment.

Variable	Strata	PT No.	HDR-BT	PT No.	LDR-BT	Log-rank *p*-value	IPTW correction			
							Log-rank *p*-value	Cox *p*-value	HR	95% CI
NCCN risk classification	Low-risk	28	100.0%	194	97.3%	0.99	0.8	0.80	1.14	0.41–3.16
	Intermediate-risk	145	95.6%	250	94.3%	0.19	0.7	0.68	0.84	0.36–1.93
	High-risk	179	89.6%	42	94.9%	0.26	0.3	0.40	1.60	0.53–4.74
	High-risk excluding T3b-4 and iPSA ≥50	121	93.1%	42	94.9%	0.98	0.8	0.80	0.87	0.41–3.16
	Total	352	92.9%	486	95.6%	0.25	1	0.97	1.01	0.53–1.91

Abbreviations: CI = confidence interval; HR = hazard ratio.

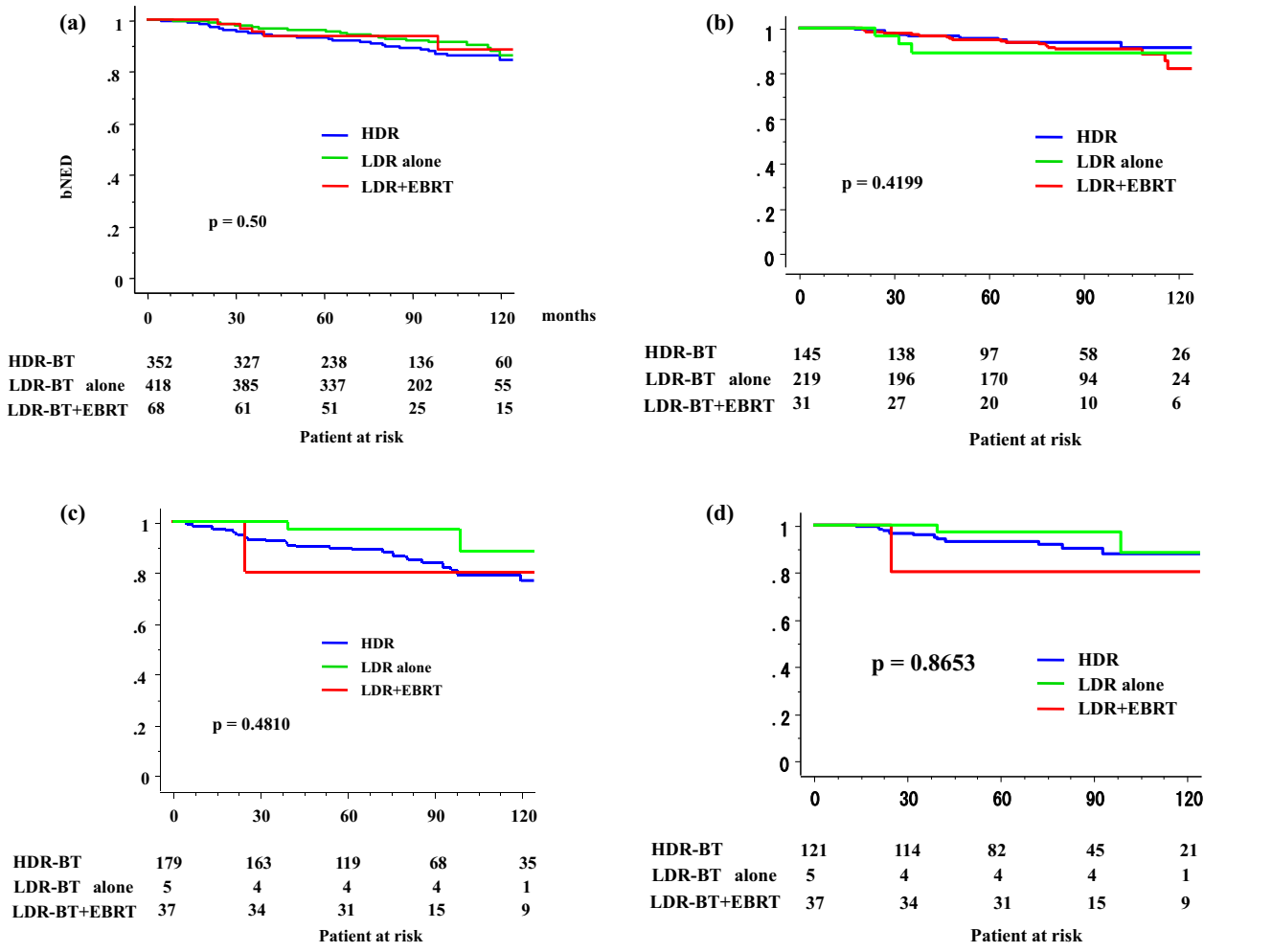

Fig. 2. Biochemical control rates among HDR-BT monotherapy, LDR-BT alone, and LDR-BT with EBRT. (a) Biochemical control rates among HDR-BT monotherapy, LDR-BT alone, and LDR-BT with EBRT in the total population. (b) Biochemical control rates among HDR-BT monotherapy, LDR-BT alone, and LDR-BT with EBRT in intermediate-risk group. (c) Biochemical control rates among HDR-BT monotherapy, LDR-BT alone, and LDR-BT with EBRT in high-risk group. (d) Biochemical control rates among HDR-BT monotherapy, LDR-BT alone, and LDR-BT with EBRT in high-risk group excluding T3b-4 and/or iPSA ≥50. bNED = no biochemical evidence of disease.

Table 4
Comparisons between HDR-BT and LDR-BT for toxicities.

Toxicities	Grade	HDR-BT		LDR-BT		*p*-value	LDR-BT alone		LDR-BT plus EBRT		*p*-value
		n = 352		*n* = 486			*n* = 418		*n* = 68		
		No.	(%)	No.	(%)		No.	(%)	No.	(%)	
(a) Acute toxicity											
Gastrointestinal	0	314	(88%)	435	(90%)	**0.2532**	383	(92%)	52	(76%)	*__<0.0001__
	1	32	(9%)	49	(10%)		35	(8%)	14	(21%)	
	2	5	(1%)	2	(0.4%)		0	(0%)	2	(3%)	
	3	1	(0.3%)	0	(0%)		0	(0%)	0	(0%)	
		352		486							
Genitourinary	0	105	(30%)	37	(8%)	**<0.0001**	33	(8%)	4	(6%)	**0.8379**
	1	203	(57%)	239	(49%)		207	(50%)	32	(47%)	
	2	43	(12%)	209	(43%)		177	(42%)	32	(47%)	
	3	1	(0.3%)	1	(0%)		1	(0%)	0	(0%)	
(b) Late toxicity											
Gastrointestinal	0	308	(87%)	443	(91%)	**0.2526**	392	(94%)	51	(75%)	*__<0.0001__
	1	33	(9%)	35	(7%)		22	(5%)	13	(19%)	
	2	10	(3%)	8	(2%)		4	(1%)	4	(6%)	
	3	1	(0.3%)	0	(0%)		0	(0%)	0	(0%)	
Genitourinary	0	185	(52%)	211	(43%)	**0.0007**	183	(44%)	28	(41%)	**0.7891**
	1	100	(28%)	196	(40%)		166	(40%)	30	(44%)	
	2	57	(16%)	75	(15%)		65	(16%)	10	(15%)	
	3	10	(3%)	4	(0.8%)		4	(1%)	0	(0%)	

HDR-BT = high-dose-rate brachytherapy, LDR-BT = low-dose-rate brachytherapy, EBRT = external beam radiotherapy.
* *p*-value was calculated excluding columns of grade 3.

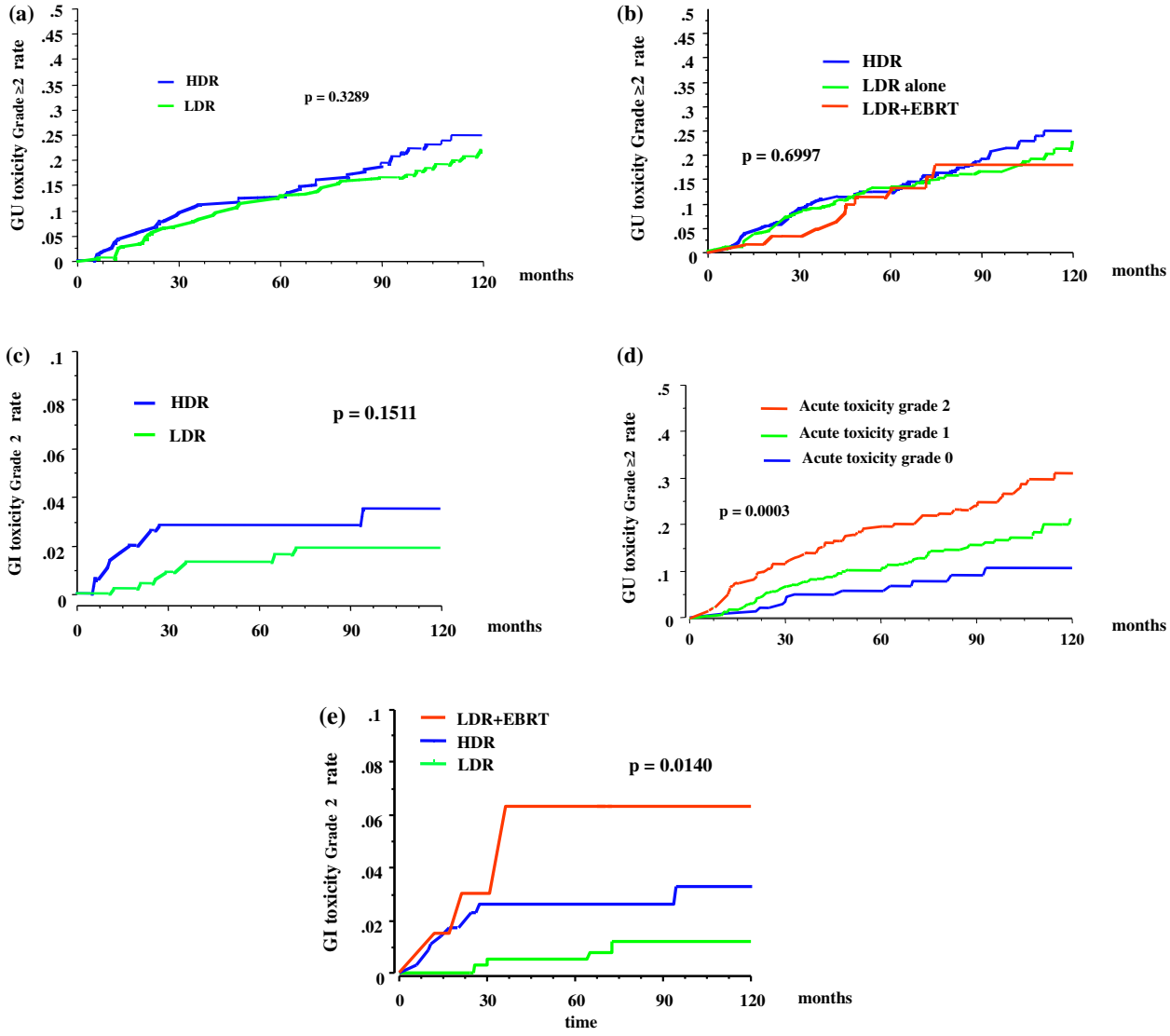

Fig. 3. Accumulated incidence of grade ≥2 toxicity. (a) Genitourinary toxicity according to treatment modality. (b) Genitourinary toxicity according to three treatment modalities. (c) Gastrointestinal toxicity according to treatment modality. (d) Genitourinary toxicity according to acute toxicity. (e) Gastrointestinal toxicity according to three treatment modalities.

Table 5
Multi-variate analysis of late grade ≥2 GI/GU toxicity.

Variable	Strata	GI grade ≥2 toxicity			GU grade ≥2 toxicity		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age, years	<75	0.827	0.268–2.553	0.7417	1	(referent)	
	75 ≤	1	(referent)		1.072	0.700–1.642	0.746
NCCN	Low	1	(referent)		1	(referent)	
risk group category	Intermediate	1.87	0.355–9.843	0.46	0.83	0.538–1.280	0.3383
	High	1.845	0.247–12.408	0.529	0.799	0.441–1.450	0.4609
Hormonal therapy	No	1	(referent)	–	1	(referent)	
	Yes	0.556	0.187–1.656	0.2916	1.103	0.727–1.675	0.644
Treatment modalities	LDR-BT	1	(referent)		1.022	0.497–2.100	0.9533
	LDR-BT + EBRT	5.5865	1.156–27.02	**0.0323**	1	(referent)	
	HDR-BT	1.692	0.486–5.88	0.408	1.635	0.813–3.289	0.1679
Acute toxicity	Grade 0	* NA			1	(referent)	
	Grade 1				2.062	1.164–4.018	**0.0016**
	Grade 2–3				3.855	2.014–7.377	**<0.0001**

Bold values indicate statistically significance.
Abbreviations: CI = confidence interval; HR = hazard ratio, NA = not available.
* Incidence of GI acute toxicity was too low to analysis.

disease (i.e., T3b-4 or iPSA 50 ng/mL or more), who were not included in the LDR-BT with or without EBRT groups.

For HDT-BT monotherapy, the longest follow-up for outcomes is reported for moderate hypofraction (4–9 fractions); however, excellent preliminary results are being reported with ultrahypofractionation (1–3 fractions) [18–20]. The emergence of ultrahypofractionation with only 1–2 treatments makes HDR logistically comparable to seed implant and adds a high degree of dosimetry control and accuracy in brachytherapy. Single-fraction HDR monotherapy is now being investigated, and if the data are confirmed with longer follow-up, it may well become the treatment-of-choice for many men with localized prostate cancer.

The radiation dose of an LDR-BT implant is delivered over 6 months (the half-life of Iodine-125 is 60 days; 87.5% of the dose is delivered in three half-lives) compared to 10–15 minutes for HDR. Therefore LDR-BT requires a more prolonged recovery period and may escalate the acute GU toxicity compared to that of HDR [7,21]. Grills et al. reported significantly lower occurrence of acute grade 1 to 3 dysuria (67% vs 36%), urinary frequency/urgency (92% s 54%) and rectal pain (20% vs 6%) in HDR (38 Gy/4fr) than those of LDR-BT [7]. Patients receiving HDR-BT reported less chronic urinary frequency and urgency, with a decreased rate of sexual impotency. A Canadian group performed a non-randomized prospective study, reporting decreased GU and GI toxicity in patients treated with EBRT and HDR-BT boost compared to those who received an LDR-BT boost [21]. Based on those findings, a randomized Phase II trial (H13-02139) comparing HDR boost and LDR boost with toxicity endpoint is underway.

Our data partly concurred with these previous results. A higher ratio of acute grade 2 GU toxicity occurred in the LDR-BT (43%) group than that in the HDR-BT monotherapy group (12.3%, $p < 0.0001$). However, the ratio decreased to grade 1 in the late phase and no difference was observed in grade $\geq$2 GU toxicities between the LDR-BT and HDR-BT groups. Accordingly, the seven-year cumulative incidences of grade $\geq$2 late GU toxicities were 17.6% and 15.8% in the HDR-BT and LDR-BT groups, respectively. This transient elevation and recover of GU toxicity in LDR was already well documented by Kollmeier et al. [22]. The HDR-BT toxicity rates compare well with those in other reports (10–20% grade 2 $\geq$GU toxicity) [14,15,19]. Acute GU toxicity predicted grade $\geq$2 late GU toxicity. This correlation is already reported in EBRT or IMRT series [23]. EBRT plus LDR-BT elevated GI toxicity than LDR-BT only group, which reconfirmed results of phase III trial [24]. In general, the results of the present study show that most patients did not experience long-term treatment-related severe GU toxicity.

ADT has established its role in combination with EBRT [25,26], high-risk patients should be offered long-term ADT with 24 months of duration (18 months to 36 months). However, there is no clear high evidence (randomized controlled trial) to add ADT with BT. Shilkrut et al. reported improvement of bNED with long-term ADT [27]. However, Stock et al reported that LDR-BT with ADT for a duration of more than 3 months improved bNED for the BED group (<150 Gy) but not for higher BED groups (150–200 Gy) [28]. Kraus et al. and Merrick et al. also reported no benefit of ADT [29,30]. At present, we used short term neoadjuvant ADT for combination with BT.

This study has several limitations. First, the retrospective study included a limited number of institutes dealing with rather small number of patients; a longer follow-up with larger numbers of patients is needed before reaching concrete conclusions. Second, we did not examine several other potential factors that may have influenced the PSA control rate. Our propensity score model could not replace a randomized controlled study because it only depended on known confounders; therefore, unknown confounders were not included. For example, in the United States, diabetes affects outcomes and toxicities [31]. Although these are not common cases in Asian populations, there are epidemics in the US and several European countries.

In conclusion, HDR-BT monotherapy showed an equivalent outcome to that of LDR-BT with or without EBRT for low-, intermediate- and selected high-risk patients. LDR-BT showed equivalent rates of grade $\geq$2 GU and GI toxicities as that of HDR-BT as a monotherapy except for a higher rate of moderate genitourinary toxicity in early-phase and mild in late-phase. Acute GU toxicity was related to late GU toxicity grade $\geq$2. Both LDR-BT and HDR-BT are excellent treatment options for appropriately selected patients, with comparable outcomes and acceptable toxicities.

Conflict of interest disclosure

The authors made no disclosure.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.10.020.

References

[1] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) prostate cancer 2015 version 4.
[2] Chin J, Rumble RB, Kollmeier M, et al. Brachytherapy for patients with prostate cancer: American society of clinical oncology/cancer care ontario joint guideline update. J Clin Oncol 2017;35:1737–43.
[3] Bittner NH, Orio 3rd PF, Merrick GS, et al. The American College of Radiology and the American Brachytherapy Society practice parameter for transperineal permanent brachytherapy of prostate cancer. Brachytherapy 2017;16:59–67.
[4] 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.
[5] 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.
[6] Yoshida K, Yamazaki H, Takenaka T, et al. High-dose-rate interstitial brachytherapy in combination with androgen deprivation therapy for prostate cancer: are high-risk patients good candidates? Strahlenther Onkol 2014;190:1015–20.
[7] Grills IS, Martinez AA, Hollander M, et al. High dose rate brachytherapy as prostate cancer monotherapy reduces toxicity compared to low dose rate palladium seeds. J Urol 2004;171:1098–104.
[8] Major T, Polgár C, Jorgo K, et al. Dosimetric comparison between treatment plans of patients treated with low-dose-rate vs. high-dose-rate interstitial prostate brachytherapy as monotherapy: Initial findings of a randomized clinical trial. Brachytherapy 2017;16:608–15.
[9] Morimoto M, Yoshioka Y, Konishi K, et al. Comparison of acute and subacute genitourinary and gastrointestinal adverse events of radiotherapy for prostate cancer using intensity-modulated radiation therapy, three-dimensional conformal radiation therapy, permanent implant brachytherapy and high-dose-rate brachytherapy. Tumori 2014;100:265–71.
[10] Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41–55.
[11] Khor R, Duchesne G, Tai KH, et al. Direct 2-arm comparison shows benefit of high-dose-rate brachytherapy boost vs external beam radiation therapy alone for prostate cancer. Int J Rad Oncol Biol Phys 2013;85:679–85.
[12] Wong YN, Mitra N, Hudes G, et al. Survival associated with treatment vs observation of localized prostate cancer in elderly men. JAMA 2006;296:2683–93.
[13] Kobayashi K, Okihara K, Iwata T, et al. Evaluation of dosimetry and excess seeds in permanent brachytherapy using a modified hybrid method: a single-institution experience. J Radiat Res 2013;54:479–84.
[14] Yamada Y, Masui K, Iwata T, et al. Permanent prostate brachytherapy and short-term androgen deprivation for intermediate-risk prostate cancer in Japanese men: outcome and toxicity. Brachytherapy 2015;2015(14):118–23.
[15] Okihara K, Kobayashi K, Iwata T, et al. Assessment of permanent brachytherapy combined with androgen deprivation therapy in an intermediate-risk prostate cancer group without a Gleason score of 4 + 3: a single Japanese institutional experience. Int J Urol 2014;21:271–6.
[16] Yoshioka Y, Kotsuma T, Komiya A, et al. Nationwide, multicenter, retrospective study on high-dose-rate brachytherapy as monotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2017;97:952–61.

[17] R-project home page: https://www.r-project.org/. Accessed Feb 2, 2018.
[18] Hoskin P, Rojas A, Ostler P, et al. High-dose-rate brachytherapy with two or three fractions as monotherapy in the treatment of locally advanced prostate cancer. Radiother Oncol 2014;112:63–7.
[19] 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.
[20] 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.
[21] Rose T, Garcia E, Bachand F, et al. QOL comparison of acute side effect from a high dose rate vs. low dose rate brachytehrapy boost combined with external beam radiotherapy. Brachytherapy 2015;3(supple 1):S36.
[22] Kollmeier MA, McBride S, Taggar A, et al. Salvage brachytherapy for recurrent prostate cancer after definitive radiation therapy: a comparison of low-dose-rate and high-dose-rate brachytherapy and the importance of prostate-specific antigen doubling time. Brachytherapy 2017;16:1091–8.
[23] Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:1124–9.
[24] Prestidge B, Winter K, Sanda M, et al. Initial report of NRG Oncology/RTOG 0232: a phase 3 study comparing combined external beam radiation and transperineal interstitial permanent brachytherapy with brachytherapy alone for selected patients with intermediate-risk prostatic carcinoma. Int J Radiat Oncol Biol Phys 2016;96:S4.
[25] Sasse AD, Sasse E, Carvalho AM, et al. Androgenic suppression combined with radiotherapy for the treatment of prostate adenocarcinoma: a systematic review. BMC Cancer 2012;12:54.
[26] Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localized prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. Lancet Oncol 2015;16:320–7.
[27] Shilkrut M, Merrick GS, McLaughlin PW, et al. The addition of low-dose-rate brachytherapy and androgen-deprivation therapy decreases biochemical failure and prostate cancer death compared with dose-escalated external-beam radiation therapy for high-risk prostate cancer. Cancer 2013;119:681–90.
[28] Stock RG, Yalamanchi S, Hall SJ, et al. Impact of hormonal therapy on intermediate risk prostate cancer treated with combination brachytherapy and external beam irradiation. J Urol 2010;183:546–50.
[29] Krauss D, Kestin L, Ye H, Brabbins D, et al. Lack of benefit for the addition of androgen deprivation therapy to dose-escalated radiotherapy in the treatment of intermediate- and high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2011;80:1064–71.
[30] Merrick GS, Butler WM, Wallner KE, et al. Androgen-deprivation therapy does not impact cause-specific or overall survival after permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys 2006;65:669–77.
[31] Zaorsky NG, Shaikh T, Ruth K, et al. Prostate cancer patients with unmanaged diabetes or receiving insulin experience inferior outcomes and toxicities after treatment with radiation therapy. Clin Genitourin Cancer 2017;15:326–35.