Two-Fraction High-Dose-Rate Brachytherapy within a Single Day Combined with External Beam Radiotherapy for Prostate Cancer: Single Institution Experience and Outcomes

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CONFLICTS OF INTEREST

The authors state that there is no conflict of interest related to this study.

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ABSTRACT

We investigated the outcomes of treatment for patients with localized prostate cancer (PCa) treated with three-dimensional conformal radiation therapy (3D-CRT) followed by two-fraction high-dose-rate brachytherapy within a single day (2-fr.-HDR-BT/day) at a single institution. A total of 156 consecutive Asian males (median age, 67 years) were enrolled. To compare our findings with those of other studies, we analyzed our results using the D'Amico classification, assigning the patients to low- (n=5; 3.2%), intermediate- (n=36; 23.1%), and high-risk (n=115; 73.7%) groups (stage T3 PCa patients were classified as high-risk). One patient in the D'Amico low-risk group (20%), 13 intermediate-risk patients (36.1%) and 99 high-risk patients (86.1%) underwent androgen deprivation therapy. We administered a prescription dose of 39 Gy in 13 fractions of 3D-CRT combined with 18 Gy of HDR-BT in two 9-Gy fractions delivered within a single day. We did not distinguish between risk groups in determining the prescription dose. The median follow-up period was 38 months. Of the 156 patients, one died from primary disease and five died from other diseases. The 3-year overall survival (OS) rates were 100%, 100% and 93.7% and the 3-year 'biochemical no evidence of disease (bNED)' rates were 100%, 100% and 96.9% for the D'Amico low-, intermediate- and high-risk groups, respectively. No patient developed ≥ Grade 3 early toxicity. The Grade 3 late genitourinary toxicity rate was 2.6%, and no ≥ Grade 3 late gastrointestinal toxicity occurred. The efficacy and safety of this study were satisfactory, and longer-term follow-up is necessary.

KEYWORDS

High-dose-rate; Brachytherapy; HDR-BT; Radiotherapy; Prostate cancer; Toxicity

INTRODUCTION

External beam radiation therapy (EBRT) combined with high-dose-rate brachytherapy (HDR-BT) is one of the standard definitive therapies for prostate cancer (PCa). Dose-escalation strategies for PCa have improved local control, and higher-dose irradiation has consistently provided improved outcomes. Based on the above requirement and the features of brachytherapy, HDR-BT as monotherapy or boost therapy combined with EBRT has been highly recommended, and positive outcomes are anticipated [1, 2]. HDR-BT is the use of sealed radioactive sources (e.g., ^{192}Ir [iridium]) placed close to or inside the tumor, enabling the delivery of high radiation doses to the prostate, which can improve biochemical and clinical results for PCa patients; HDR-BT also provides a steep dose fall-off with sparing of normal tissue [3-6]. Compared with EBRT, HDR-BT can deliver a higher localized dose of radiation to the lesion without any boost plan [7].

However, the monotherapy or even boost HDR-BT schedule generally takes several days and/or may require multiple sessions of applicator insertions, which causes discomfort to patients [1, 5, 6, 8-10]. Considering the balance between tumor control and toxicity, and to alleviate the patients' discomfort, our institution has been administering two fractions of HDR-BT within a single day (2-fr.-HDR-BT/day) and has sought to apply a dose fractionation of EBRT such that the biologically equivalent dose (BED) corresponds to the average tolerable dose to the prostatic urethra and the rectum near the prostate. In this study we investigated this initial experience regarding the safety and efficacy of 2-fr.-HDR-BT/day.

Methods and materials

Patient characteristics

A total of consecutive 156 Asian males with stage T1c-3bN0M0 prostate cancer (Union for International Cancer Control; 7th edition) treated at our institution between June 2009 and December 2013 were enrolled (Table 1). The eligibility/inclusion criteria had to satisfy the following conditions: no other malignancy, life expectancy over 5 years, no history of pelvic radiotherapy, Eastern Cooperative Oncology Group performance status of 0–2, and written informed consent. Patients were excluded from this treatment if they had severe co-morbidities, severe psychosis or if achieving the applicator puncture to the entire prostate was difficult due to pubic bone interference. There were no enrollment restrictions regarding the prostate-specific antigen (PSA) level or the volume of the prostate.

Examination for staging

Patients were categorized based on the results of a digital rectal examination and image diagnosis (computed tomography [CT], magnetic resonance imaging [MRI], and bone scintigraphy) before radiation therapy (RT) in principle.

Risk classification

At our institution, we use both the UCSF Cancer of the Prostate Risk Assessment (UCSF-CAPRA) classification and the D'Amico classification. The UCSF-CAPRA

classification which we used to shape the androgen deprivation therapy (ADT) policy, incorporates the highest PSA level recorded before diagnosis, the biopsy Gleason score, the clinical T stage, the percent of positive biopsies and the patient's age to generate a score ranging from 0 to 10 points, with a greater score correlating with an increased risk of recurrence. The details of the UCSF-CAPRA classification are provided elsewhere (Table 2) [11]. For the sake of comparing our findings with those of other studies, we analyzed our results using the D'Amico classification [12, 13]. Patients with stage T3 PCa are not defined by the D'Amico classification; in our study, we classified these patients as being in the high-risk group.

Radiation therapy

EBRT:

The prescription dose in the present study was 39 Gy in 13 fractions (five fractions of treatment per week) of 6 or 10 MV X-ray three-dimensional conformal radiation therapy (3D-CRT). Each risk group followed the above prescription dose. The clinical target volume (CTV) was defined for the entire prostate gland and the base of the seminal vesicle, however, if the case was T3b, the entire seminal vesicle was included. The planning target volume (PTV) was defined as the volume including 8 mm anterior, lateral and superior-inferior to the CTV, and 6 mm toward the posterior.

HDR-BT:

To maintain the normal tissue recovery, a $\geq$6-hr interval between the two fractions within a single day was needed. In addition, we made a new plan before the second fraction of HDR-BT by considering any error induced by movement of the applicator during the 6-hr interval (Supplementary Fig. 1) [14]. The treatment planning for HDR-BT was based on the CT results. The CTV was defined for the prostate with a 3-mm margin in the lateral and craniocaudal directions and at the base of the seminal vesicle (including the seminal vesicle if T3b), and the PTV was equal to the CTV. The prescribed dose was 9 Gy to 100% of the PTV in each fraction.

Each risk group followed the above prescription dose. The dose constraint followed the volume of PTV receiving 100% of the prescribed dose (PTV-V100%) $\geq$ 90%, rectum-V75% $<$ 1 cm^3, urethra-V125% $<$ 1 cm^3, with no restriction on the bladder. The treatment planning was created automatically by the planning system, and then optimized by manually planning maker. The treatment planning systems were PLATO BPS ver. 14.X (Nucletron, Columbia, MD, USA) and Oncentra MasterPlan ver. 3.3 sp3 (Nucletron).

We also referred to the MRI findings before HDR-BT to improve the accuracy of the plan, and to abide by the above dose constraint we increased the dose ratio on the local lesion detected by MRI as possible. The HDR-BT source that we used was iridium-192, and the equipment was a Nucletron MicroSelectron-HDR v2 (Elekta, Stockholm, Sweden). The 3D-CRT followed by HDR-BT schedule is shown in Supplementary Figure 2.

Androgen deprivation therapy (ADT)

The ADT strategies were as follows: patients with low or intermediate risk by UCSF-CAPRA did not undergo ADT; patients with a high risk and those at stage T3 were prescribed a ≥6-month course of neoadjuvant ADT, and then an approximately 3-year course of adjuvant ADT.

Follow-up

The follow-up cycle was every 3 months for 2 years and every 6 months thereafter. At each follow-up visit, patients were tested for PSA and underwent a urinalysis. If patients were suspected or were diagnosed with recurrence or metastasis, they underwent imaging evaluations (CT, MRI and bone scintigraphy).

Recurrence definition

If any of the conditions below were observed, the case was considered a recurrence: A case was considered a biochemical recurrence if the Radiation Therapy Oncology Group and American Society for Therapeutic Radiology and Oncology (RTOG-ASTRO) Phoenix definition (of PSA nadir + 2 ng/mL, or the initiation of salvage therapy) [15], excluding PSA bounce (i.e., the PSA kinetics showed a transient rise and then recovered without any intervention) occurred. A case was considered a clinical recurrence if any findings of recurrence in diagnostic imaging (by CT, MRI or bone scintigraphy) or pathologic finding of prostate biopsy were observed.

Toxicity definition, overall survival and 'biochemical no evidence of disease'

The assessment of genitourinary (GU) and gastrointestinal (GI) toxicities was done using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). We defined 'early toxicity' as toxicity that occurred at ≤3 months after the HDR-BT, and 'late toxicity' as toxicity that occurred at >3 months after the HDR-BT. We calculated the overall survival (OS) and 'biochemical no evidence of disease (bNED)' survival periods from the day when the patients' HDR-BT was completed.

Statistical analysis and ethical aspects

The OS rate and bNED rate were calculated with the Kaplan-Meier method, and this analysis was performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [16]. This study was approved by the School of Medicine, Niigata University Ethical Committee (no. 2056).

RESULTS

For all 156 patients, the median follow-up period was 38 months (range 3–53 months). Regarding the staging method, 146 (93.7%) of the patients underwent MRI before RT. All patients underwent CT and bone scintigraphy. The PTV and organ at risk (OAR) values of the HDR-BT irradiation dose results (median, range) were as follows: PTV-V100%, 95.06% (64–100); rectum-V75%, 0.53 cm^3 (0–1.11); ure-

thra-V125%, 0.37 cm^3 (0–1.28); bladder-V75%, 5.70 cm^3 (0–31.19).

Regarding ADT, 111 (71.2%) of the 156 patients were treated with ADT; among them 13 (8.3%) patients were treated only with neoadjuvant ADT, and the other 98 (62.8%) patients were treated with both neoadjuvant and adjuvant ADT. The total 3-year OS rate was 95.8%; for the D'Amico low-, intermediate- and high-risk groups, the 3-year OS rates were 100%, 100% and 93.7%, respectively (Fig. 1a). Of the six deaths, one patient died of primary disease (bone metastases were observed) and the other five patients died from other diseases (one each from lung cancer, gastric cancer, cholangiocarcinoma, pancreatic cancer and bronchial asthma).

The total 3-year bNED rate was 97.8%; analyzed by D'Amico risk grouping, these rates were 100%, 100% and 96.9% for the low-, intermediate- and high-risk patients, respectively (Fig. 1b). Biological recurrence was found in three patients (all three were in both the D'Amico group and the UCSF-CAPRA high-risk group) in whom bone metastasis was observed by imaging.

We evaluated the Grade 2 or higher early and late toxicities of the 156 patients. Regarding early toxicities, only 27 (17.3%) patients showed Grade 2 GU toxicities. In this study, we did not evaluate acute hematuria in the toxicity profile when removing the applicator. For late toxicities, 27 (17.3%) GU and seven (4.5%) GI toxicities of Grade 2 were observed, and there were also five cases in which Grade 3 GU toxicity (two urinary tract obstructions, two urinary retention and one hematuria) was observed (Table 3).

In one of the urinary tract obstruction cases among the five Grade 3 GU cases, the toxicity event occurred at 30 months after the patient's HDR-BT, and was then resolved after the patient underwent a urethrotomy. In another urinary tract obstruction case, the toxicity event occurred at 27 months after the patient's HDR-BT, and it then became a Grade 2 urinary tract obstruction after the urethrotomy. In one of the Grade 3 urinary retention cases, the toxicity event occurred at 36 months after the HDR-BT, and after 2 weeks of an indwelling foley catheter, the patient recovered the auto-urination function. In another urinary retention case, a Grade 3 event occurred at 27 months after the HDR-BT, and after undergoing 6 weeks of urethral bougienage and then an urethrotomy, the patient was cured. Of the Grade 3 hematuria cases, the event occurred at 33 months after the HDR-BT, and during the patient's 1-month hospitalized hemostatic treatment, the event became Grade 2.

DISCUSSION

HDR-BT combined with EBRT is considered an effective means of dose-escalation in radiotherapy for prostate cancer and has provided better outcomes. Compared with conventional doses of EBRT alone, some studies indicated that HDR-BT as a boost therapy combined with EBRT improved the bNED rates for prostate cancer, and the benefit was more pronounced in intermediate- and high-risk patients; however, an increased incidence of late toxici-

ties was noted [17-19].

In the present patient population, we adopted a method using 2-fr.-HDR-BT/day and its combination with EBRT before HDR-BT. This protocol was decided upon in the context of ensuring a therapeutic effect while reducing the treatment time and alleviating the patients' treatment-related discomfort as much as possible. EBRT (conventional 2 Gy/fr.) takes 7 weeks to complete, but the schedule of our present method was completed within 1 month. In studies by Demanes et al. [9] and Martinez-Monge et al. [10], two fractions of 5.5-Gy-fraction and 4.75-Gy-fraction HDR-BT were administered within a single day, respectively, and no severe complications were observed. The safety and efficacy of the present higher-dose 9-Gy-fraction prescription (2-fr.-HDR-BT/day) had not been established.

With the MRI findings obtained before the HDR-BT, we were able to identify the specific location of the lesions, and we could thus improve the coverage of PTV-V100% to some extent. The examination by MRI allowed us to find the patients with stage T3 PCa, and it also allowed us to increase the region of the CTV setting to stem extracapsular and seminal vesicle invasion.

HDR-BT is a technique that allows the delivery of a very high biologically equivalent dose (BED) to the prostate. In our study, all 156 patients were treated with 39 Gy in 13 fractions of EBRT combined with 18 Gy of 2-fr.-HDR-BT/day. The total BED (defined as the BED of EBRT plus the BED of HDR-BT, α/β ratio of 1.5) was 243 Gy. We compared our results to those of Martinez et al. [6], Demanes et al. [9], Martinez-Monge et al. [10], Astrom et al. [5] and Kaprealian et al. [20] and have summarized these outcomes in Table 4. Compared to the toxicities of these studies, the occurrence rate of Grade 3 events of our study was neither the highest nor the lowest. Our protocol thus did not show any obvious disparity in toxicity.

Regarding HDR-BT without an EBRT combination as a monotherapy for localized PCa, great developments point to the intrinsic advantages of HDR-BT; the indications can include the extracapsular lesion, without any problem of organ motion [21]. Some studies reported excellent clinical outcomes, with few instances of severe toxicity [22-24] (Table 5). Although HDR-BT monotherapy would provide shorter schedules, it demands a higher degree of technical and planning expertise than boost HDR-BT [1], and the patients need to remain in bed for a long time, even with epidural anesthesia or multiple applicator insertions, which causes discomfort for the patients; in addition, the movement of applicators is a problem. The above studies showed favorable results regarding late toxicities.

We propose that since EBRT cannot exclude the urethral radiation dose, HDR-BT combined with an EBRT radiation dose to the urethra may be excessive. However, with HDR-BT as monotherapy, radiation dose restriction to the urethra can be formulated [22-24], and the radiation dose to the urethra can technically be excluded if the applicator can be arranged in the proper position. The follow-up periods for the

above 3 studies were not long, and results obtained with longer-term follow-ups may be more significant.

ADT for high-risk PCa was related to an improved bNED rate and may thereby prevent distant metastasis [25]. Ishiyama et al. studied a total of 200 consecutive patients with National Comprehensive Cancer Network (NCCN) high- and very high-risk PCa with 31.5 Gy/ 5-fraction HDR-BT combined with 10 fractions of 3-Gy EBRT. An >6-month period of neoadjuvant ADT and a 36-month period of adjuvant ADT were prescribed. A five-year OS rate of 96.9% and a bNED rate of 90.6% respectively were demonstrated, and the Grade 3 GU and GI late toxicities were 9.6% and 0% [26]. Vora et al. reported on a total of 302 patients with a median dose of 75.6 Gy EBRT. They also combined short-course ADT for NCCN intermediate-risk patients and 2-year ADT for the high-risk group. Spratt et al. reported on 1,002 patients who received 86.4 Gy EBRT in 32 fractions combined with a 6-month ADT for NCCN low- and intermediate-risk patients, and a 6- to 24-month course for high-risk patients.

The outcomes of the above two studies were 3-year bNED rates of 96%, 95%, 82% and 99%, 98%, 94% for low-, intermediate- and high-risk groups respectively, with ≥ Grade 3 GU and GI late toxicity rates of 0.7%, 0% and 2.2%, 0.7%, respectively [27, 28]. In the present study, patients with UCSF-CAPRA high-risk or stage T3 PCa underwent ≥6-month neoadjuvant ADT, and 3-year adjuvant ADT could also be a favorable factor for the biochemical control.

Regarding the side effects of ADT, severe cardiovascular or cerebrovascular events did not occur in the present patient series. However, patients with ADT have experienced liver dysfunction, adiposity, diabetes, erectile dysfunction or hot flashes. In addition, ADT may influence the GU and GI toxicity results. These side effects disturb the patients' quality of life. Thus, considering the balance between the tumor control and the quality of life, a few of our patients needed an early termination of the 3-year adjuvant ADT. Larger numbers of patients and longer follow-up periods in future studies can be expected to clarify and confirm the positive results of our ADT strategy.

As for this study's limitations, the MRI examination before RT may have caused the patients to register at a higher stage compared to other studies. The 3-year control rate was better than other studies' 3-year outcomes; however, because our median follow-up period was only 38 months, our 3-year control rate might actually be lower. In addition, considering the follow-up period and the effect of ADT, we have reason to believe that 3-year adjuvant ADT (performed on 62.8% of our 156 patients) would likely have an effect on the outcomes; in addition 30 (19.2%) of our patients had not finished their adjuvant ADT at the time of our analysis. These factors may well have caused the recurrence-free rate to be overestimated.

Concerning toxicity, since HDR-BT is an invasive therapy, the insertion of the applicator and repeated urethral catheterization during and after the HDR-BT may have been the risk factors for acute urinary tract obstruction, urinary retention and hematuria.

Considering that two Grade 3 late urinary tract obstructions were observed between the membranous urethra and bulbous urethra, we note that the physical trauma should not be ignored. Because our main goal was to provide a sufficient dose at the base of the prostate, we imposed no dose limitation on the bladder, and due to the short follow-up period, the GU late toxicities were probably underestimated [5, 29-32]. We used the UCSF-CAPRA risk classification for adapting ADT. Considering the differences between the UCSF-CAPRA and D'Amico risk category tools, even though we did not distinguish between risk groups when determining the dose and the method of 3D-CRT + HDR-BT, our three risk groups created using the D'Amico classification experienced inconsistent variations of ADT. We are thus not able to make exact comparisons of the groupwise results with those in the literature.

In light of the disease control and toxicities observed to date, the efficacy and safety of 2-fraction-HDR-BT administered within a single day (2-fr.-HDR-BT/day) were satisfactory. However, the follow-up period was short, and longer-term follow-up is necessary. In addition, the outcomes will be more significant after the completion of ADT.

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JL worked out the HDR-BT planning, oversaw the collection and analysis of the data, performed the statistical analyses and drafted the manuscript. MK took charge of the final approval of the treatment planning, carried out the follow-up work, conceived of the study, participated in its design and coordination and helped draft the manuscript. RS conceived of the study, participated in its design and coordination and helped draft the manuscript. FA took charge of the final approval of treatment planning, carried out the follow-up work, helped with the statistical analyses, participated in the study design and coordination, and helped draft the manuscript. NY carried out the follow-up work, participated in the study design and coordination and helped draft the manuscript. HS participated in the HDR-BT planning and carried out the follow-up work. KT participated in the HDR-BT planning, carried out the follow-up work, participated in the study design and coordination, and helped draft the manuscript. GK worked out the HDR-BT planning, participated in the study design and coordination, and helped draft the manuscript. AO participated in the HDR-BT planning and the study design and coordination, and helped draft the manuscript. KM participated in the HDR-BT planning, carried out the follow-up work, participated in the study design and coordination, and helped draft the manuscript. EA conceived of the study and participated in its design and coordination and helped create the manuscript. TK carried out the urologic surgical procedures and the follow-up work, participated in the study design and coordination, and helped create the manuscript. TN handled the eligibility of patients, performed urologic surgical procedures and carried out the follow-up work. YT participated in the study design and coordination and helped draft the manuscript. HA con-

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Table 1. Patient characteristics (n = 156)

	Median (range)	
Age (year)	67 (47-77)	
PSA (ng/ml)	9.7 (3.3-131)	
PSA class (ng/ml)	n (%)	
<10	80 (51.3)	
10-20	47 (30.1)	
20<	29 (18.6)	
T stage	n (%)	
T1c	10 (6.4)	
T2a	30 (19.2)	
T2b	10 (6.4)	
T2c	52 (33.3)	
T3a	42 (26.9)	
T3b	12 (7.7)	
Gleason score	n (%)	
2-6	11 (7)	
7	77 (49.4)	
8-10	68 (43.6)	
Risk group	UCSF-CAPRA	D'Amico
	n (%)	n (%)
Low	6 (3.8)	5 (3.2)
Intermediate	65 (41.7)	36 (23.1)
High	85 (54.5)	115 (73.7)

Table 2. Standard for evaluation of UCSF-CAPRA classification. (9)

Variable	Specific patient's level	Point
Age at diagnosis	Under 50	0
	50 or older	1
PSA at diagnosis	≤6	0
	6.1-10	1
	10.1-20	2
	20.1-30	3
	>30	4
Gleason score of the biopsy	No pattern 4 or 5	0
	Secondary pattern 4 or 5	1
	Primary pattern 4 or 5	3
Clinical stage	T1 or T2	0
	T3a*	1
Percent of biopsy cores involved with cancer	<34%	0
	≥34%	1

0 to 2 indicates low-risk, 3 to 5 indicates intermediate-risk, 6 to 10 indicates high-risk; it does not use MRI to estimate the T stage in definition; *T3b was not existed in the standard for evaluation of this classification, in present study, T3b was counted as 1 point.

Table 3. The number of toxicity events.

CTCAE v4.0 term	n (%)	n (%)	n (%)
	Early Grade-2 GU	Late Grade-2 GU	Late Grade-3 GU
Urinary tract obstruction	18 (11.5)	12 (7.7)	2 (1.3)
Urinary retention	4 (2.6)	1 (.6)	2 (1.3)
Urinary tract pain	3 (1.9)	5 (3.2)	-
Urinary urgency	1 (.6)	2 (1.3)	-
Urinary frequency	12 (7.7)	7 (4.5)	-
Urinary incontinence	3 (1.9)	2 (1.3)	-
Hematuria	-	3 (1.9)	1 (.6)
	Early Grade-2 GI	Late Grade-2 GI	Late Grade-3 GI
Anal pain	-	2 (1.3)	-
Hematochezia	-	4 (2.6)	-
Constipation	-	1 (.6)	-

Table 4. The contract with other literatures

Authors	n	P-EBRT(Gy/fr)	HDR-BT (Gy/fr/dys)	Total BED (α/βratio of 1.5)	Median F/U(yrs)	Control rate (%)	ADT situation (%)	G3 early toxicities (%)		G3 late toxicities (%)	
								GU	GI	GU	GI
Martinez	167	46Gy/23fr	16.5-19.5Gy/2-3fr/2dys	184.3-226.9	8.9-11.2	55.2(10yrs)	51.3	--	--	4	--
	305	46Gy/23fr	19-23Gy/2fr/2dys	246.6-306.6	6.2-9.7	71.9(10yrs)		--	--	4	--
Demanse[#]	209	36Gy/20fr	22-24Gy/4fr/2dys	181.9-199.2	7.3	90(5yrs)	0	--	--	7.7	0
Martinez-Monge*	200	54Gy/27fr	19Gy/4fr/2dys	205.2	3.7	85.1(5yrs)	100	--	--	9.5	3
Astrom[§]	214	50Gy/25fr	20Gy/2fr/2dys	207	4	82(5yrs)	70	0	0	10	0
Kaprealian	165	45Gy/15fr	18-19Gy/3-2fr/2dys	225-274.3	3.6-8.8	89.7(5yrs)	86.7	.6	0	1.2	0
Present study[*]	156	39Gr/13fr	18Gy/2fr/1dy	243	3.2	97.8(3yrs)	71.2	0	0	3.2	0

P-EBRT = plan of EBRT; Risk category tools: [#]did not mention, *NCCN risk category, [§]WHO tumor grade, [*]D'Amico

Table 5. HDR-BT for PCa as monotherapy.

Authors	n	HDR-BT (Gy/fr/dys.)	Total BED (α/β ratio of 1.5)	Median F/U (yrs)	Control rate (%)	ADT situation (%)	Risk group			G3 late toxicities (%)	
							Low	Inter-	High	GU	GI
Rogers	284	39Gy/6fr/mean 19 dys	208	2.7	94.4 (5yrs)	16.2	--	284 (100%)	--	0	0
Yoshioka	190	45.5-54Gy/7-9fr/4-5dys	240-270	7.7	Inter-risk: 91 (8yrs) High-risk: 77 (8yrs)	73.2	--	79 (41.6%)	111 (58.4%)	1	2
Kukielka	77	45Gy/3fr/21dys	495	4.8	96.7 (5yrs)	87	47 (61.1%)	27 (35%)	3 (3.9%)	1.3	0

FIGURE LEGENDS

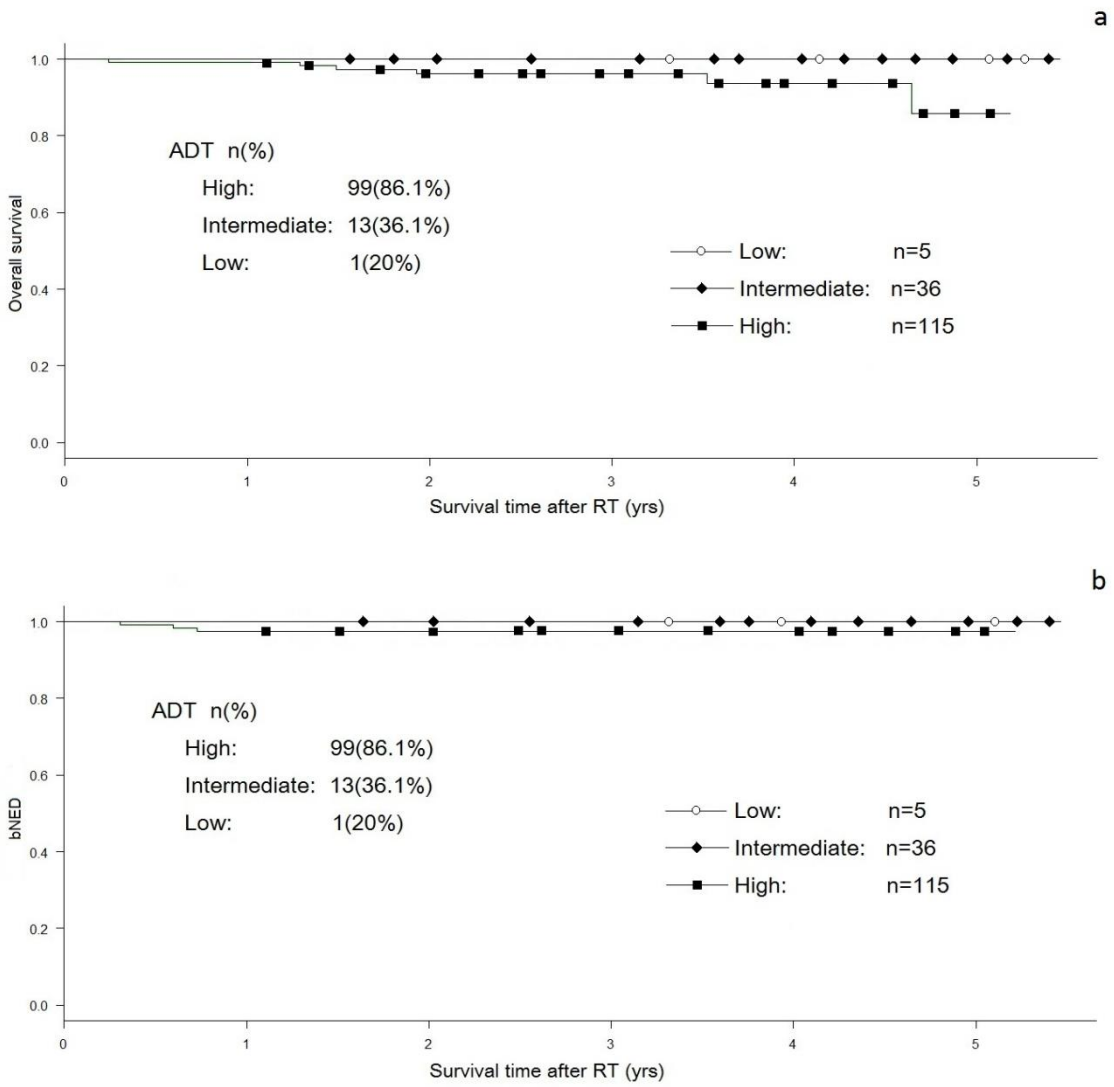
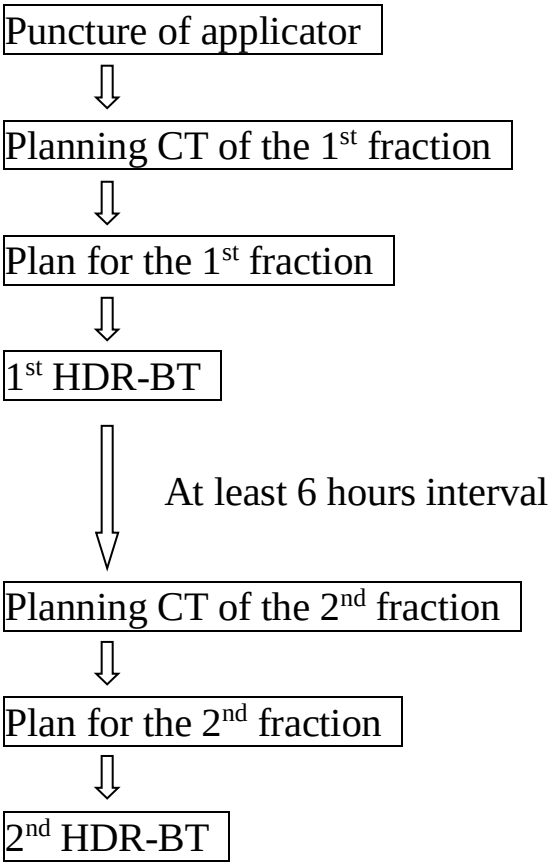


Fig. 1. a. Survival rate calculated by the Kaplan-Meier method. b. The 'biochemical no evidence of disease' (bNED) rate calculated by the Kaplan-Meier method.

SUPPLEMENTARY FIGURE LEGENDS

Sun	Mon	Tue	Wed	Thurs	Fri	Sat
			Examination	Planning of 3D-CRT		
		Linacgraphy	Initiation of 3D-CRT	→	→	
	→	→	→	→	→	
	→	→	→	→	39Gy/13fx.	
			Hospitalization	HDR-BT 18Gy/2fx.		
	Discharge					

Supplementary Fig. 1. The schedule of 3D-CRT and HDR-BT



Supplementary Fig. 2. The HDR-BT protocol.