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Long-term outcomes of salvage high-dose-rate brachytherapy for localized recurrence of prostate cancer following definitive radiation therapy: a retrospective analysis

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Abstract

Background Salvage high-dose-rate brachytherapy (HDR-BT) is a potential treatment for localized recurrence of prostate cancer following definitive radiation therapy. This study aimed to evaluate the long-term safety and efficacy of HDR-BT alone, without androgen deprivation therapy (ADT), in this patient population.

Methods We conducted a retrospective analysis of patients with prostate cancer who developed pathologically confirmed local recurrence after definitive radiation therapy and were treated with salvage HDR-BT alone at Kawasaki Medical School Hospital between 2007 and 2021. The prescribed HDR-BT dose was 22 Gy in 2 fractions. Biochemical relapse-free survival (bRFS), cause-specific survival (CSS), and overall survival (OS) were assessed using the Kaplan–Meier method. Adverse events were evaluated based on the Common Terminology Criteria for Adverse Events.

Results Thirty-five patients were included, with a median follow-up of 66.0 months (range, 8.1–169.1). The 5-year bRFS, CSS, and OS rates were 29.7%, 100%, and 89.3%, respectively. Biochemical recurrence occurred in 21 patients (60.0%). Grade 2 adverse events were reported in eight patients (22.9%), while two (5.7%) experienced grade 3 adverse events. All grade 3 adverse events occurred in patients who had HDR-BT as their initial definitive radiation therapy.

Conclusions Salvage HDR-BT without ADT is a safe and effective treatment option for localized prostate cancer recurrence after definitive radiation therapy. It provides excellent CSS rates with acceptable toxicity while potentially reducing the need for ADT. Further prospective studies are warranted to confirm these findings.

Keywords Prostate cancer, Radiation therapy, High, Dose, Rate brachytherapy, Salvage therapy, Biochemical recurrence, Local recurrence, Androgen deprivation therapy, Long, Term outcomes, Toxicity, Cause, Specific survival

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Background

Prostate cancer is the second most common cancer among men globally, following lung cancer [1]. Radiation therapy, including external beam radiation therapy (EBRT) and brachytherapy, is a well-established definitive treatment for localized prostate cancer, offering outcomes comparable to surgery [2, 3]. However, biochemical recurrence (BCR), defined as a prostate-specific

antigen (PSA) increase of at least 2.0 ng/mL above the post-treatment PSA nadir, can occur after definitive radiation therapy [2–6]. BCR may indicate local or metastatic recurrence or both.

When imaging modalities such as bone scintigraphy, prostate magnetic resonance imaging (MRI), computed tomography (CT), and fluorodeoxyglucose (FDG) ^{18}F positron emission tomography (PET)/CT fail to reveal metastatic recurrence, local recurrence is suspected. In such cases, a biopsy with pathological confirmation is recommended to guide further treatment decisions [7].

Salvage prostatectomy with pelvic lymph node dissection is the standard treatment for pathologically confirmed local recurrence, providing long-term disease control. However, this procedure is limited to experienced centers due to its technical difficulty and is often associated with significant complications such as impotence and urinary incontinence [8]. Alternative local treatment options include EBRT [9–11], high-dose-rate brachytherapy (HDR-BT) [9, 12–17], low-dose-rate brachytherapy (LDR-BT) [9, 17–20], cryotherapy [9, 21], and high-intensity focused ultrasound (HIFU) [9, 22].

Despite the availability of local salvage therapies, most patients with local recurrence are managed by observation or androgen deprivation therapy (ADT) [23]. While ADT avoids invasive procedures, it is associated with adverse events such as hot flashes, osteoporosis, obesity, metabolic changes, diabetes, and increased cardiovascular risk, particularly with prolonged use [24–26]. Additionally, long-term ADT can lead to hormone resistance, reducing its therapeutic effectiveness.

Local salvage therapy, such as HDR-BT, offers a potentially curative approach for patients with pathologically confirmed local recurrence. HDR-BT delivers high-dose, localized radiation over a short duration and provides dosimetric and radiobiological advantages for prostate cancer treatment [12].

This study aimed to evaluate the long-term efficacy and safety of salvage HDR-BT for patients with pathologically confirmed local recurrence of prostate cancer following definitive radiation therapy.

Patients and methods

Patients

This study was approved by the Institutional Review Board of Kawasaki Medical School (approval number: 5329–03) and Okayama University (approval number: 2501–024), and the study was conducted in accordance with the Declaration of Helsinki and its amendments. A notification on the institution's website allowed patients the opportunity to withdraw from the study. We retrospectively evaluated patients with prostate cancer who had undergone definitive radiation therapy, developed BCR, and received salvage HDR-BT for pathologically confirmed local recurrence between 2007 and 2021. Patients with distant metastases at the time of initial treatment were excluded. Patient data, including age, PSA levels, T stage, Gleason score (GS), the percentage of the tumor within the core in the biopsy before salvage HDR-BT, and details of initial radiation therapy, were collected. When multiple biopsy cores were positive in the biopsy before salvage HDR-BT, the biopsy core with the highest GS and the largest tumor percentage was used to determine the tumor percentage within the core. All patients underwent systematic CT and prostate MRI before salvage HDR-BT. HDR-BT was administered without concurrent ADT in all patients.

Treatment

Salvage HDR-BT was performed using a MicroSelectron V2 (Nucletron; Elekta Company, Elekta AB, Stockholm, Sweden) device. The treatment planning systems were PLATO (Nucletron) before 2008 and Oncentra (Nucletron) thereafter. When the treatment planning system was PLATO, a two-dimensional plan was created using X-ray images. When the system was Oncentra, a CT-based treatment plan was used. CT imaging was performed before each irradiation session. Under spinal subarachnoid anesthesia, the HDR-BT applicators were inserted under transrectal ultrasound guidance with patients in the lithotomy position. The treatment area was defined based on biopsy results and classified as whole gland, half-gland, quarter-gland, or ultrafocal [27]. Patients received two irradiations daily (morning and evening), delivering a dose of 11 Gy per fraction, for a total of 22 Gy over two fractions. The iridium-192 (^{192}Ir) source was delivered through the applicators using a remote after-loading system. Dose constraints included ensuring the prescribed dose covered at least 95% of the planning target volume (PTV), limiting the urethral maximum dose to 110% of the prescribed dose, and the rectal maximum dose to 60%. When these constraints could not be met, priority was given to limiting urethral and rectal exposure, which occasionally resulted in compromises to PTV coverage. CT imaging was performed before each irradiation to verify applicator placement. BCR after salvage HDR-BT was defined using the Phoenix criteria as a PSA increase of 2 ng/mL above the nadir [6]. After BCR, some patients started ADT, while others were monitored without it. The decision to introduce ADT was made after consulting with the patient, taking into account factors such as PSA levels and doubling time.

Toxicity

Data on late adverse events were collected from medical records and graded according to the Common Terminology Criteria for Adverse Events version 5.0.

Statistical analyses

Biochemical relapse-free survival (bRFS), cause-specific survival (CSS), and overall survival (OS) rates were calculated using the Kaplan–Meier method. Univariate Cox regression analysis was conducted to evaluate the associations between survival outcomes (bRFS and OS) and patient or treatment factors. Univariate logistic regression analysis was performed to assess the relationship between grade 2 or higher adverse events and patient or treatment factors. Multivariate analysis was not conducted due to the small sample size. Statistical analyses were performed using IBM SPSS version 28.0 (Chicago, IL, USA), and a p-value of < 0.05 was considered statistically significant.

Results

Patient characteristics

Thirty-six patients received salvage HDR-BT, but one was excluded due to distant metastasis at initial treatment, leaving 35 eligible patients. The median follow-up period was 66.0 months (range, 8.1–169.1). The median age was 67 (range, 57–80) years, and the median PSA level before salvage treatment was 4.8 (range, 0.4–15.8) ng/mL. The initial PSA (iPSA) value at diagnosis was 7.6 ng/mL (range, 2.2–142.3). Initial definitive radiation therapy included HDR-BT alone in 11 patients, EBRT combined with HDR-BT in 12 patients, EBRT with X-rays alone in one patient, EBRT with proton beams in 10 patients, and EBRT with carbon beams in one patient. The prescribed doses of EBRT with X-rays, proton beams, and carbon beams were 70 Gy/35 fractions, 74 Gy (relative biological effectiveness [RBE])/37 fractions, and 66 Gy (RBE)/20 fractions, respectively. The median doses for EBRT combined with HDR-BT were 36.8 (range, 32–38.5) Gy/16 fractions [13–15] and 24 Gy/4 fractions [17–23]. HDR-BT alone delivered a dose of 37.5 Gy/5 fractions [2, 3, 28]. The median interval between initial definitive radiation therapy and salvage HDR-BT was 53.9 months (range, 27.2–136.2). The GS before salvage HDR-BT was $\leq 6/7/\geq 8$ in 2/12/13 cases, with 8 missing values. The percentage of the tumor within the core had a median of 40% (range: 10–90%), with 5 missing values.

We summarized patient characteristics in Table 1 and initial definitive radiation therapy in Table 2.

Table 1 Patient and tumor characteristics. Patient and tumor characteristics of the cohort treated with salvage HDR-BT for local recurrence of prostate cancer. T stage and Gleason score distribution are summarized to provide insight into disease severity

Characteristics	Value
Patients (n)	35
Age (years), median (range)	67 (57–80)
Follow-up period (months), median (range)	66.0 (8.1–169.1)
iPSA (ng/mL), median (range)	7.6 (2.2–142.3)
T stage (1c/2a/2b/2c/3a/3b)	8/13/6/1/6/1
Initial GS ($\leq 6/7/> 8$)	15/14/6
Period from initial definitive radiotherapy to salvage HDR-BT (months), median (range)	53.9 (27.2–136.2)
PSA before salvage HDR-BT (ng/mL), median (range)	4.8 (0.4–15.8)
GS before salvage HDR-BT ($\leq 6/7/\geq 8$)	2/12/13
the percentage of tumor involving in the core before salvage HDR-BT (%), median (range)	40 (10–90)

iPSA initial prostate-specific antigen, *GS* Gleason score, *HDR-BT*, high-dose-rate brachytherapy, *PSA* prostate-specific antigen

Treatment and disease control

The prescribed salvage HDR-BT dose was 22 Gy in 2 fractions for all patients. Treatment planning systems included PLATO for 17 patients and Oncentra for 18 patients. All patients successfully completed salvage HDR-BT. The irradiated area was classified as follows: whole prostate gland in 12 patients, half-gland in 19 patients, quarter-gland in three patients, and ultrafocal in one patient. Initially, when carcinoma was detected in both glands of the prostate via biopsy, the whole prostate gland was typically selected as the irradiation area. When the carcinoma was detected in only half of the gland, half-gland irradiation was preferred. Subsequently, when carcinoma was detected solely through targeted biopsy based on high-signal regions in diffusion-weighted images of MRI, quarter-gland irradiation tended to be selected. Furthermore, ultra focal irradiation was introduced following the implementation of MRI-ultrasound fusion image-guided biopsy. Biopsies prior to salvage HDR-BT included systematic biopsies in all cases. However, the final determination of the treatment area was made upon consultation between a radiation oncologist and a urologist.

The 5-year bRFS, CSS, and OS rates were 29.7%, 100%, and 89.3%, respectively. The survival curves of the bRFS, CSS, and OS rates are shown in Figs. 1, 2 and 3. The bRFS rate by treatment range is shown in Fig. 4. During the median follow-up period of 66.0 months, one patient died from prostate cancer, and four died from other causes. BCR occurred in 21 patients (60.0%) with a median time to recurrence of 30.8 months

Table 2 Initial definitive radiotherapy. Initial definitive radiotherapy details, including prescribed doses for EBRT and HDR-BT across various treatment modalities

Initial definitive radiotherapy	n	Prescribed dose of EBRT (Gy/fractions), median (Range)	Prescribed dose of HDR-BT (Gy/fractions), Median (Range)
HDR-BT	11	–	37.5 Gy/5 fractions
EBRT with X-rays and HDR-BT	12	36.8 (32.2–38.5) Gy/16 [13–15] fractions	24 (18–24) Gy/4 [2, 3, 28] fractions
EBRT with X-rays	1	70 Gy/35 fractions	–
EBRT with proton bean	10	74 Gy (RBE)/37 fractions	–
EBRT with carbon bean	1	66 Gy (RBE)/20 fractions	–

EBRT external beam radiation therapy, *HDR-BT* high-dose-rate brachytherapy, *RBE* relative biological effectiveness

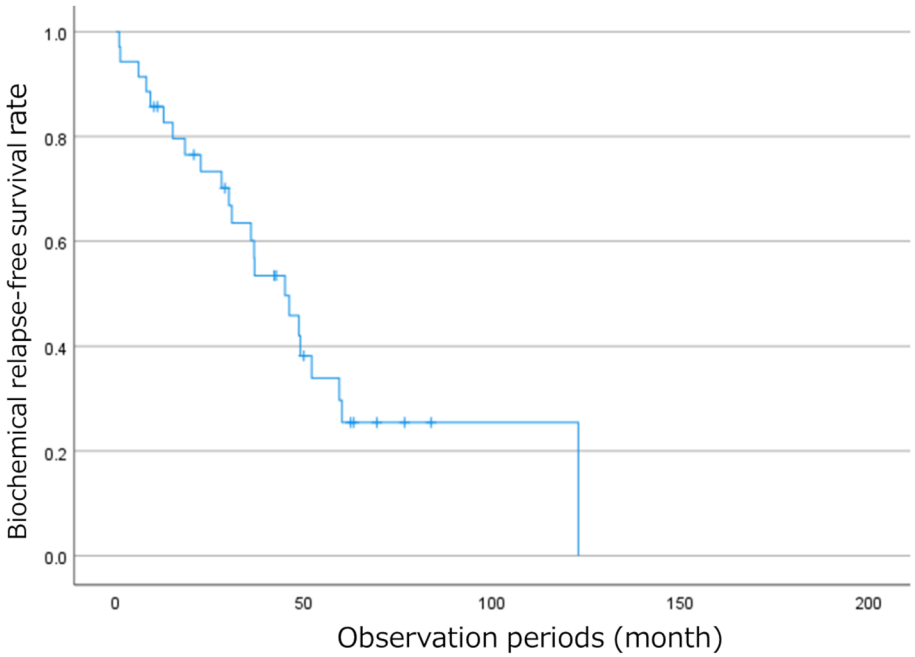

Fig. 1 Biochemical relapse-free survival rate after salvage high-dose-rate brachytherapy

(range, 0.8–122.9). Seventeen (48.6%) patients received further salvage ADT at a median time of 38.3 months (range, 5.0–87.0) post-salvage treatment. The remaining 18 patients (51.4%) did not require ADT.

Clinical recurrence was confirmed in 9 patients (25.7%) after salvage HDR-BT, with a median time to recurrence of 66.9 months (range, 15.5–135.6). Four cases of intraprostatic recurrence were observed, two of which occurred at sites treated with salvage HDR-BT. Recurrences were detected using contrast-enhanced MRI. Repeat biopsy was not performed for detecting intraprostatic recurrence. Five patients developed distant metastases. Distant metastases were detected using CT, bone scintigraphy, or ^{18}F-FDG-PET/CT. Prostate-specific membrane antigen (PSMA) PET was not used for detecting recurrence after salvage HDR-BT.

Table 3 summarizes the results of the Cox regression analysis of the association between the bRFS rate and patient or treatment factors, and Table 4 summarizes the association between the OS rate and patient or treatment factors. In the univariate analysis, iPSA ($p=0.002$), T stage ($p=0.003$), and PSA > 5 ng/mL before salvage HDR-BT ($p=0.03$) were significantly associated with bRFS rate, and age was significantly associated with the OS rate ($p=0.03$). In addition, the period from initial treatment ($p=0.08$) and initial GS ($p=0.07$) tended to be associated with bRFS.

Toxicity

Eight patients experienced grade 2 late adverse events, all of which were urogenital. These included one case of hematuria requiring bladder lavage and seven cases of urethral strictures. Urethral strictures were managed

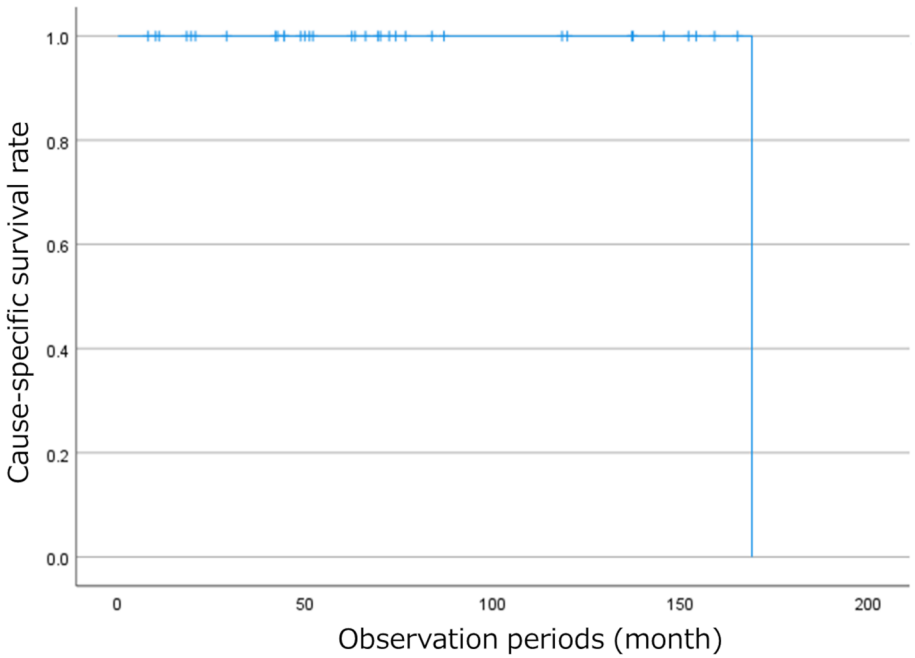

Fig. 2 Cause-specific survival rate after salvage high-dose-rate brachytherapy

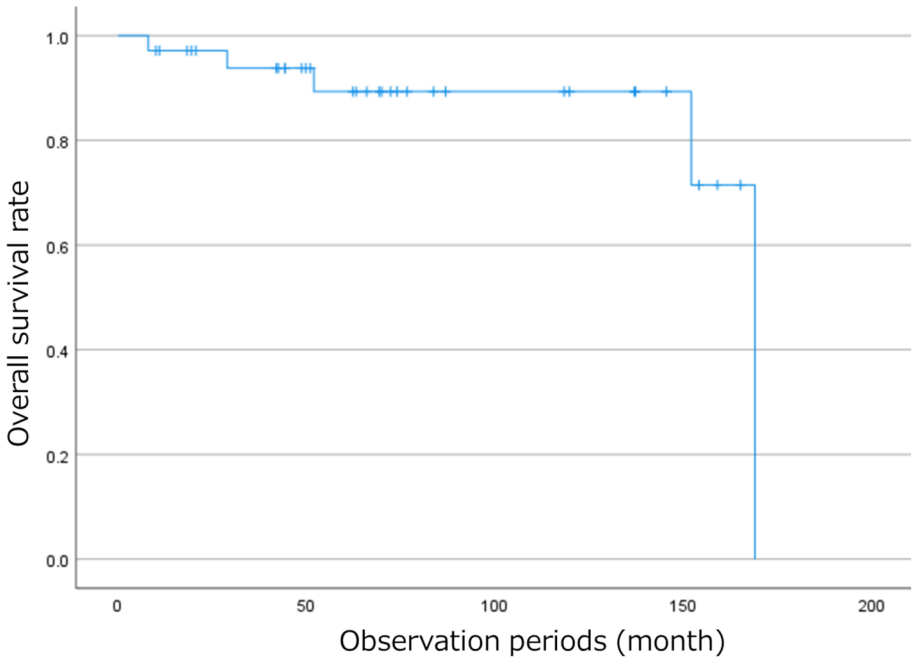

Fig. 3 Overall survival rate after salvage high-dose-rate brachytherapy

with urethral dilatation in two cases, urethrotomy in one case, and catheter placement in four cases. Two patients experienced grade 3 adverse events, both of which were recto-urethral fistulas that required surgical intervention. The median time to urethral stricture and hematuria was 45.2 months (range, 11.0–75.2) post-irradiation. Recto-urethral fistulas occurred significantly later at 137.3 and 149.6 months. No biopsies had been performed just before fistula formation. For cases with Grade 2 genitourinary adverse events, the total maximum urethral dose

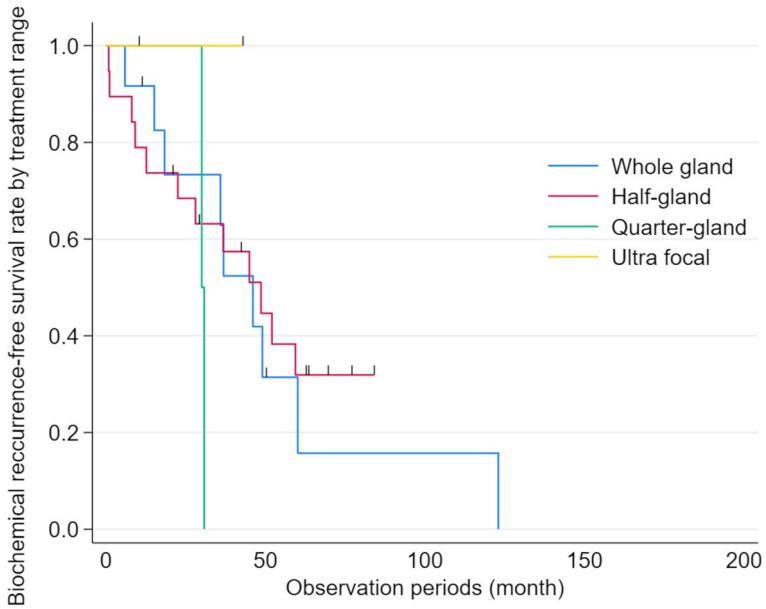

Fig. 4 Biochemical relapse-free survival rate by treatment range after salvage high-dose-rate brachytherapy

Table 3 Cox regression analysis of the factors associated with biochemical relapse-free survival rate (bRFS). Cox regression analysis identifying factors associated with biochemical relapse-free survival (bRFS) in patients undergoing salvage HDR-BT. Significant associations ($p < 0.05$) are indicated with an asterisk (*)

Characteristics	N	Univariate analysis		
		HR	95% CI	*p*-value
Age (years)	–	0.98	0.91–1.06	0.66
First definitive radiation therapy				
HDR-BT/EBRT with X-ray + HDR-BT/EBRT with X-ray/EBRT with proton beam/EBRT with carbon beam	11/12/1/10/1	1.10	0.80–1.52	0.53
The BED of first definitive radiation therapy (Gy)	–	1.00	0.98–1.02	0.93
iPSA (ng/mL)	–	1.05	1.02–1.09	0.002*
T stage				
1c/2a/2b/2c/3a/3b	8/13/6/1/6/1	1.65	1.19–2.30	0.003*
iGS				
≤ 6/7/ > 8	15/14/6	1.32	0.74–2.36	0.34
Treatment range of salvage HDR-BT				
Whole gland/half-gland/quarter-gland/ultrafocal	12/19/3/1	0.91	0.48–1.75	0.78
Period from initial treatment to salvage HDR-BT (months)	–	0.99	0.97–1.00	0.08
PSA before salvage HDR-BT (ng/mL)	–	1.10	0.97–1.24	0.13
PSA before salvage HDR-BT				
PSA > 5 (ng/mL)/ < 5 (ng/mL) PSA	19/16	2.58	1.08–6.18	0.03*
GS before salvage HDR-BT				
≤ 6/7/ > 8	2/12/13	2.14	0.85–5.41	0.11
The percentage of tumor involving in the core before salvage HDR-BT (%)	–	1.01	0.99–1.03	0.36

HR hazard ratio, *CI* confidence interval, *HDR-BT* high-dose-rate brachytherapy, *EBRT* external beam radiation therapy, *BED* biological effective dose, *iPSA* initial prostate-specific antigen, *iGS* initial Gleason score, *PSA* prostate-specific antigen

in salvage HDR-BT had a median of 21.0 Gy (range: 18.0–28.3 Gy). While one case exceeded the initially defined dose constraint, seven cases met our criteria. For cases with Grade 3 adverse events, the total maximum urethral and rectal doses in salvage HDR-BT were 23.8 Gy and 28.4 Gy in the first case, and 21.8 Gy and 7.3 Gy in

Table 4 Cox regression analysis of the factors associated with overall survival (OS) rate. Cox regression analysis identifying factors associated with overall survival (OS) in patients undergoing salvage HDR-BT. Significant associations ($p < 0.05$) are indicated with an asterisk (*)

Characteristic	N	Univariate analysis		
		HR	95% CI	*p*-value
Age (years)	–	1.25	1.02–1.53	0.03*
First definitive radiation therapy				
HDR-BT/EBRT with X-ray + HDR-BT/EBRT with X-ray/EBRT with proton beam/EBRT with carbon beam	11/12/1/10/1	1.47	0.60–3.56	0.4
The BED of first definitive radiation therapy (Gy)	–	0.98	0.93–1.03	0.33
iPSA (ng/mL)	–	0.79	0.48–1.29	0.34
T stage				
1c/2a/2b/2c/3a/3b	8/13/6/1/6/1	0.66	0.28–1.59	0.35
iGS				
≤ 6/7/ > 8	15/14/6	4.17	0.91–19.00	0.07
Treatment range of salvage HDR-BT				
Whole gland/half-gland/quarter-gland/ultrafocal	12/19/3/1	1.91	0.44–8.34	0.39
Period from initial treatment to salvage HDR-BT (months)		0.99	0.95–1.04	0.73
PSA before salvage HDR-BT (ng/mL)		0.58	0.29–1.16	0.13
PSA before salvage HDR-BT				
PSA > 5 (ng/mL)/5 (ng/mL) < PSA	19/16	0.008	33.87	0.26
GS before salvage HDR-BT				
≤ 6/7/ > 8	2/12/13	1.28	0.24–6.85	0.78
The percentage of tumor involving in the core before salvage HDR-BT (%)	–	1.06	1.00–1.13	0.054

HR hazard ratio, *CI* confidence interval, *HDR-BT* high-dose-rate brachytherapy, *EBRT* external beam radiation therapy, *BED* biological effective dose, *iPSA* initial prostate-specific antigen, *iGS* initial Gleason score, *PSA* prostate-specific antigen

the second case, respectively. The rectal dose constraint in the first case exceeded our criteria, whereas both dose constraints were met in the second case.

Both grade 3 adverse events occurred in patients who had HDR-BT as their initial definitive radiation therapy. Notably, no grade 2 or higher adverse events were observed in patients with salvage HDR-BT targeting smaller treatment volumes (quarter-gland or ultrafocal areas).

Logistic regression analysis showed no significant factors associated with grade 2 or higher adverse events. However, a trend was observed regarding the modality of initial definitive radiation therapy ($p = 0.07$), particularly with HDR-BT ($p = 0.056$). No significant associations were found between the irradiated treatment range and adverse events ($p = 0.12$). Tables 5, 6 and 7 summarize adverse events, treatment range, and regression results.

Table 5 Initial definitive radiotherapy and adverse events of salvage high-dose-rate brachytherapy (HDR-BT). Initial definitive radiotherapy modalities and the corresponding grade 2 and grade 3 adverse events observed following salvage HDR-BT for local prostate cancer recurrence

Initial definitive radiotherapy	Patients (n)	Adverse events of salvage HDR-BT	
		Grade 2 (n)	Grade 3 (n)
HDR-BT	11	2	2
EBRT with X-rays + HDR-BT	12	5	0
EBRT with X-rays	1	1	0
EBRT with proton beam	10	0	0
EBRT with carbon beam	1	0	0

HDR-BT high-dose-rate brachytherapy, *EBRT* external beam radiation therapy

Discussion

Salvage HDR-BT for local recurrence of prostate cancer after definitive radiation therapy was feasible and relatively safe within a short treatment period. The 5-year CSS and OS rates were 100% and 89.3%, respectively, reflecting favorable long-term outcomes. This study included patients with diverse prior radiation treatments, such as HDR-BT alone, HDR-BT combined with EBRT with X-rays, EBRT with X-rays, EBRT with proton beams, and EBRT with carbon beams. Notably, salvage HDR-BT appeared safe in patients without a history of HDR-BT as their initial treatment.

Previous studies have reported 5-year bRFS rates of 51–70.8% with salvage HDR-BT [12–14, 17, 29]. In our study, the 5-year bRFS rate was lower at 29.7% than the

Table 6 Treatment range and adverse events of salvage high-dose-rate brachytherapy (HDR-BT). Adverse events associated with salvage HDR-BT categorized by treatment range (whole gland, half-gland, quarter-gland, and ultrafocal) for local prostate cancer recurrence

Treatment range	Patient (n)	Adverse events of salvage HDR-BT	
		Grade 2 (n)	Grade 3 (n)
Whole gland	11	3	2
Half-gland	19	5	0
Quarter-gland	3	0	0
Ultra focal	1	0	0

HDR-BT high-dose-rate brachytherapy

rates reported in previous studies, with a median time to BCR of 30.8 (range, 0.8–122.9) months. This discrepancy may be explained by the higher proportion of patients in our study (45.7%) with PSA levels ≥ 5 ng/mL before salvage HDR-BT in our study. According to the National Comprehensive Cancer Network guidelines, salvage therapy is most effective when PSA levels are < 5 ng/mL at the time of treatment [30]. Our Cox univariate analysis also showed a significantly poorer bRFS rate in patients with PSA ≥ 5 ng/mL before salvage treatment. Another potential factor contributing to lower bRFS rate may be the presence of undetectable distant metastasis, as novel imaging modalities with higher sensitivity, such as PSMA-PET/CT and diffusion-weighted whole-body imaging, were not used in this study.

Another possible reason for our lower treatment outcomes compared to other reports is the relatively lower radiation dose. In our study, the prescribed salvage HDR-BT dose of 22 Gy in 2 fractions corresponds to a biologically effective dose (BED) of 183.3 Gy. BED was calculated as follows: $\alpha/\beta = 1.5$. In contrast, previous reports have described higher doses, such as 32 Gy in 4 fractions (BED = 202.7 Gy) [12], 30 Gy in 3 fractions (BED = 230 Gy) [13], and 27 Gy in 2 fractions (BED = 270 Gy) [16]. However, even our salvage HDR-BT prevented the need for ADT in 51.4% of the patients. Among the 48.6% of patients who eventually required ADT, the median time to induction was 38.3 months (range, 5.0–87.0). These findings highlight the potential of salvage HDR-BT to reduce the burden of hormonal therapy, which is particularly relevant given the adverse effects and risk of hormone resistance associated with long-term ADT.

Grade 3 late adverse events were observed in 2 patients (5.7%), which is consistent with previous reports (0–32%) [15, 17]. We would like to emphasize that rectourethral fistulas could develop even after more than 10 years. To detect such fistulas, long-term follow-up is recommended for patients who have undergone salvage HDR-BT. Both grade 3 adverse events occurred in patients who had previously received HDR-BT as their initial definitive radiation therapy. This association is likely due to the higher single doses used in HDR-BT, which may increase

Table 7 Logistic regression analysis of factors associated with the grade 2 or higher adverse events. Logistic regression analysis of clinical and treatment-related factors associated with grade 2 or higher adverse events following salvage HDR-BT

Characteristic	Univariate analysis *p*-value
Age (years)	0.33
First definitive radiation therapy	
HDR-BT/EBRT with X-ray + HDR-BT/EBRT with X-ray/EBRT with proton beam/EBRT with carbon beam	0.07
History of HDR-BT	0.056
The BED of first definitive radiation therapy (Gy)	0.16
iPSA (ng/mL)	0.29
T stage	
1c/2a/2b/2c/3a/3b	0.49
iGS	
≤ 6/7/ > 8	0.77
Treatment range of salvage HDR-BT	
Whole gland/half-gland/quarter-gland/ultrafocal	0.12
Period from initial treatment to salvage HDR-BT (months)	0.99
PSA before salvage HDR-BT (ng/mL)	0.30

HDR-BT high-dose-rate brachytherapy, *EBRT* external beam radiation therapy, *BED* biological effective dose, *iPSA* initial prostate-specific antigen, *iGS* initial Gleason score, *PSA* prostate-specific antigen

toxicity in normal tissues. Logistic regression analysis showed that grade 2 or higher adverse events tended to occur more frequently in patients with HDR-BT as the initial treatment ($p=0.056$). Additionally, the treatment volume for salvage HDR-BT may influence adverse events; both grade 3 adverse events occurred in patients receiving whole-gland irradiation, and all grade 2 events occurred with more than half-gland irradiation, although no statistically significant difference was observed in our study owing to the small number of cases. Smaller treatment volumes, such as quarter-gland or ultrafocal therapy, appear to reduce the dose to critical organs, including the urethra and rectum, potentially lowering toxicity [12, 29, 31].

Recent evidence suggests that limiting the irradiated area while using advanced imaging techniques, such as MRI fusion and ultrasound guidance, can improve safety and reduce adverse events [31]. Our prior study demonstrated that the ultrafocal technique enabled highly localized irradiation with a median PTV of 4.1 cm^3 (range, 2.0–6.8) [27]. Although this technique was originally reported for initial treatment, it may be a promising option for salvage HDR-BT. In this study, one patient received ultrafocal salvage HDR-BT with no adverse events, suggesting the potential feasibility of this approach. On the other hand, our study included cases in which recurrence occurred in other areas within the prostate gland, suggesting the potential risk of reducing the irradiation field. Therefore, careful consideration is required when determining the treatment area. However, since ultra focal HDR-BT is highly localized, it may offer the advantage of allowing several times of salvage treatments, which could be a potential benefit of this approach.

One approach to improving local control rates is dose escalation; however, careful attention must be paid to the potential increase in adverse events. The advantage of our dose regimen lies in its relatively safe administration of salvage treatment. This may be particularly beneficial for elderly patients, those with multiple comorbidities, cases requiring whole-gland salvage treatment, or instances where the initial definitive treatment was HDR-BT. It is generally observed that reducing the treatment volume tends to lower the risk of adverse events. Therefore, in cases where the salvage treatment area is limited to one-quarter or less of the prostate, increasing the dose—such as the 27 Gy/2 fractions reported in previous studies [16]—may be a viable option to enhance both safety and local control. Further accumulation and analysis of cases are warranted to determine the optimal dose for salvage HDR-BT. Moreover, with the widespread adoption of PSMA-PET/CT, the detection rate of microscopic distant metastases is expected to improve, potentially leading to a reduction in the distant metastatic recurrence following salvage HDR-BT.

In high-risk prostate cancer with an initial clinical stage of T3 and/or a GS of 8 or higher, ADT is often combined with the initial treatment as the standard approach. Therefore, the incorporation of ADT in future salvage treatments should also be considered. However, in our previous study, we demonstrated that high-risk prostate cancer could be relatively controlled without the use of ADT, solely with HDR-BT and EBRT (with a 5-year biochemical freedom from failure rate of 85.2%) [32]. This suggests that, with thorough systemic evaluation to confirm the absence of metastases and an appropriately high radiation dose, salvage HDR-BT alone may achieve disease control even in high-risk cases. In this context, the use of PSMA-PET and dose escalation may hold promise for further improving salvage HDR-BT outcomes.

HDR-BT delivers high doses of radiation to localized areas over a short treatment period, offering radiobiological and dosimetric advantages for prostate cancer [12]. Compared to other radiation therapies, HDR-BT reduces prostate and organ motion uncertainties, ensuring accurate dose delivery to the prostate while minimizing exposure to nearby organs, including the bladder, urethra, and rectum [12]. These characteristics make HDR-BT a valuable salvage treatment option for local recurrence after definitive radiation therapy.

The limitations of this study include its retrospective design, small sample size, and lack of systemic evaluation using advanced imaging modalities. These factors may limit the generalizability of our findings. Nevertheless, the study's strengths include a long-term follow-up period, a high CSS rate, comprehensive reporting of adverse events, and the inclusion of patients with diverse initial radiation treatments.

Conclusion

Salvage HDR-BT for pathologically proven local recurrence of prostate cancer after definitive radiation therapy is a feasible and effective treatment option with a high CSS rate and the potential to reduce or delay ADT initiation. Adverse events were acceptable, particularly in smaller treatment volumes. Further prospective studies are warranted to confirm these findings and optimize treatment strategies.

Abbreviations

ADT	Androgen deprivation therapy
BCR	Biochemical recurrence
BED	Biologically effective dose
bRFS	Biochemical relapse-free survival
CSS	Cause-specific survival
CT	Computed tomography
EBRT	External beam radiation therapy
FDG	Fluorodeoxyglucose
GS	Gleason score

HDR-BT	High-dose-rate brachytherapy
HIFU	High-intensity focused ultrasound
iPSA	Initial prostate-specific antigen
LDR-BT	Low-dose-rate brachytherapy
MRI	Magnetic resonance imaging
OS	Overall survival
PET	Positron emission tomography
PSMA	Prostate-specific membrane antigen
PTV	Planning target volume
PSA	Prostate-specific antigen
RBE	Relative biological effectiveness

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Authors' contributions
All authors contributed to the study design, read, and approved the final manuscript. KW collected the data, performed the statistical analyses, and drafted the manuscript. NK and KK supervised this study.

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Data availability
The datasets generated and/or analyzed during the current study are not publicly available because of the institutional review board's requirements. Still, they are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Kawasaki Medical School (approval number: 5329–03, 577 Matsushima, Kurashiki City, Okayama 701–0192, Japan) and Okayama University (approval number: 2501–024, 2–5-1 Shikatacho, Kita-ku, Okayama City, Okayama 700–8558, Japan). This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to treatment, and they were provided the option to opt out of the study via a notification on the institution's website.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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