scientific reports

Check for updates

OPEN

Biochemical response to neoadjuvant hormonal therapy predicts long-term prostate cancer survival outcomes after high-dose-rate brachytherapy with external beam radiotherapy

Tomoyuki Makino[1]✉, Takayuki Sakurai[2], Shigeyuki Takamatsu[2], Hiroshi Kano[1], Renato Naito[1], Hiroaki Iwamoto[1], Hiroshi Yaegashi[1], Shohei Kawaguchi[1], Kazuyoshi Shigehara[1], Takahiro Nohara[1], Kouji Izumi[1] & Atsushi Mizokami[1]

We evaluated the long-term treatment outcomes and toxicities in patients with clinically localized and locally advanced prostate cancer (PC) who underwent high-dose-rate brachytherapy (HDR-BT) with external beam radiotherapy (EBRT). We retrospectively analyzed 417 patients with PC who underwent HDR-BT with EBRT. The treatment dose was 19- and 13-Gy HDR-BT in two and single fractions, respectively, both combined with external irradiation of 46 Gy in 23 fractions, and hormonal therapy (HT). The median observation period was 7.2 (range, 2.0–17.6) years. The 7-year recurrence-free, PC-specific, and overall survival rates were 93.3%, 99.1%, and 94.8%, respectively, with only six PC mortalities. Multivariable analysis showed that pre-radiotherapy prostate-specific antigen (PSA) of > 0.05 ng/mL after neoadjuvant HT was an independent poor prognostic factor of recurrence (HR, 4.44; 95% CI 1.56–12.63; $p = 0.005$) and overall mortality (HR, 2.20; 95% CI 1.11–4.39; $p = 0.025$). The 7-year cumulative incidence rate of grade ≥ 2 toxicities in genitourinary and gastrointestinal tracts were 15.7% and 2.0%, respectively. HDR-BT combined with EBRT shows promising disease control and tolerant toxicities for PC. Poor PSA response to neoadjuvant androgen deprivation predicts worse survival measures. These patients may require more intensive multidisciplinary treatment in combination with radiotherapy.

Keywords High-dose-rate brachytherapy, Radiotherapy, Prostate cancer, Androgen deprivation therapy, Prostate-specific antigen

Despite recent advances in early detection and treatment of localized prostate cancer (PC), management of the disease remains controversial. In the ProtecT trial, active monitoring, prostatectomy, and radiotherapy (RT) were compared in a technical manner, but PC-specific mortality remained low after 15 years of follow-up, regardless of the assigned treatment[1]. Therefore, the selection of treatment should consider the balance between the potential benefits and risks involved in managing localized PC.

Based on mature results from randomized trials regarding external beam RT (EBRT), increasing radiation dose improves the biochemical control of the disease[2–4]. High-dose-rate brachytherapy (HDR-BT) can locally deliver high radiation doses to the prostate, enabling excellent biochemical control and tolerable adverse events. In Japan, HDR-BT can be used effectively alone or in combination with EBRT for patients with localized and locally advanced PC[5–10]. Although long-term follow-up data exceeding 10 years have been reported from other countries[11–15], mature studies with long-term follow-up on Japanese subjects are still insufficient.

[1]Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8641, Japan. [2]Department of Radiology, Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8641, Japan. ✉email: mackeeen511@gmail.com

This study aimed to evaluate the long-term outcome and safety of patients with PC who underwent HDR-BT and EBRT at Kanazawa University Hospital and identify prognostic factors predictive of outcomes.

Methods

Ethics statement

This study was approved by the Medical Ethics Committee of Kanazawa University (2017–036 [2,499]) and informed consent was obtained from all patients by means of an opt-out system. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and relevant named guidelines and regulations.

Patient criteria

Between January 2006 and December 2020, 495 consecutive patients with PC underwent HDR-BT with EBRT at Kanazawa University Hospital. Of the 495 patients, 31, 27, 8, 10, and 2 patients were excluded because of inadequate dose radiation protocols, a follow-up period of < 2 years, distant metastases, without neoadjuvant hormonal therapy (HT), and incomplete clinical information, respectively. Thus, we retrospectively analyzed the remaining 417 patients by using their medical records.

Lesions were categorized based on the tumor–node–metastasis classification[16]. The risk group was stratified based on the National Comprehensive Cancer Network (NCCN) guidelines[17]. All patients initially received 6 months of combined androgen blockade therapy consisting of 80 mg/day bicalutamide plus androgen deprivation therapy (ADT) as neoadjuvant HT. ADT featured a gonadotropin-releasing hormone agonist, 3 months depot of leuprorelin acetate 11.25 mg or 3 months formulation of goserelin acetate 10.8 mg. We recommend adjuvant combined androgen blockade therapy for 2 years for patients with ≥ 2 high-risk factors based on localized high-risk categories according to NCCN (≥ cT3 or ≥ Grade Group 4 or prostate-specific antigen [PSA] > 20 ng/mL), or locally advanced PC such as ≥ cT3b. HDR-BT is recommended for regional LN metastasis regardless of the size or number of nodes; however, it is not indicated suitable for metastases outside the pelvic external irradiation field.

High-dose-rate brachytherapy

The HDR-BT protocol has been reported previously[18]. Figure 1 shows the flow diagram of the selected and included patients. An interstitial catheter was implanted under spinal anesthesia in awaking with transrectal ultrasound guidance in lithotomy position using a perineal template in an operating room. Even if the invasion was present in the seminal vesicles or bladder, we consciously punctured the applicators into those areas and irradiated the invaded areas. We inserted three gold markers to mark the bilateral base and apex of the prostate. After catheter implantation, the patient was transferred to a computed tomography table for treatment planning using a treatment planning system (Oncentra Brachy, Elekta AB, Stockholm, Sweden) based on the following dose constraints: prostate volume receiving 100% of the dose (> 90%), urethral volume receiving 125% of the dose (< 1 cm^3), urethral volume receiving 150% of the dose (0 cm^3), rectal volume receiving 75% of the dose (< 1 cm^3), and rectal volume receiving 100% of the dose (0 cm^3) based on the national/institutional/international radiotherapy protocols[18–20]. During HDR-BT planning, 150 ml of saline solution was instilled into the bladder to ensure a consistent level of bladder distension. Subsequently, the patient was transferred to a treatment table in an HDR unit room and irradiated with ^{192}Ir remote afterloading system (microSelectron, Nucletron, Veenendaal, the Netherlands) at 19 Gy in two fractions (2006 to March 2014) or 13 Gy in single fraction (from April 2014). The needles were removed after the irradiation session, and the patient kept the 20-Fr triple-lumen urethral catheter with continuous irrigation with saline until the next day. The urethral catheter was removed, and the patient was discharged the following day.

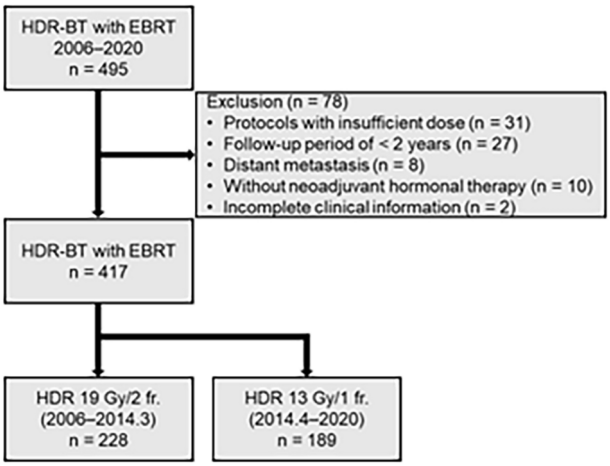

Fig. 1. Flow diagram of the patients included in the study.

External beam radiotherapy

The EBRT protocol has been reported previously[18]. Intensity-modulated RT was used to initially deliver EBRT at 46 Gy in 23 fractions usually 1 or 2 weeks after the HDR procedure and performed with a Monaco treatment planning system. The linear accelerator was an Elekta Infinity scanner (Elekta AB, Stockholm, Sweden). Irradiation to the small pelvic cavity comprised internal/external iliac, obturator, and anterior sacral LN, and included in the external beam fields for pelvic LN metastases. If the pelvic metastatic LNs were sufficiently reduced by neoadjuvant HT, irradiation was completed without boosting the LN metastatic sites. However, if the LN metastases were not adequately reduced, an additional 14 Gy in 7 fractions was administered to the LN metastases. In the current protocol, the biologically effective dose was 241 (19 Gy in two fractions) and 233 (13 Gy in a single fraction) Gy using an α/β ratio of 1.5 Gy.

Toxicity evaluation

We recorded toxicities based on the Common Terminology Criteria for Adverse Events v5.0. Adverse events are defined as events ≤ 3 or ≥ 3 months as acute or late toxicities, respectively.

Statistical analyses

We calculated intervals for survival from the first day of irradiation treatment to the event. Recurrence was defined as radiographic or biochemical recurrence based on the Phoenix criteria[21] and initiation of salvage HT. The differences between the patients' clinicopathological characteristics were compared using Chi–squared test, Fisher's exact test, and Mann–Whitney test appropriately. The Kaplan–Meier method was used to estimate recurrence-free survival (RFS), cancer-specific survival (CSS), overall survival (OS), and cumulative incidence of toxicities. In addition, the log-rank test was used to compare the differences. A Cox proportional hazards model was used for multivariate analysis. Statistical analyses were performed using GraphPad Prism version 6.07 (GraphPad Software Inc., San Diego, CA, USA) and IBM SPSS Statistics version 29 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a $p < 0.05$.

Results

Patient demographics

The demographics of overall patients are shown in Table 1. The overall median follow-up was 7.2 (range, 2.0–17.6) years, and the median age was 69 (range, 50–83) years. Of the 417 patients, clinical T3 or higher locally advanced cancer was observed in 204 patients (48.9%), and regional LN metastasis was involved in 27 patients (6.5%). The most common Grade Group was 4 (136; 32.6%), followed by 5 (104; 24.9%). The median initial PSA level and pre-RT PSA were 12.48 (range, 2.04–2465.76) and 0.046 (range, 0–25.442) ng/mL, respectively. Based on the NCCN risk classification criteria, the most common risk group was high-risk (146; 35.0%), followed by very high-risk (140; 33.6%). When the pre-RT PSA cutoff was set at 0.05, comparisons of patient backgrounds revealed significant differences in PSA at diagnosis, clinical T stage, NCCN risk classification, and the use of adjuvant HT as shown in Table 1.

Treatment outcomes

During the observation period, 24 patients (5.8%) had disease recurrences (4 radiographic recurrences, 17 biochemical recurrences, and 3 initiations of salvage HT). The recurrent sites of radiographic progression were the bone, followed by the lung and perineum. Moreover, 40 patients (9.6%) died, including six PC mortalities. The 7-year RFS, CSS, and OS rates were 93.3% (95% confidence interval [CI], 89.9–95.5), 99.1% (95% CI 97.0–99.7), and 94.8% (95% CI 91.6–96.8), respectively (Fig. 2). The corresponding values at 10 years were 92.7% (95% CI 89.2–95.1), 98.6% (95% CI 96.2–99.5), and 89.5% (95% CI 84.7–92.9), respectively. Based on clinical and oncological parameters, the Kaplan–Meier curves indicated significantly inferior RFS in patients with higher clinical T stage and in the regional group based on NCCN ($p = 0.0085$ and $p = 0.0096$, respectively; Supplementary Fig. S1), but none of initial PSA level and Grade Group level affected RFS. Although higher clinical T stage and involvement regional LNs were significantly associated with CSS in the Kaplan–Meier analysis ($p = 0.0156$ and $p = 0.0005$, respectively; Supplementary Fig. S2), OS was not significantly associated with none of these clinicopathological factors other than age (Supplementary Fig. S3).

Prognostic factors related to treatment outcomes

Table 2 shows the results of univariate and multivariate Cox proportional hazard regression analyses, which showed that pre-RT PSA > 0.05 ng/mL was an independent prognostic factor of recurrence (hazard ratio [HR], 4.44; 95% CI 1.56–12.63; $p = 0.005$) and overall mortality (HR, 2.20; 95% CI 1.11–4.39; $p = 0.025$). The Kaplan–Meier analysis showed a significant difference between the high and low pre-RT PSA groups in terms of RFS (log-rank; HR, 4.54; 95% CI 1.74–8.67; $p = 0.0009$, Fig. 3a), CSS (log-rank; HR, 9.21; 95% CI 1.84–46.06; $p = 0.0068$, Fig. 3b) and OS (log-rank; HR, 2.26; 95% CI 1.20–4.19; $p = 0.0111$, Fig. 3c), respectively.

Incidence of acute and late toxicities

Table 3 shows the incidence of acute and late toxicities. No grade ≥ 4 treatment toxicities occurred. Seven patients (1.7%) and one patient (0.2%) had grade 3 acute genitourinary (GU) and gastrointestinal (GI) complications, respectively. In contrast, eight patients (1.9%) had grade 3 late GU events requiring internal urethrotomy due to urethral stricture. Furthermore, two patients (0.5%) had grade 3 late GI events, involving rectal bleeding, requiring argon plasma coagulation therapy. Grade 3 urethral stricture could potentially cause significant issues as late complications, but none occurred during the single fraction irradiation era. The 7-year cumulative incidence rate of grade ≥ 2 GU and GI toxicities were 15.7% (95% CI 9.2–23.8) and 2.0% (95% CI 0.04–14.5),

	Total	Pre-RT PSA ≤ 0.05	Pre-RT PSA > 0.05	P-Value
Number of patients	417	221	196	
Follow-up, years				0.3762
Median (range)	7.2 (2.0–17.6)	7.6 (2.0–16.0)	6.8 (2.0–17.6)	
Age (year), n (%)				0.1329
Median (range)	69 (50–83)	69 (55–83)	70 (50–82)	
< 70	225 (54.0)	130 (58.8)	95 (48.5)	
≥ 70	192 (46.0)	91 (41.2)	101 (51.5)	
PSA at diagnosis (ng/mL), n (%)				< 0.0001
Median (range)	12.48 (2.04–2465.76)	10.29 (2.04–2465.76)	18.90 (2.59–557.64)	
≤ 20	278 (66.7)	173 (78.3)	105 (53.6)	
> 20, ≤ 40	84 (20.1)	30 (13.6)	54 (27.6)	
> 40	55 (13.2)	18 (8.1)	37 (18.9)	
Clinical T stage, n (%)				0.0075
T2a	113 (27.1)	72 (32.6)	41 (20.9)	
T2b-c	100 (24.0)	58 (26.2)	42 (21.4)	
T3a	95 (22.8)	42 (19.0)	53 (27.0)	
T3b	82 (19.7)	40 (18.0)	42 (21.4)	
T4	27 (6.5)	9 (4.1)	18 (9.2)	
Grade group, n (%)				0.1464
≤ 3	176 (42.2)	92 (41.6)	84 (42.9)	
4	136 (32.6)	80 (36.2)	56 (28.6)	
5	104 (24.9)	48 (21.7)	56 (28.6)	
Unknown	1 (0.2)	1 (0.5)	0	
NCCN risk group, n (%)				0.0018
Low-intermediate	104 (24.9)	60 (27.1)	44 (22.4)	
High	146 (35.0)	89 (40.3)	57 (29.1)	
Very high	140 (33.6)	65 (29.4)	75 (38.3)	
Regional	27 (6.5)	7 (3.2)	20 (10.2)	
Adjuvant hormonal therapy, n (%)				0.0081
Yes	209 (50.1)	97 (43.9)	112 (57.1)	
Pre-RT PSA (ng/mL)				< 0.0001
Median (range)	0.046 (0–25.442)	0.018 (0–0.049)	0.128 (0.051–25.442)	

Table 1. Patient demographics. NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; RT, radiotherapy.

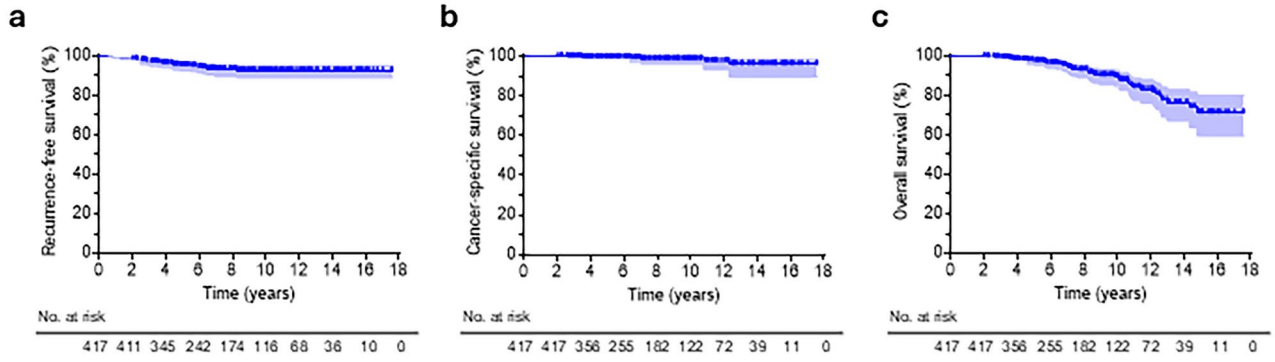

Fig. 2. Kaplan–Meier estimate of all patients. (**a**) Recurrence-free survival, (**b**) cancer-specific survival, and (**c**) overall survival.

Covariant		Recurrence-free survival				Overall survival			
		Univariate		Multivariate		Univariate		Multivariate	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	< 70	Reference		Reference		Reference		Reference	
	≥ 70	0.78 (0.34–1.80)	0.566	0.58 (0.25–1.37)	0.216	2.63 (1.40–4.97)	0.003	2.52 (1.31–4.84)	0.006
PSA at diagnosis	≤ 20	Reference		Reference		Reference		Reference	
	> 20, ≤ 40	1.96 (0.77–4.98)	0.158	1.21 (0.42–3.55)	0.722	0.78 (0.32–1.87)	0.572	0.52 (0.19–1.45)	0.212
	> 40	2.45 (0.86–6.97)	0.094	1.53 (0.40–5.80)	0.533	1.50 (0.57–3.90)	0.409	0.79 (0.21–2.94)	0.729
Clinical T stage	< T3	Reference		Reference		Reference		Reference	
	≥ T3	3.09 (1.27–7.49)	0.012	5.22 (1.09–24.95)	0.038	1.31 (0.69–2.50)	0.406	1.57 (0.50–4.95)	0.438
Grade group	≤ 3	Reference		Reference		Reference		Reference	
	4	1.70 (0.62–4.70)	0.305	2.83 (0.73–10.94)	0.132	1.05 (0.51–2.16)	0.888	1.09 (0.48–2.51)	0.836
	5	2.53 (0.94–6.82)	0.066	3.54 (0.84–14.89)	0.085	1.04 (0.45–2.36)	0.934	1.02 (0.36–2.87)	0.972
Pre-RT PSA	≤ 0.05	Reference		Reference		Reference		Reference	
	> 0.05	4.55 (1.70–12.19)	0.003	4.44 (1.56–12.63)	0.005	2.27 (1.18–4.36)	0.013	2.20 (1.11–4.39)	0.025
Adjuvant hormonal therapy	No	Reference		Reference		Reference		Reference	
	Yes	1.95 (0.85–4.47)	0.116	0.54 (0.15–1.93)	0.343	1.25 (0.65–2.39)	0.497	1.13 (0.38–3.38)	0.822
NCCN risk group	Less than very high	Reference		Reference		Reference		Reference	
	Very high	2.04 (0.85–4.90)	0.113	0.32 (0.05–2.03)	0.228	1.26 (0.62–2.57)	0.528	0.70 (0.16–3.04)	0.638
	Regional	5.42 (1.69–17.45)	0.005	0.72 (0.10–5.48)	0.755	1.91 (0.45–8.15)	0.384	1.27 (0.18–8.95)	0.810

Table 2. Uni- and multivariate analyses of factors influencing recurrence-free survival and overall survival. CI, confidence interval; HR, hazard ratio; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; RT, radiotherapy.

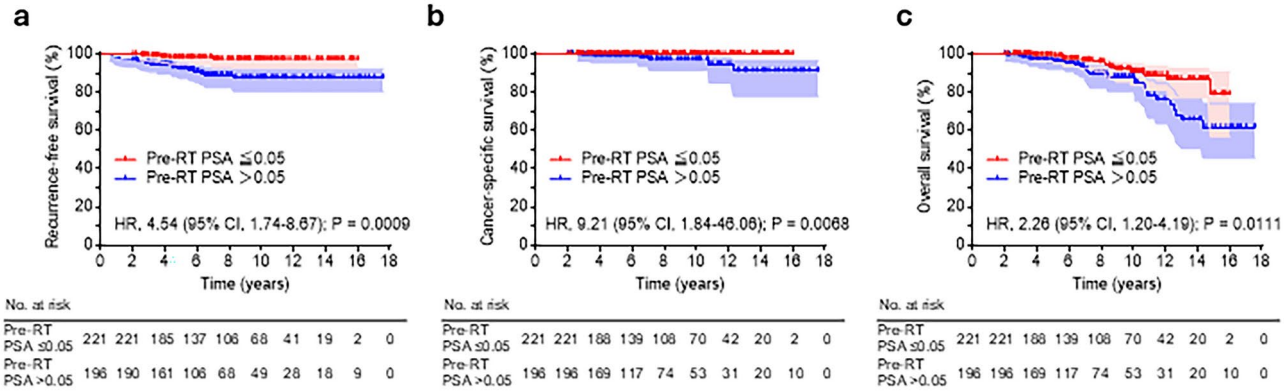

Fig. 3. Kaplan–Meier estimate between high and low pre-radiotherapy (RT) PSA groups. (**a**) Recurrence-free survival, (**b**) cancer-specific survival, and (**c**) overall survival.

	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)
Acute toxicities			
Genitourinary	71 (17.0)	21 (5.0)	7 (1.7)
Gastrointestinal	36 (8.6)	4 (1.0)	1 (0.2)
Late toxicities			
Genitourinary	24 (5.8)	34 (8.2)	8 (1.9)
Gastrointestinal	4 (1.0)	1 (0.2)	2 (0.5)

Table 3. Incidence of acute and late toxicities.

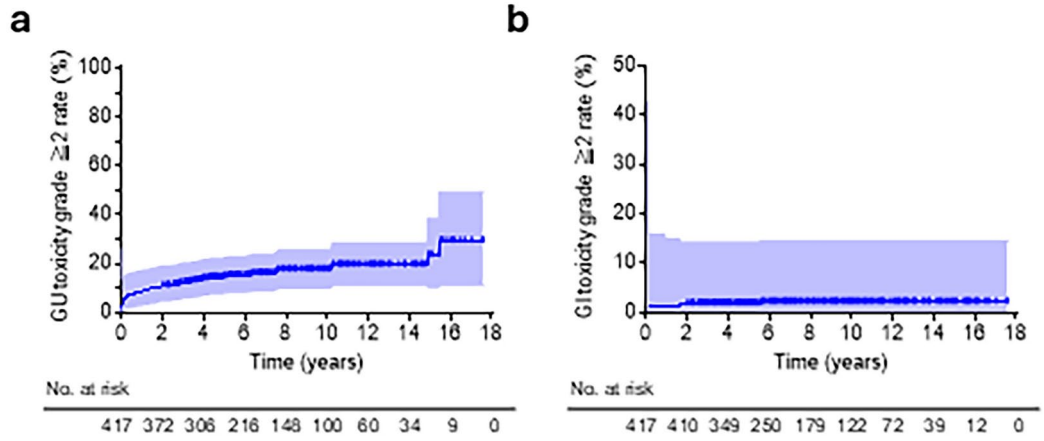

Fig. 4. Kaplan–Meier estimate of cumulative incidence of (**a**) grade ≥ 2 genitourinary (GU) toxicity and (**b**) grade ≥ 2 gastrointestinal (GI) toxicity.

respectively (Fig. 4). The corresponding values at 10 years were 17.3% (95% CI 10.4–25.7) and 2.0% (95% CI 0.04–14.5), respectively.

Discussion

Several studies have indicated that increasing the dose in PC treatment, either through advanced EBRT or a combination of EBRT and brachytherapy, enhances clinical outcomes[22–24]. In radiation biology, compared with other EBRT techniques or low dose-rate brachytherapy, the degree of dose escalation achievable with HDR-BT may be effective in inducing PC cell death[25]. Furthermore, due to a low α/β value of PC at 1.5 Gy, administering higher doses with fewer fractions is more effective in PC treatment[26,27]. Consequently, HDR-BT, which can administer a high dose per irradiation, is effective.

To date, only one randomized controlled trial compared EBRT alone (55 Gy/20 fractions or 35.75 Gy/13 fractions) with an additional HDR boost (17 Gy/2 fractions) in predominantly intermediate and high-risk disease patients[23]. The final analysis results at a median follow-up of 131 months showed that the 6- and 12-year relapse-free survival estimates were 71% and 48% for EBRT + HDR-BT compared with 55% and 27% for EBRT alone ($p = 0.008$)[15]. Although no other randomized comparisons of dose-escalated EBRT and HDR are available, a large number of single and multicenter prospective and retrospective studies have demonstrated favorable biochemical control rates. Based on the largest single-center study reporting outcomes in 2,387 consecutive patients with PC treated with EBRT and HDR-BT combined with a median follow-up of 10.2 years, the cumulative incidence of PC-specific failure at 5 and 10 years was 10.8% and 16.5%, respectively. In addition, the cumulative mortality rate at 10 years was 23%. The cumulative incidence of PC-specific death at 5, 10, and 15 years was 1.5%, 5%, and 10.2%, respectively[13]. In addition, although dosage, fractionation, brachytherapy technique, and duration of ADT usage may be diverse, the documented biochemical disease-free survival typically exceeds 90% and surpasses 80% for intermediate- and high-risk patients, respectively[28]. Thus, we demonstrated exceptionally favorable treatment outcomes, which equaled or surpassed those reported in previous studies.

The current findings indicate that PSA response to the neoadjuvant HT phase could serve as a prognostic factor regarding recurrence and survival for patients undergoing HDR-BT. Multiple studies have shown that PSA nadir values following neoadjuvant ADT significantly impact long-term biochemical RFS and may consequently yield significant improvements in survival outcomes[29]. Although the PSA nadir values cutoff points ranged between 0.1 and 2.5 ng/mL, our study showed that pre-RT PSA > 0.05 ng/mL had a significantly worse prognosis for disease control. Considering the emerging prognostic significance of the biochemical response to neoadjuvant HT in patients with PC undergoing RT, the initial PSA response to HT may indirectly reflect tumor sensitivity to hormone depletion, inherent hormone-mediated radiosensitivity of tumor cells[29], or the presence of more aggressive hormone-resistant cancer cells. Consequently, therapeutic effectiveness could be enhanced using tailoring treatment strategies based on PSA responsiveness in the initial phases of HT. For instance, transitioning to novel androgen receptor signaling inhibitors and taxane-based cytotoxic anticancer agents could enhance the treatment for patients with poor PSA responsiveness. However, these agents cannot be used as first-line treatment for non-metastatic hormone-sensitive PC in the current Japanese healthcare insurance system, which will likely become a future challenge.

Notably, this treatment is very well-tolerated. Based on prior studies, most data sets indicate that late-stage grade 3 urinary toxicity rates range from 0 to 14%, predominantly falling within the 2% to 5% range. Similarly, late-stage grade 3 bowel toxicity rates range from 0 to 4%[28]. The incidence of severe urinary and bowel events seen in our study (grade 3 late GU events, 1.9%; and grade 3 late GI events, 0.5%) was much lower than that in other studies. In contrast, late adverse events that may be problematic were urethral stricture, hematuria, and rectal hemorrhage. Several studies have reported urethral stricture cases following conventional HDR-BT with EBRT, with a urethral stricture rate of 2–10%[5,15,30,31]. The dose to the urethra correlated with late urinary symptoms and toxicity risks, emphasizing the importance of limiting the dose to the bulbomembranous urethra to prevent

late urethral stricture. Although earlier HDR boost protocols of two fractions carried the risk of over-irradiating the distal urethral sphincter due to applicator migration, contemporary single fraction boost protocols mitigate the likelihood of such migration. Therefore, this long-term follow-up study revealed no instances of urethral stricture that require surgical intervention during the single fraction irradiation era, which was consistent with prior findings[8]. Furthermore, although the observation period significantly differs between the era of two-time irradiation and the era of single-time irradiation (10.1 vs. 5.2 years; $p < 0.0001$), previous studies have reported that urethral stricture usually occur 1–3 years after treatment[32]. In this study, we believe that the observation period is sufficient to track the presence or absence of late complications.

The present study is limited by its retrospective, single-center, and nonrandomized design and the small number of events. Thus, statistical analyses results should be interpreted with caution. We were unable to assess the variances that may contribute to GU and GI toxicities originating from disparities in radiation doses between interstitial irradiation and the external beam component. Furthermore, every patient typically undergoes 6 months of neoadjuvant HT, followed by 2 years of adjuvant HT when needed, although detailed decision regarding whether to administer therapy and the duration thereof lies with the attending physician's discretion. However, this study showed outstanding long-term results by using HDR-BT in combination with EBRT, yielding minimal occurrences of severe late toxicities.

In conclusion, HDR-BT combined with EBRT showed excellent results in terms of long-term disease control and safety. Our current findings showed that early biochemical responses during the neoadjuvant phase of HT may serve as significant early surrogate markers for posttreatment survival outcomes. The role of individualized PSA response-based approaches should be investigated in well-designed randomized controlled trials are expected in the future.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Received: 8 August 2024; Accepted: 7 February 2025
Published online: 11 February 2025

References

1. Hamdy, F. C. et al. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N. Engl. J. Med.* **388**, 1547–1558. https://doi.org/10.1056/NEJMoa2214122 (2023).
2. Dearnaley, D. P. et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol.* **8**, 475–487. https://doi.org/10.1016/S1470-2045(07)70143-2 (2007).
3. Kuban, D. A. et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **70**, 67–74. https://doi.org/10.1016/j.ijrobp.2007.06.054 (2008).
4. Al-Mamgani, A. et al. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **72**, 980–988. https://doi.org/10.1016/j.ijrobp.2008.02.073 (2008).
5. Makino, T., Mizokami, A. & Namiki, M. Clinical outcomes of patients with localized and locally advanced prostate cancer undergoing high-dose-rate brachytherapy with external-beam radiotherapy at our institute. *Anticancer Res.* **35**, 1723–1728 (2015).
6. Ishiyama, H. et al. Nationwide multi-institutional retrospective analysis of high-dose-rate brachytherapy combined with external beam radiotherapy for localized prostate cancer: An Asian Prostate HDR-BT Consortium. *Brachytherapy* **16**, 503–510. https://doi.org/10.1016/j.brachy.2017.01.006 (2017).
7. Yoshioka, Y. et al. Nationwide, multicenter, retrospective study on high-dose-rate brachytherapy as monotherapy for prostate cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **97**, 952–961. https://doi.org/10.1016/j.ijrobp.2016.12.013 (2017).
8. Makino, T. et al. Health-related quality of life and toxicity after single-fraction high-dose-rate brachytherapy with external beam radiotherapy for localized and locally advanced prostate cancer. *Anticancer Res.* **39**, 477–486. https://doi.org/10.21873/anticanres.13137 (2019).
9. Makino, T. et al. The effectiveness of high-dose-rate brachytherapy with external beam radiotherapy for clinically locally advanced and node-positive prostate cancer: long-term results of a retrospective study. *Int. J. Clin. Oncol.* **26**, 2310–2317. https://doi.org/10.1007/s10147-021-02023-6 (2021).
10. Kadena, S. et al. The prognostic significance of the clinical T stage and Grade Group in patients with locally advanced prostate cancer treated via high-dose-rate brachytherapy and external beam radiation. *Int. J. Clin. Oncol.* **28**, 1092–1100. https://doi.org/10.1007/s10147-023-02359-1 (2023).
11. Astrom, L., Grusell, E., Sandin, F., Turesson, I. & Holmberg, L. Two decades of high dose rate brachytherapy with external beam radiotherapy for prostate cancer. *Radiother. Oncol.* **127**, 81–87. https://doi.org/10.1016/j.radonc.2017.12.025 (2018).
12. Wedde, T. B. et al. Ten-year survival after High-Dose-Rate Brachytherapy combined with External Beam Radiation Therapy in high-risk prostate cancer: A comparison with the Norwegian SPCG-7 cohort. *Radiother. Oncol.* **132**, 211–217. https://doi.org/10.1016/j.radonc.2018.10.013 (2019).
13. Hjalm-Eriksson, M. et al. High rate of local control and cure at 10 years after treatment of prostate cancer with external beam radiotherapy and high-dose-rate brachytherapy: a single centre experience. *Acta Oncol.* **60**, 1301–1307. https://doi.org/10.1080/0284186X.2021.1953706 (2021).
14. Hsu, I. C. et al. Long-term results of NRG oncology/RTOG 0321: A phase II trial of combined high dose rate brachytherapy and external beam radiation therapy for adenocarcinoma of the prostate. *Int. J. Radiat. Oncol. Biol. Phys.* **110**, 700–707. https://doi.org/10.1016/j.ijrobp.2020.11.008 (2021).
15. Hoskin, P. J., Rojas, A. M., Ostler, P. J., Bryant, L. & Lowe, G. J. Randomised trial of external-beam radiotherapy alone or with high-dose-rate brachytherapy for prostate cancer: Mature 12-year results. *Radiother. Oncol.* **154**, 214–219. https://doi.org/10.1016/j.radonc.2020.09.047 (2021).
16. Brierley, J., Gospodarowicz, M. & Wittekind, C. *The TNM Classification of Malignant Tumours* 8th edn. (Wiley-Blackwell, 2016).
17. Schaeffer, E. M. et al. Prostate Cancer, Version 1.2025, NCCN Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
18. Sakurai, T. et al. Toxicity and clinical outcomes of single-fraction high-dose-rate brachytherapy combined with external beam radiotherapy for high-/very high-risk prostate cancer: A dosimetric analysis of toxicity. *Jpn. J. Radiol.* **38**, 1197–1208. https://doi.org/10.1007/s11604-020-01023-2 (2020).
19. Yamada, Y. et al. American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy. *Brachytherapy* **11**, 20–32. https://doi.org/10.1016/j.brachy.2011.09.008 (2012).

20. Xu, M. J. et al. Single-fraction brachytherapy as monotherapy for early-stage prostate cancer: The UCSF experience. *Brachytherapy* **18**, 470–476. https://doi.org/10.1016/j.brachy.2019.03.002 (2019).
21. Roach, M. 3rd. et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int. J. Radiat. Oncol. Biol. Phys.* **65**, 965–974. https://doi.org/10.1016/j.ijrobp.2006.04.029 (2006).
22. Zietman, A. L. et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* **294**, 1233–1239. https://doi.org/10.1001/jama.294.10.1233 (2005).
23. Hoskin, P. J. et al. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother. Oncol.* **103**, 217–222. https://doi.org/10.1016/j.radonc.2012.01.007 (2012).
24. Michalski, J. M. et al. Effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. *JAMA Oncol.* **4**, e180039–e180039. https://doi.org/10.1001/jamaoncol.2018.0039 (2018).
25. King, C. R., DiPetrillo, T. A. & Wazer, D. E. Optimal radiotherapy for prostate cancer: predictions for conventional external beam, imrt, and brachytherapy from radiobiologic models. *Int. J. Radiat. Oncol. Biol. Phys.* **46**, 165–172. https://doi.org/10.1016/s0360-3016(99)00406-x (2000).
26. Brenner, D. J. & Hall, E. J. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int. J. Radiat. Oncol. Biol. Phys.* **43**, 1095–1101. https://doi.org/10.1016/s0360-3016(98)00438-6 (1999).
27. Brenner, D. J. et al. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. *Int. J. Radiat. Oncol. Biol. Phys.* **52**, 6–13. https://doi.org/10.1016/s0360-3016(01)02664-5 (2002).
28. Morton, G. C. & Alrashidi, S. M. High dose rate brachytherapy in high-risk localised disease—why do anything else?. *Clin. Oncol. (R. Coll. Radiol.)* **32**, 163–169. https://doi.org/10.1016/j.clon.2019.11.003 (2020).
29. Zilli, T., Dal Pra, A., Kountouri, M. & Miralbell, R. Prognostic value of biochemical response to neoadjuvant androgen deprivation before external beam radiotherapy for prostate cancer: A systematic review of the literature. *Cancer Treat. Rev.* **46**, 35–41. https://doi.org/10.1016/j.ctrv.2016.03.016 (2016).
30. Sullivan, L. et al. Urethral stricture following high dose rate brachytherapy for prostate cancer. *Radiother. Oncol.* **91**, 232–236. https://doi.org/10.1016/j.radonc.2008.11.013 (2009).
31. Sekiguchi, A. et al. Relationship between the dose to the bulbomembranous urethra and stricture after high dose-rate brachytherapy for prostate cancer: Matched-pair analysis. *Int. J. Urol.* **26**, 938–939. https://doi.org/10.1111/iju.14045 (2019).
32. Herschorn, S., Elliott, S., Coburn, M., Wessells, H. & Zinman, L. SIU/ICUD consultation on urethral strictures: posterior urethral stenosis after treatment of prostate cancer. *Urology* **83**, S59-70. https://doi.org/10.1016/j.urology.2013.08.036 (2014).

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by T.M. The first draft of the manuscript was written by T.M. and all authors commented on previous versions of the manuscript. A.M. supervised the project. All authors have read and agreed to the published version of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-89771-x.

Correspondence and requests for materials should be addressed to T.M.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.