

ORIGINAL ARTICLE

Highly hypofractionated biaxially rotational dynamic radiation therapy (BROAD-RT) for high-risk prostate cancer

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Abstract

To report clinical outcomes following highly hypofractionated biaxially rotational dynamic radiation therapy (BROAD-RT), a unique radiation therapy method that facilitates non-coplanar volumetric-modulated arc therapy (VMAT) without the need to rotate the couch or reposition the patient, for high-risk prostate cancer (PCa) with simultaneous integrated boost (SIB) for intra-prostatic dominant lesions (IPDLs), we performed a single-center prospective pilot study. In this study, patients with high-risk PCa according to the D'Amico classification or those with cT3aN0M0 PCa were eligible. VMAT was performed using BROAD-RT, and a dose of 54 Gy in 15 fractions was prescribed for the prostate in combination with SIB for IPDLs at a dose of 57 Gy in 15 fractions. Short-term neoadjuvant androgen-deprivation therapy (median: 6.9 months) was conducted. Neither adjuvant androgen-deprivation therapy nor fiducial marker implantation to the prostate was applied for any patient. In total, 26 patients were registered in this study between August 2018 and November 2020. Their median age was 73 years at the initiation of RT. The median follow-up period was 49.7 months. The 4-year cumulative incidence rates of grade 2 late GU and GI toxicities were 15.4 and 3.8%, respectively. No grade 3 or higher acute or late toxicities were observed. The 4-year biochemical failure-free survival rates were 87.7%. In conclusion, highly hypofractionated RT using BROAD-RT for high-risk PCa with SIB for IPDLs was feasible and facilitated favorable oncological outcomes. Therefore, this approach is considered a promising method to achieve safe dose escalation and shorten the treatment duration.

KEYWORDS

biaxially rotational dynamic radiation therapy, hypofractionation, intra-prostatic dominant lesions, non-coplanar volumetric-modulated arc therapy, prostate cancer, simultaneous integrated boost

Abbreviations: ADT, androgen-deprivation therapy; BED, biologically equivalent dose; BF, biochemical failure; BROAD-RT, biaxially rotational dynamic radiation therapy; CF, clinical failure; CI, confidence interval; CT, computed tomography; CTV, clinical target volume; EQD2, equivalent dose in 2-Gy fraction; GI, gastrointestinal; GS, Gleason score; GTV, gross tumor volume; GU, genitourinary; HR, high risk; IMRT, Intensity-modulated radiation therapy; IPDLs, intra-prostatic dominant lesions; OARs, organs at risks; PCa, prostate cancer; PSA, prostate-specific antigen; PSMA-PET/CT, prostate-specific membrane antigen-targeted positron emission tomography/computed tomography; PTV, planning target volume; RT, radiation therapy; SIB, simultaneous integrated boost; VHR, very high risk; VMAT, volumetric-modulated arc therapy.

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1 | INTRODUCTION

IMRT is a sophisticated treatment modality for non-metastatic PCa.^{1,2} VMAT, which is rotational IMRT with the advantage of a reduced treatment delivery time compared with conventional static field IMRT, has become widely applied in clinical practice, especially in PCa treatment.³ Meanwhile, local intra-prostatic recurrence is an important recurrence pattern that needs to be resolved in IMRT for PCa. Local intra-prostatic recurrence has been reported to primarily occur at the site of the primary tumor.^{4,5} The effectiveness of focal dose escalation for IPDLs has been reported as one of the promising methods to improve tumor control without increasing toxicity.⁶⁻⁸

Compared with most other malignant tumors, a low alpha/beta ratio of PCa, in the range of 1–2 Gy, has been reported, being lower than that of adjacent dose-limiting normal structures, such as the rectum or bladder.^{9,10} Owing to this relationship of the alpha/beta ratio between PCa and normal tissue, the application of hypofractionation could further improve the therapeutic ratio of RT for PCa. According to the hypofractionated RT guidelines for localized PCa set by ASTRO, ASCO, and AUA, the hypofractionation size is classified into the following two fractionation categories: moderate hypofractionation with a fraction size between 2.4 and 3.4 Gy, and ultra-hypofractionation with a fraction size ≥ 5 Gy.¹¹ However, a fraction size between moderate hypofractionation and ultra-hypofractionation (3.4–5 Gy per fraction) has not been defined due to the lack of high-level evidence regarding this fraction range. In addition, although there have been several reports on this fractionation, most studies have investigated clinical outcomes primarily in low-risk and intermediate-risk populations.¹²⁻¹⁹ To date, clinical data on this fractionation among high-risk populations have been limited.

We previously conducted a prospective pilot study of hypofractionated IMRT for patients with low-risk and intermediate-risk PCa employing dose fractionation that was intermediate between those two categories (3.6 Gy per fraction), and reported its usefulness and long-term safety.^{12,13} In addition, we have developed a unique RT method, BROAD-RT, previously known as three-dimensional uncusl irradiation (Dynamic WaveArc).^{20,21} BROAD-RT facilitates non-coplanar VMAT without the need to rotate the couch or reposition the patient, and has facilitated improved dose distribution across various treatment sites.²²⁻²⁶ Here, we performed a prospective pilot study of hypofractionated RT using BROAD-RT for patients with HR PCa with the same dose fractionation in combination with focal dose escalation to IPDLs.

2 | PATIENTS AND METHODS

2.1 | Study design and participants

This single institutional prospective pilot study followed the tenets of the Declaration of Helsinki, with approval from the institutional ethics committee (approval numbers: C1388-1 and R1048-2). Written informed consent was required prior to participation. This

study was registered in the University hospital Medical Information Network (UMIN) database (UMIN000033344).

Inclusion criteria were as follows: pathologically confirmed PCa, categorized as high risk according to D'Amico classification²⁷ or T3aN0M0 diseases, received ADT as neoadjuvant therapy (less than 12 months at the initiation of RT), aged 50–85 years, and Eastern Cooperative Oncology Group PS of 0–1. Pretreatment evaluations involving chest-abdominal CT, pelvic MRI, bone scintigraphy, and blood examination including the serum PSA level were mandatory. Exclusion criteria were as follows:

- (1) patients with all of the following unfavorable risks: clinical T3a, GS sum ≥ 8 , and PSA ≥ 30 ng/mL (as we selectively used long-term ADT for those risks²⁸);
- (2) presence of overlapping or asynchronous cancer within 5 years (except carcinoma in situ, intramucosal cancer, or T1N0M0 glottic cancer);
- (3) severe diabetes mellitus;
- (4) severe concomitant illnesses, such as cardiovascular, respiratory, or hepatic diseases;
- (5) severe psychosis;
- (6) history of radiation therapy to the pelvis;
- (7) history of surgery in the pelvic area (except appendectomy, inguinal hernia, or area not overlapping RT field);
- (8) history of prostate surgery (such as transurethral resection of the prostate, or sub-capsular enucleation), orchidectomy, or high-intensity focused ultrasound of the prostate;
- (9) history of chemotherapy for prostate cancer;
- (10) history of inflammatory bowel disease;
- (11) difficulty of withdrawing from an anticoagulant;
- (12) difficulty of meeting the dose constraints for the small or large bowel due to factors such as their location;
- (13) cases with diffuse tumor spread in the prostate or in which a large portion of the prostate had been replaced by the tumor;
- (14) severe artifact on CT images due to procedures such as bipolar hip arthroplasty;
- (15) patients not meeting dose constraints on RT planning.

2.2 | Radiation therapy

RT was performed using BROAD-RT.^{20,21} This is a unique RT method, facilitating continuous beam delivery of non-coplanar VMAT without the need to rotate the couch or reposition the patient through simultaneous rotation of the gantry and body of Linac (O-ring) around two axes.

Details of the treatment planning have been described previously.²⁹ In brief, a dose of 54 Gy in 15 fractions (3.6 Gy per fraction, daily) was prescribed for the prostate (EQD2 of 78.7 Gy, assuming an alpha/beta ratio of 1.5), in combination with a SIB to IPLs at a dose of 57 Gy in 15 fractions (3.8 Gy per fraction) (EQD2 of 86.3 Gy, assuming an alpha/beta ratio of 1.5).

The CTV consisted of the prostate and proximal two-thirds of seminal vesicles. The PTV of the prostate and seminal vesicles

(PTV_PSV), which received 54 Gy in 15 fractions, was defined by adding an 8-mm margin (except for 6 mm in the rectal direction) to CTV. The GTV was defined as IPDLs. For delineation of GTV, we fused pre-treatment MRI to CT, and contoured IPDLs in consideration of the PI-RADS ver.2 recommendation.³⁰ No maximum number of IPDLs was stipulated. The PTV_boost, involving 57 Gy in 15 fractions, was set by adding a 3-mm margin universally to GTV. Elective regional lymph node irradiation was not performed. The prescribed dose (57 Gy) was defined as the dose prescribed to 50% of the volume of the PTV_boost (D50 for the PTV_boost). In addition, IMRT optimization was performed to cover PTV_PSV with 95% of 54 Gy universally, except in the posterior direction (90% of 54 Gy in the posterior direction). The details of dose constraints are shown in Table S1. An example of the structure delineation and dose distribution is shown in Figure 1.

The treatment plans were created using a single arc trajectory or two non-coplanar arc trajectories, which were selected based on the physician's choice, and used a 6-MV photon beam from the Vero4DRT System (Hitachi High-Tech Ltd., Tokyo, Japan). An example of arc trajectory is shown in Figure 1.²⁹

Patients were instructed to void their urinary bladder and rectum 1–1.5 h before CT simulation and each treatment session. Our methods of image guidance have been described previously.³¹ In brief, prostate position-based image-guided RT using cone-beam CT was employed in each treatment session. Fiducial markers were not used in any patients.

2.3 | Androgen-deprivation therapy

The use of neoadjuvant ADT (6–12 months) was mandatory. No adjuvant ADT following RT completion was permitted in any patients. Instead, salvage ADT was initiated if PSA levels were >4 ng/mL, in a monotonically increasing manner, or when any CF was detected. Details of the salvage ADT method were previously described.³²

2.4 | Study endpoints and follow-up

The primary endpoints were the rates of acute GU and GI toxicities (within the first 90 days after RT initiation). The prespecified secondary endpoints were the cumulative incidence rate of late GU and GI toxicities and BF-free survival at 2 years. As the un-prespecified endpoints, we evaluated the cumulative incidence rate of late GU and GI toxicities, BF-free survival rate, and CF-free survival rate at 4 and 5 years.

GU and GI toxicities were evaluated based on the Common Terminology Criteria for Adverse Events version 4.0. BF was based on the Phoenix definition (>2.0 ng/mL above the nadir after treatment).³³ CF was defined as a recurrent disease confirmed via radiographic evaluations.

Patients were clinically assessed and had their PSA concentration measured at least every 4 months for 2 years, and then every

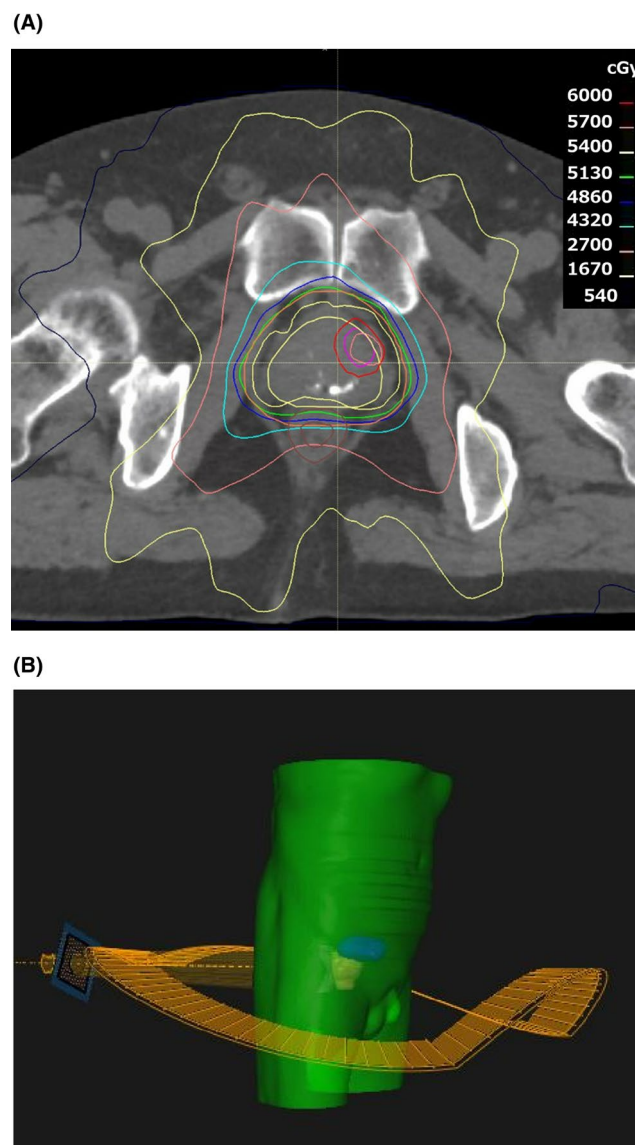


FIGURE 1 An example of structure delineation and dose distribution (A). Each colored line shows the targets and organs at risk (OARs). Key: yellow prostate, orange planning target volume (PTV) of the prostate and seminal vesicles (PTV_PSV), purple Gross tumor volume (GTV), red PTV_boost, brown rectum wall. An example of arc arrangement of biaxially rotational dynamic radiation therapy (BROAD-RT) (B). The orange band shows the non-coplanar trajectory of BROAD-RT.

6 months thereafter. No additional radiographic evaluation after RT was required, unless an increase in the PSA level or symptom suggesting CF was observed.

2.5 | Statistical analysis

This was a single institutional pilot study. The sample size was set at 25, which was estimated pragmatically. We previously performed a pilot study of highly hypofractionated IMRT for patients with low-risk and intermediate-risk PCa to evaluate its safety and efficacy.^{12,13}

The sample size of the current study was set as the same as that used in this previous pilot study.

For the calculation of each endpoint, time zero was defined as the date of RT initiation. Rates of acute GU and GI toxicities were calculated as the ratios of patients developing toxicities (incidence of worst-grade toxicities) within 90 days after RT initiation. The cumulative incidence method accounting for death without each event being a competing risk was used to assess the rates of late GU and GI toxicities. For toxicities persisting from the acute phase, events were counted as occurrences on day 91. The Kaplan–Meier method was used to assess BF-free and CF-free survival rates.

All statistical analyses were performed using EZR version 1.41,³⁴ which is a graphical user interface for R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Between August 9, 2018 and November 4, 2020, 26 patients were enrolled and gave signed consent. All proceeded to RT (all cases met dose constraints on RT planning).

The median patient age was 73 (range: 56–82) years at the initiation of RT. The median initial PSA level was 14.8 (range: 5.0–33.5) ng/mL. More than half of the patients ($N=15$) had $\geq$ T3a disease, and approximately 70% of the patients ($N=18$) had a GS sum ≥ 8 . Consequently, 3.8, 11.5, 38.5, and 46.2% of the patients were categorized into favorable intermediate-risk, unfavorable intermediate-risk, high-risk, and very high-risk groups according to the National Comprehensive Cancer Network (NCCN) risk classification (version 1, 2024),³⁵ respectively. The median duration of neoadjuvant ADT was 6.9 (range: 6.0–9.8) months. Numbers of IPDLs were one in 84.6% ($N=22$) and two in 15.4% ($N=4$), respectively. Details of patient and treatment characteristics and dose results for targets and organs at risk are summarized in Table 1 and Table S2.

The median follow-up period was 49.7 (range: 29.3–63.3) months. No patient died during follow-up. Although the follow-up protocol specified on-site visits, some patients were switched to telephone-based follow-up between April 2020 and April 2022 due to the COVID-19 pandemic.

Incidences of grade 2 acute GU and GI toxicities were 26.9% ($N=7$) and 7.7% ($N=2$), respectively. No $\geq$ grade 3 acute toxicities were noted. Of observed toxicities, 71% ($N=5/7$) of acute GU toxicities and 100% ($N=2/2$) of acute GI toxicities had improved to grade 0–1 at 90 days after RT. Details of the acute toxicities are shown in Table 2. Regarding late GU toxicities, grade 2 urinary retention and urinary frequency continued from the acute to late phases in 7.7% ($N=2$) and 3.8% ($N=1$), respectively, and 3.8% ($N=1$) developed grade 2 urinary urgency 19.1 months after RT. One patient developed gross hematuria 12 months after RT, considered to be due to bladder cancer. Regarding late GI toxicities, 3.8% ($N=1$) developed grade 2 rectal bleeding 11.3 months after RT. No $\geq$ grade 3 late GU or GI toxicities were observed. Cumulative incidence rates of $\geq$ grade 2 late GU and GI toxicities were 15.4% (95%

TABLE 1 Patient and treatment characteristics.

Characteristics		
Number of patients	26	
Age (years), median (range)	73	(56–82)
Performance status, n (%)		
0	25	(96.2%)
1	1	(3.8%)
Initial PSA (ng/mL), median (range)	14.8	(5.0–33.5)
Clinical T stage, n (%)		
T2a	3	(11.5%)
T2b	1	(3.9%)
T2c	7	(26.9%)
T3a	15	(57.7%)
Gleason score		
7	8	(30.8%)
8	10	(38.4%)
9	8	(30.8%)
NCCN risk group (ver. 1, 2024)		
Favorable intermediate	1	(3.8%)
Unfavorable intermediate	3	(11.5%)
High	10	(38.5%)
Very high	12	(46.2%)
Neoadjuvant ADT (months), median (range)	6.9	(6.0–9.8)
Adjuvant ADT	–	
Number of IPDLs		
1	22	(84.6%)
2	4	(15.4%)
Ratio of the target volume (%)		
PTV_boost / PTV_PSV, median (range)	5.6%	(1.6–12.8)

Abbreviations: ADT, androgen-deprivation therapy; IPDLs, intra-prostatic dominant lesions; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; PTV_boost, planning target volume for intra-prostatic dominant lesions; PTV_SV, planning target volume of the prostate and seminal vesicles.

CI: 4.7–31.8) and 3.8% (95% CI: 0.3–16.8) at 2 years, and same at 4, and 5 years, respectively (Figure 2A,B). Details of the late toxicities are shown in Table 3.

During the follow-up, 11.5% ($N=3$) of patients developed BF, of which PSA decreased without any treatments in one patient. Of those, 66.7% ($N=2$) developed CF. Initial sites of CF were the mediastinal lymph nodes in 50% ($N=1$) and seminal vesicles in 50% ($N=1$), with both detected on PSMA-PET/CT evaluation. No patients developed intra-prostatic local failure. The 2-, 4-, and 5-year BF-free survival rates were 92.3% (95% CI: 72.6–98.0), 87.7% (95% CI: 66.3–95.9), and 75.2% (95% CI: 39.4–91.6), respectively (Figure 3A). The 2-, 4-, and 5-year CF-free survival rates were 96.2% (95% CI: 75.7–99.4), 92.0% (95% CI: 71.5–97.9), and 80.5% (95% CI: 44.4–94.4), respectively (Figure 3B).

TABLE 2 Summary of acute toxicities.

Number of patients with GU Grade 2	7	(26.9%)
Urinary frequency	6	(23.1%)
Urinary retention	4	(15.4%)
Urinary urgency	1	(3.8%)
Urinary tract pain	1	(3.8%)
Number of patients with GU $\geq$ Grade 3	0	(0%)
Number of patients with GI Grade 2	2	(7.7%)
Diarrhea	1	(3.8%)
Rectal bleeding	1	(3.8%)
Number of patients with GI $\geq$ Grade 3	0	(0%)

Abbreviations: GI, gastrointestinal; GU, genitourinary.

TABLE 3 Summary of late toxicities.

Number of patients with GU Grade 2	4	(15.4%)
Urinary frequency	1	(3.8%)
Urinary retention	2	(7.7%)
Urinary urgency	1	(3.8%)
Number of patients with GU $\geq$ Grade 3	0	(0%)
Number of patients with GI Grade 2	1	(3.8%)
Rectal bleeding	1	(3.8%)
Number of patients with GI $\geq$ Grade 3	0	(0%)

Abbreviations: GI, gastrointestinal; GU, genitourinary.

4 | DISCUSSION

To the best of our knowledge, this is the first prospective study to investigate the clinical outcomes of hypofractionated RT mainly for patients with high-risk PCa with focal boosting for IPDLs employing a fraction size between moderate and ultra-hypofraction. Specifically, 54Gy to the prostate and 57Gy to IPDLs were prescribed in 15 fractions. Our approach was considered safe in terms of acute and late toxicities, and facilitated favorable tumor control (5-year BF-free survival rate: 75.2%). In addition, BROAD-RT was used as the RT method. To date, no prospective clinical data exclusively on PCa treatment using this RT method have been reported.

In the current study, the dose to the prostate was an EQD2 of 78.7Gy at an α/β ratio of 1.5, which has been commonly used as a total dose of conventional fractionation (78Gy in 39 fractions). The increased dose to IPDLs was EQD2 of 86.3Gy at an α/β ratio of 1.5 and a $BED_{1.5}$ of 201.4Gy. According to the meta-analysis that investigated the association of BED via various radiation fractionation regimens and clinical outcomes,³⁶ although an increase in $BED_{1.5}$ to 200Gy was associated with increased disease control, doses above $BED_{1.5}$ of 200Gy did not result in any additional clinical benefit among patients with HR PCa. Specifically, the 5-year freedom from BF rates increased from 55% to 79%, with a BED escalation to $BED_{1.5}$ of 200Gy; however, that plateaued at 81.0% above a $BED_{1.5}$ of 200Gy and no additional improvement was observed. Therefore, we set the dose applied to IPDLs as 57Gy in 15 fractions

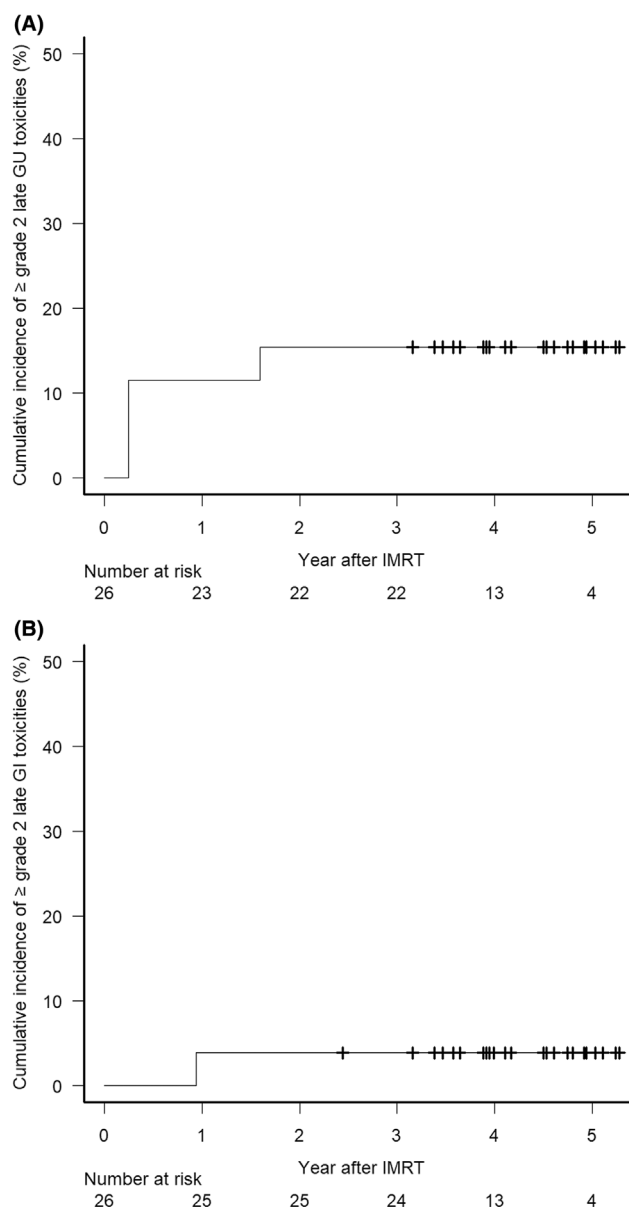


FIGURE 2 Cumulative incidence curves of (A) $\geq$ grade 2 late genitourinary toxicities or (B) gastrointestinal toxicities after intensity-modulated radiation therapy. GI, gastrointestinal; GU, genitourinary.

($BED_{1.5}$ of 201.4Gy). In the FLAME phase III trial, which investigated the benefits of focal dose escalation mainly among patients with HR PCa (84%), a dose of 77Gy in 35 fractions (2.2Gy per fraction) was prescribed for the prostate, and the dose applied to IPDLs was increased up to 95Gy (2.7Gy per fraction, EQD2 of >110 Gy),⁶ which was higher than that of our study. After a median follow-up of 72 months, significant improvement in biochemical disease-free survival was demonstrated without increasing RT-related toxicities (92 vs. 85% at 5 years, respectively, hazard ratio: 0.45; 95% CI: 0.28–0.71, $p < 0.001$). Similarly, in the hypo-FLAME phase II trial, which investigated safety outcomes of focal boosting in the setting of ultra-hypofractionation (35Gy in 5 weekly fraction to the prostate), the dose applied to IPDLs was increased to 50Gy.⁸ The optimal

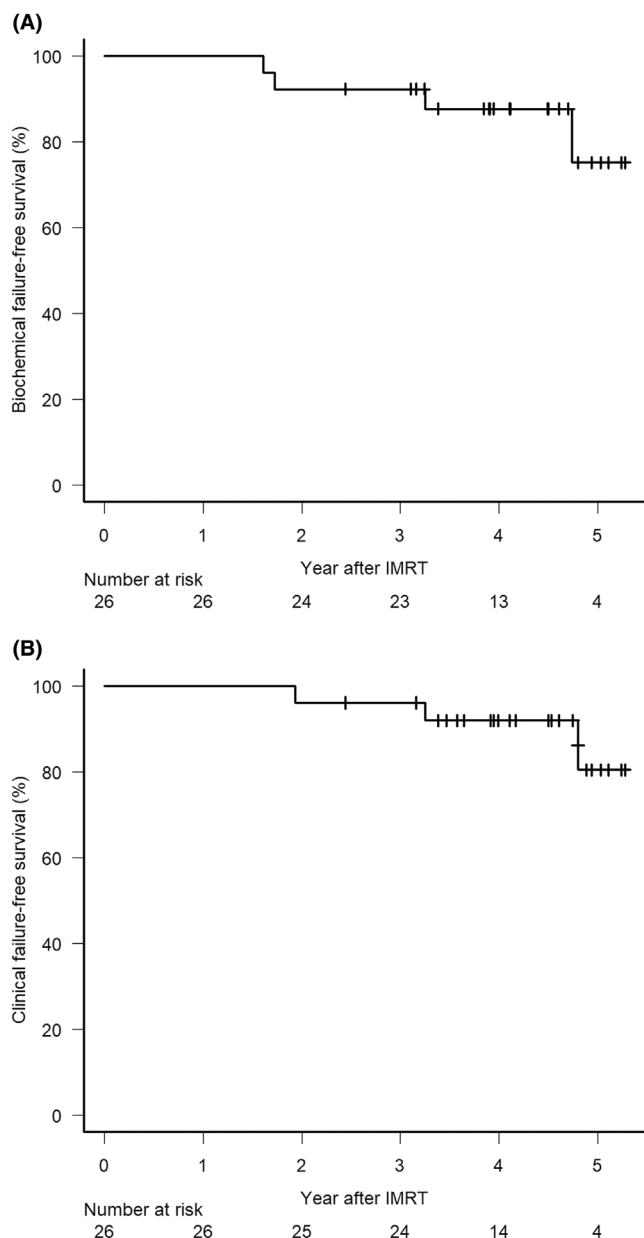


FIGURE 3 Kaplan-Meier curves of (A) biochemical failure-free survival and (B) clinical failure-free survival rates after intensity-modulated radiation therapy. BF, biochemical failure; CF, clinical failure.

dose for IPDLs requires further investigation to clarify the optimal balance between tumor control and toxicity.

With regards to the normal tissue dose, the dose to normal tissue in the current study was EQD2 of 71.3 Gy (54 Gy per 15 fractions) or 77.5 Gy (57 Gy per 15 fractions) at an alpha/beta ratio of 3.0. As the dose to IPDLs was equivalent to the typically applied dose of conventional fractionated IMRT, our method was considered safe even in the presence of dose-limiting tissues, such as the rectum or urethra being close to IPDLs, although we added 3-mm PTV margins around IPDLs. As a result, our approach was considered safe and feasible. Specifically, grade 2 GU and GI late-toxicity rates were only 15.4 and 3.8% at 5 years,

respectively, and no severe toxicities ($\geq$ grade 3) were observed. For further dose escalation, we acknowledge the need to reduce the PTV margin for IPDLs. Indeed, neither the aforementioned FLAME phase III trial nor the hypo-FLAME phase II trial added PTV margins for IPDLs.

Other strengths of our fractionation regimen are the short treatment duration and non-invasiveness. The treatment duration of the currently used moderate hypofractionation regimen ranges from 4 to 6 weeks, while that of our regimen is 3 weeks, being convenient for both patients and clinicians. In addition, fiducial markers to correct errors in prostate location, mainly employed in ultra-hypofractionation, were not necessary as delivery involved 15 fractions. Therefore, our fractionation regimen is considered promising, with its optimal balance between tumor control and toxicities, shortened treatment duration, and lack of invasiveness.

In the current study, we used BROAD-RT as the RT method, facilitating sequential coplanar beam delivery without the need to rotate the couch by being able to simultaneously rotate the gantry and O-ring around two axes, consequently eliminating the need to reposition the patient. Non-coplanar irradiation could improve the target-dose concentration,^{37,38} consequently having the potential to lower RT-induced toxicities. According to a dosimetric analysis by Shafo et al., which compared non-coplanar with coplanar VMAT in SBRT for patients with localized PCa, the use of non-coplanar VMAT significantly reduced the dose to both the rectum ($p < 0.001$) and bladder ($p < 0.001$).³⁹ However, the application of non-coplanar beams in a frequently used C-arm linear accelerator requires prolonged treatment time due to couch rotation, which may result in decreased treatment accuracy due to intra-fractional motion error of the prostate. This decreased treatment accuracy may be critical, especially regarding focal dose escalation for IPDLs. In this regard, BROAD-RT can use non-coplanar beams without impairing the accuracy as it does not prolong the treatment time. According to a planning study by Miura et al., the use of BROAD-RT facilitated a reduced dose for the OARs (bladder and femoral heads) and more favorable homogeneity compared with coplanar VMAT.²⁶ Therefore, BROAD-RT is also considered an ideal RT method for focal dose escalation for IPDLs, and would be particularly advantageous if further dose escalation to IPDLs is necessary.

Our study had several limitations. Due to the nature of a pilot study to primarily investigate toxicities, our cohort was considered too small to draw any definitive conclusion regarding disease control. Furthermore, our clinical data were based on medium-term results (median follow-up: 49.7 months), and so a longer follow-up is needed. However, our study generated clinical data on patients with HR and VHR PCa, for whom focal dose escalation is considered the most beneficial. In addition, as long-term adjuvant ADT, which is recommended for HR and VHR PCa in current treatment guidelines,^{35,40} was not used in the current study, our results enable an observation of a direct effect of dose escalation on IPDLs. Given the growing enthusiasm for hypofractionation and focal dose escalation for IPDLs, as well as non-invasiveness, our data are considered of particular importance.

In conclusion, highly hypofractionated RT using BROAD-RT for patients with HR PCa with SIB for IPDLs was feasible and facilitated favorable oncological outcomes. Therefore, this approach is considered a promising method to achieve safe dose escalation and shorten the treatment duration. To clarify the optimal dose for the IPDLs, further investigations are warranted.

AUTHOR CONTRIBUTIONS

Rihito Aizawa: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; writing – original draft. **Takashi Ogata:** Investigation; writing – review and editing. **Takayuki Goto:** Investigation; writing – review and editing. **Kiyonao Nakamura:** Investigation; writing – review and editing. **Kenji Takayama:** Investigation; writing – review and editing. **Ryo Ashida:** Investigation; writing – review and editing. **Yuki Kita:** Investigation; writing – review and editing. **Takayuki Sumiyoshi:** Investigation; writing – review and editing. **Kaoru Murakami:** Investigation; writing – review and editing. **Kei Mizuno:** Investigation; writing – review and editing. **Takashi Kobayashi:** Investigation; project administration; supervision; writing – review and editing. **Takashi Mizowaki:** Conceptualization; funding acquisition; investigation; methodology; project administration; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Takashi Mizowaki reported receiving grants or scholarship donations from Hitachi Ltd., research funds from Varian Medical Systems, Hitachi Ltd., and Brainlab AG, and honoraria for lectures or presentations from Varian Medical Systems and Janssen Pharmaceutical K.K. Rihito Aizawa, Takashi Ogata, Takayuki Goto, Kiyonao Nakamura, Kenji Takayama, Ryo Ashida, Yuki Kita, Takayuki Sumiyoshi, Kaoru Murakami, Kei Mizuno, Takashi Kobayashi reported no conflicts of interest related to the subject matter of this study.

ETHICS STATEMENT

- Approval of the research protocol by an Institutional Reviewer Board: This single institutional prospective pilot study followed the tenets of the Declaration of Helsinki, with approval from the institutional ethics committee (approval numbers: C1388-1 and R1048-2).
- Informed Consent: Written informed consent was required prior to participation.
- Registry and the Registration No. of the study/trial: This study was registered in the UMIN database (UMIN000033344).
- Animal studies: N/A

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REFERENCES

1. Hatano K, Tohyama N, Kodama T, Okabe N, Sakai M, Konoeda K. Current status of intensity-modulated radiation therapy for prostate cancer: history, clinical results and future directions. *Int J Urol*. 2019;26(8):775-784. doi:[10.1111/iju.14011](https://doi.org/10.1111/iju.14011)
2. Nakamura K, Nihei K, Saito Y, et al. A Japanese multi-institutional phase II study of moderate hypofractionated intensity-modulated radiotherapy with image-guided technique for prostate cancer. *Int J Clin Oncol*. 2024;29(6):847-852. doi:[10.1007/s10147-024-02517-z](https://doi.org/10.1007/s10147-024-02517-z)
3. Davidson MT, Blake SJ, Batchelar DL, Cheung P, Mah K. Assessing the role of volumetric modulated arc therapy (VMAT) relative to IMRT and helical tomotherapy in the management of localized, locally advanced, and post-operative prostate cancer. *Int J Radiat Oncol Biol Phys*. 2011;80(5):1550-1558. doi:[10.1016/j.ijrobp.2010.10.024](https://doi.org/10.1016/j.ijrobp.2010.10.024)
4. Aizawa R, Otani T, Ogata T, et al. Spatial pattern of Intraprostatic recurrence after definitive external-beam radiation therapy for prostate cancer: implications for focal boost to Intraprostatic dominant lesion. *Adv Radiat Oncol*. 2024;9(6):101489. doi:[10.1016/j.adro.2024.101489](https://doi.org/10.1016/j.adro.2024.101489)
5. Arrayeh E, Westphalen AC, Kurhanewicz J, et al. Does local recurrence of prostate cancer after radiation therapy occur at the site of primary tumor? Results of a longitudinal MRI and MRSI study. *Int J Radiat Oncol Biol Phys*. 2012;82(5):e787-e793. doi:[10.1016/j.ijrobp.2011.11.030](https://doi.org/10.1016/j.ijrobp.2011.11.030)
6. Kerkmeijer LGW, Groen VH, Pos FJ, et al. Focal boost to the intraprostatic tumor in external beam radiotherapy for patients with localized prostate cancer: results from the flame randomized phase iii trial. *J Clin Oncol*. 2021;39(7):787-796. doi:[10.1200/JCO.20.02873](https://doi.org/10.1200/JCO.20.02873)
7. Groen VH, van Schie M, Zuihof NPA, et al. Urethral and bladder dose-effect relations for late genitourinary toxicity following external beam radiotherapy for prostate cancer in the FLAME trial. *Radiother Oncol*. 2022;167:127-132. doi:[10.1016/j.radonc.2021.12.027](https://doi.org/10.1016/j.radonc.2021.12.027)
8. Draulans C, van der Heide UA, Haustermans K, et al. Primary endpoint analysis of the multicentre phase II hypo-FLAME trial for intermediate and high risk prostate cancer. *Radiother Oncol*. 2020;147:92-98. doi:[10.1016/j.radonc.2020.03.015](https://doi.org/10.1016/j.radonc.2020.03.015)
9. Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: alpha/beta=1.4 (0.9-2.2) Gy. *Int J Radiat Oncol Biol Phys*. 2012;82(1):e17-e24. doi:[10.1016/j.ijrobp.2010.10.075](https://doi.org/10.1016/j.ijrobp.2010.10.075)
10. Proust-Lima C, Taylor JM, Secher S, et al. Confirmation of a low alpha/beta ratio for prostate cancer treated by external beam radiation therapy alone using a post-treatment repeated-measures model for PSA dynamics. *Int J Radiat Oncol Biol Phys*. 2011;79(1):195-201. doi:[10.1016/j.ijrobp.2009.10.008](https://doi.org/10.1016/j.ijrobp.2009.10.008)
11. Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated radiation therapy for localized prostate cancer: an ASTRO, ASCO, and AUA evidence-based guideline. *J Clin Oncol*. 2018;36(34):3411-3434. doi:[10.1200/JCO.18.01097](https://doi.org/10.1200/JCO.18.01097)
12. Nakamura K, Ikeda I, Inokuchi H, et al. A pilot study of highly hypofractionated intensity-modulated radiation therapy over 3 weeks for localized prostate cancer. *J Radiat Res*. 2018;59(5):656-663. doi:[10.1093/jrr/rry060](https://doi.org/10.1093/jrr/rry060)

13. Nakamura K, Ikeda I, Inokuchi H, et al. Long-term outcomes of a prospective study on highly Hypofractionated intensity modulated radiation therapy for localized prostate cancer for 3 weeks. *Pract Radiat Oncol*. 2023;13:e530-e537. doi:[10.1016/j.prro.2023.06.004](https://doi.org/10.1016/j.prro.2023.06.004)
14. Ritter MA, Kupelian PA, Peteret DG, et al. A prospective multi-institutional phase I/II trial of step-wise dose-per-fraction escalation in low and intermediate risk prostate cancer. *Pract Radiat Oncol*. 2020;10(5):345-353. doi:[10.1016/j.prro.2020.02.013](https://doi.org/10.1016/j.prro.2020.02.013)
15. Brower JV, Forman JD, Kupelian PA, et al. Quality of life outcomes from a dose-per-fraction escalation trial of hypofractionation in prostate cancer. *Radiother Oncol*. 2016;118(1):99-104. doi:[10.1016/j.radonc.2015.12.018](https://doi.org/10.1016/j.radonc.2015.12.018)
16. Fonteyne V, Soete G, Arcangeli S, et al. Hypofractionated high-dose radiation therapy for prostate cancer: long-term results of a multi-institutional phase II trial. *Int J Radiat Oncol Biol Phys*. 2012;84(4):e483-e490. doi:[10.1016/j.ijrobp.2012.04.012](https://doi.org/10.1016/j.ijrobp.2012.04.012)
17. Achard V, Jorcano S, Rouzaud M, Escude L, Miralbell R, Zilli T. Twice-vs. thrice-weekly moderate hypofractionated radiotherapy for prostate cancer: does overall treatment time matter? *J Cancer Res Clin Oncol*. 2019;145(6):1581-1588. doi:[10.1007/s00432-019-02893-4](https://doi.org/10.1007/s00432-019-02893-4)
18. Wu JS, Brasher PM, El-Gayed A, et al. Phase II study of hypofractionated image-guided radiotherapy for localized prostate cancer: outcomes of 55 Gy in 16 fractions at 3.4 Gy per fraction. *Radiother Oncol*. 2012;103(2):210-216. doi:[10.1016/j.radonc.2011.12.020](https://doi.org/10.1016/j.radonc.2011.12.020)
19. Valeriani M, Di Staso M, Facondo G, et al. Hypofractionated radiotherapy in intermediate-risk prostate cancer patients: long-term results. *J Clin Med*. 2022;11(16):4783. doi:[10.3390/jcm11164783](https://doi.org/10.3390/jcm11164783)
20. Mizowaki T, Takayama K, Nagano K, et al. Feasibility evaluation of a new irradiation technique: three-dimensional uncursal irradiation with the Vero4DRT (MHI-TM2000). *J Radiat Res*. 2013;54(2):330-336. doi:[10.1093/jrr/rrs076](https://doi.org/10.1093/jrr/rrs076)
21. Hiraoka M, Mizowaki T, Matsuo Y, Nakamura M, Verellen D. The gimbaled-head radiotherapy system: rise and downfall of a dedicated system for dynamic tumor tracking with real-time monitoring and dynamic WaveArc. *Radiother Oncol*. 2020;153:311-318. doi:[10.1016/j.radonc.2020.07.002](https://doi.org/10.1016/j.radonc.2020.07.002)
22. Burghelma M, Verellen D, Dhont J, et al. Treating patients with dynamic wave arc: first clinical experience. *Radiother Oncol*. 2017;122(3):347-351. doi:[10.1016/j.radonc.2017.01.006](https://doi.org/10.1016/j.radonc.2017.01.006)
23. Burghelma M, Verellen D, Poels K, et al. Initial characterization, dosimetric benchmark and performance validation of Dynamic Wave Arc. *Radiat Oncol*. 2016;11(63). doi:[10.1186/s13014-016-0633-7](https://doi.org/10.1186/s13014-016-0633-7)
24. Ono Y, Yoshimura M, Hirata K, et al. Dosimetric advantages afforded by a new irradiation technique, dynamic WaveArc, used for accelerated partial breast irradiation. *Phys Med*. 2018;48:103-110. doi:[10.1016/j.ejmp.2018.03.015](https://doi.org/10.1016/j.ejmp.2018.03.015)
25. Uto M, Mizowaki T, Ogura K, et al. Volumetric modulated dynamic WaveArc therapy reduces the dose to the hippocampus in patients with pituitary adenomas and craniopharyngiomas. *Pract Radiat Oncol*. 2017;7(6):382-387. doi:[10.1016/j.prro.2017.04.004](https://doi.org/10.1016/j.prro.2017.04.004)
26. Miura H, Nakao M, Doi Y, Ozawa S, Kenjo M, Nagata Y. Treatment planning comparison between dynamic wave arc and volumetric modulated arc therapies for prostate-cancer treatment. *Med Dosim*. 2022;47(1):48-53. doi:[10.1016/j.meddos.2021.08.001](https://doi.org/10.1016/j.meddos.2021.08.001)
27. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280(11):969-974. doi:[10.1001/jama.280.11.969](https://doi.org/10.1001/jama.280.11.969)
28. Ogata T, Aizawa R, Nakamura K, et al. Impact of long-term adjuvant hormonal therapy in high-dose IMRT for unfavorable locally advanced prostate cancer. *Anticancer Res*. 2023;43(8):3589-3596. doi:[10.21873/anticancer.16538](https://doi.org/10.21873/anticancer.16538)
29. Ashida R, Nakamura K, Aizawa R, et al. Highly hypofractionated intensity-modulated radiation therapy for nonmetastatic prostate cancer with a simultaneous integrated boost to intraprostatic lesions: a planning study. *Jpn J Radiol*. 2022;40(2):210-218. doi:[10.1007/s11604-021-01186-6](https://doi.org/10.1007/s11604-021-01186-6)
30. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS prostate imaging—reporting and data system: 2015, version 2. *Eur Urol*. 2016;69(1):16-40. doi:[10.1016/j.eururo.2015.08.052](https://doi.org/10.1016/j.eururo.2015.08.052)
31. Aizawa R, Inokuchi H, Ikeda I, et al. Impact of prostate position-based image-guidance in intensity-modulated radiation therapy for localized prostate cancer. *Int J Clin Oncol*. 2024;29(3):325-332. doi:[10.1007/s10147-023-02456-1](https://doi.org/10.1007/s10147-023-02456-1)
32. Aizawa R, Takayama K, Nakamura K, et al. Ten-year outcomes of high-dose intensity-modulated radiation therapy for nonmetastatic prostate cancer with unfavorable risk: early initiation of salvage therapy may replace long-term adjuvant androgen deprivation. *Int J Clin Oncol*. 2019;24(10):1247-1255. doi:[10.1007/s10147-019-01478-y](https://doi.org/10.1007/s10147-019-01478-y)
33. Roach M 3rd, Hanks G, Thames H Jr, 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*. 2006;65(4):965-974. doi:[10.1016/j.ijrobp.2006.04.029](https://doi.org/10.1016/j.ijrobp.2006.04.029)
34. Kanda Y. Investigation of the freely available easy-to-use software "EZ" for medical statistics. *Bone Marrow Transplant*. 2013;48(3):452-458. doi:[10.1038/bmt.2012.244](https://doi.org/10.1038/bmt.2012.244)
35. NationalComprehensiveCancernetwork. NCCN guidelines; prostate cancer version 4. 2024. The category of prostate cancer. https://www.nccn.org/guidelines/category_1 2024.
36. Zaorsky NG, Palmer JD, Hurwitz MD, Keith SW, Dicker AP, Den RB. What is the ideal radiotherapy dose to treat prostate cancer? A meta-analysis of biologically equivalent dose escalation. *Radiother Oncol*. 2015;115(3):295-300. doi:[10.1016/j.radonc.2015.05.011](https://doi.org/10.1016/j.radonc.2015.05.011)
37. MacDonald RL, Thomas CG. Dynamic trajectory-based couch motion for improvement of radiation therapy trajectories in cranial SRT. *Med Phys*. 2015;42(5):2317-2325. doi:[10.1118/1.4917165](https://doi.org/10.1118/1.4917165)
38. Smyth G, Evans PM, Bamber JC, et al. Non-coplanar trajectories to improve organ at risk sparing in volumetric modulated arc therapy for primary brain tumors. *Radiother Oncol*. 2016;121(1):124-131. doi:[10.1016/j.radonc.2016.07.014](https://doi.org/10.1016/j.radonc.2016.07.014)
39. Sharfo AWM, Rossi L, Dirx MLP, Breedveld S, Aluwini S, Heijmen BJM. Complementing prostate SBRT VMAT with a two-beam non-coplanar IMRT class solution to enhance rectum and bladder sparing with minimum increase in treatment time. *Front Oncol*. 2021;11:620978. doi:[10.3389/fonc.2021.620978](https://doi.org/10.3389/fonc.2021.620978)
40. Aizawa R, Ishikawa H, Kato M, et al. Significance of androgen-deprivation therapy for intermediate- and high-risk prostate cancer treated with high-dose radiotherapy: a literature review. *Int J Urol*. 2024;31:1068-1079. doi:[10.1111/iju.15535](https://doi.org/10.1111/iju.15535)

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