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ORIGINAL ARTICLE

The 5-year outcomes of moderately hypofractionated radiotherapy (66 Gy in 22 fractions, 3 fractions per week) for localized prostate cancer: a retrospective study

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Abstract

Background Hypofractionated radiotherapy using fewer and larger fractional doses may be more beneficial than conventional external-beam radiotherapy for localized prostate cancer. We evaluated the 5-year outcomes of moderately hypofractionated radiotherapy for localized prostate cancer.

Methods We retrospectively evaluated 195 patients with localized prostate cancer (T1–3N0M0) who underwent intensity-modulated radiotherapy (IMRT) (66 Gy delivered in fractions of 3 Gy every other weekday) between May 2005 and December 2011. Patients received androgen deprivation therapy depending on the perceived intermediate or high risk of their disease. A prostate-specific antigen nadir +2.0 ng/ml indicated biochemical failure. We assessed toxicity using the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria, and patient-reported outcomes using the Expanded Prostate Cancer Index Composite (EPIC).

Results The risk classifications (proportion) were low risk (13.8%), intermediate risk (35.9%), and high risk (50.3%). The median follow-up was 69 months. Thirteen (6.66%) patients experienced biochemical failure within a median of 40 months (interquartile range, 25–72 months). The 5-year overall survival rate and no biological evidence of disease rate were 97.7% and 92.4%, respectively. Based on the RTOG/EORTC criteria, no patient experienced acute or late toxicity of grade 3 or higher. The EPIC scores revealed significant differences in the average value of all domains ($p < 0.01$). At 1 month postradiotherapy completion, the general urinary and bowel domain scores had decreased, but these scores returned to baseline level by 3 months post radiotherapy.

Conclusions The moderately hypofractionated radiotherapy protocol yielded short-term satisfactory clinical outcomes with acceptable toxicity.

Keywords Hypofractionation · Intensity-modulated radiotherapy · Patient-reported outcome · Prostate cancer · Prostate-specific antigen · Quality of life

Abbreviations

ADT	Androgen deprivation therapy
ANOVA	Analysis of variance
BED	Biologically effective dose
bNED	No biochemical evidence of disease
CHHiP	Conventional or hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer
CTCAE	Common terminology criteria for adverse events
EORTC	European Organization for Research and Treatment of Cancer
EPIC	Expanded Prostate Cancer Index Composite
HYPRO	HYpofractionated irradiation for PROstate cancer
OS	Overall survival
OTT	Overall treatment time

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PROFIT	PROstate fractionated irradiation trial
PRO	Patient-reported outcome
PSA	Prostate-specific antigen
QOL	Quality of life
RTOG	Radiation Therapy Oncology Group

Introduction

Data from several clinical trials and recent advances in the understanding of radiobiology indicate that the alpha–beta ratio of prostate cancer (1.4–1.5 Gy) [1, 2] is lower than that of surrounding normal tissues, such as the rectum and bladder (3–5 Gy) [3, 4]. Hypofractionated radiotherapy may be more beneficial than conventional fractionated radiotherapy for prostate cancer, assuming the former is an iso-effective treatment with less toxicity or is a more effective treatment with similar toxicity as the latter [5–7]. A shorter radiotherapy course would also reduce hospital visits for patients, the resource burden on the treating facility, and the cost on society. Based on the aforementioned factors, several recent phase III trials [8–11] have investigated and reported on the efficacy and toxicity of hypofractionation.

Hypofractionation using the conventional delivery schedule (e.g., five fractions per week) substantially shortens the overall treatment time (OTT) compared to conventional fractionation. Shortening the OTT enhances the local control rates for rapidly growing diseases such as head and neck cancer and small cell lung cancer. However, this may not have much additional benefit on treatment efficacy because prostate cancer is a relatively slow-growing tumor. Furthermore, shortening the OTT could impair the repairing process of surrounding normal tissues during each fractionation, which consequently may contribute to increasing the rate of acute or late toxicity. Hypofractionated radiotherapy at a schedule of 3 days per week, which maintains an OTT as long as that of conventional fractionation and exploits the biological feature of a low alpha–beta ratio, may theoretically be more effective and have less morbidity than the conventional fractionation protocol in radiotherapy for localized prostate cancer.

When treating prostate cancer, it is important to evaluate the toxic effect and efficacy of a treatment because of the long life expectancy of affected patients. Patient-reported outcomes (PROs) are of particular concern because patients may be more sensitive in detecting a change in their quality of life (QOL), compared to provider-based objective toxicity profiling as clinician-reported outcomes [12–14]. Few reports exist concerning PROs of hypofractionated radiotherapy for prostate cancer. In the current study, we retrospectively investigated the treatment outcomes, toxicity, and PROs of moderately hypofractionated radiotherapy (i.e., 66 Gy over 22 fractions) using a 3-days-per-week delivery schedule.

Patients and methods

Patients

We retrospectively evaluated the records of consecutive patients with clinically localized prostate cancer (T1–3N0M0 [15]) who received treatment at our institution between May 2005 and December 2011. All patients provided informed consent. The study design was approved by the institutional ethics review board of Tokyo Women's Medical University (Tokyo, Japan; protocol number 637). All patients had biopsy-proven adenocarcinoma of the prostate; histological classification was based on the Gleason score grading. The pretreatment serum level of prostate-specific antigen (PSA) was also measured in all patients. Patient clinical risk level was defined using the D'Amico risk classification [16]. Patients with uncontrolled diabetes mellitus or those unable to discontinue oral anticoagulants were excluded from this study because of the high risk of rectal bleeding.

Radiotherapy

Simulation

All patients underwent computed tomography-based simulation. Before the simulation, the patients were instructed to hold their urine for at least 30 min after drinking 300 ml water to expand the bladder. The patients were immobilized supine on an individually adjusted device and then underwent helical simulation computed tomography. The obtained images were reconstructed to 3-mm-thick axial images and sent to the radiotherapy planning system (RTPS). At every radiotherapy session, all patients underwent image-guided intensity-modulated radiotherapy (IMRT) using ultrasonography.

Target delineation and dose prescription

Based on diagnostic computed tomography or magnetic resonance imaging, the clinical target volume included the whole prostate gland and the proximal portion of the seminal vesicles for T1–3a disease and comprised the entire seminal vesicles for T3b disease. The planning target volume was generated with the expansion of the clinical target volume with a three-dimensional margin of 10 mm for the anterior, left, and right directions; 9 mm for the superior and inferior directions; and 3–6 mm for the posterior direction. Elective nodal regions were not irradiated. The rectum wall, bladder

wall, and bilateral femur heads constituted the organs at risk. Inverse planning was conducted using the radiotherapy planning Eclipse RTP system (version 7.3.10; Varian Medical Systems, Palo Alto, CA, USA); a moderately hypofractioned regimen delivering 66 Gy in 3-Gy fractions was generated. The dose prescription policy of the IMRT plan was based on the percentage of the prescribed dose covering 95% of the volume (D95) of the clinical target volume (CTV). The biologically effective dose (BED) of the regimen was 198.0 Gy, assuming 1.5 Gy as the alpha–beta ratio of prostate cancer, which was equivalent to a total dose of 84.9 Gy administered as the conventional radiotherapy with the fraction dose [2 Gy per fraction equivalent dose when an alpha–beta ratio of 1.5 was applied ($EQD2_{1.5}$)]. The BED was calculated using the formulation reported by Lennernas and Nilsson [17]. For IMRT delivery, fixed seven-field coplanar 10-MV X-ray beams and dynamic multileaf collimator were utilized. Irradiation was delivered three times weekly (i.e., Monday, Wednesday, Friday) for 7 weeks. Before each treatment session, the target position was verified using a transabdominal ultrasonography system (SonArray; Varian Medical Systems).

Androgen deprivation therapy

Patients with intermediate- or high-risk disease generally received androgen deprivation therapy (ADT), which combines an antiandrogen and a luteinizing hormone-releasing hormone agonist. These patients received 3–6 months of neoadjuvant ADT and ADT during the course of IMRT. Patients with high-risk disease received an additional 6 months of adjuvant ADT.

Evaluation of outcomes and toxicity

Patients were routinely assessed to evaluate outcomes and toxicity after the completion of radiotherapy. In the first year post radiotherapy, the interval of the patient visits was every 1–2 months; in the second year, the interval was every 3–4 months. The follow-up evaluation included a physical examination, serum PSA testing, and imaging studies, when necessary.

Acute toxicity was evaluated weekly during treatment and within 3 months postradiotherapy completion. Late toxicity was evaluated thereafter. Acute and late toxicity, primarily gastrointestinal (GI) and genitourinary (GU) toxicity, were scored using the criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC) [18]. Biochemical failure was based on the Phoenix definition [19]: a nadir +2.0 ng/ml elevation in the serum PSA level. Patients who had been diagnosed with biochemical failure underwent diagnostic imaging studies to detect any clinical failure such as local recurrence and distant metastases.

Patient-reported outcomes on the Expanded Prostate Cancer Index Composite

To evaluate prostate-related function and bother after treatment, questionnaires of the Expanded Prostate Cancer Index Composite (EPIC) Japanese version [20], which have been validated as a reliable PROs evaluation tool, were distributed to patients at six points: pre-radiotherapy (i.e., baseline), and then at 1 month, 3 months, 6 months, 12 months, and 24 months postradiotherapy completion. At each hospital visit, a physician gave a questionnaire to each patient. The patients completed the questionnaire in the consulting room and then returned it to the physician during the visit. The data of the collected questionnaires were aggregated using an authorized calculating formula. We focused on the scores of the urinary, bowel, sexual, and hormonal domains from pre-radiotherapy (i.e., baseline) up to 24 months post radiotherapy.

Statistics

Cumulative overall survival (OS) rates were calculated from the start of radiotherapy to time of death. The no biochemical evidence of disease (bNED) survival rate was calculated from the start of radiotherapy to the event of biochemical failure (i.e., serum PSA nadir +2.0 ng/ml), local/distant recurrence (including the reinitiation of ADT), or death from any cause. All patients who were lost to follow-up were censored at the last follow-up visit. The Kaplan–Meier method was used to estimate each survival rate, and the Mantel–Cox log-rank test was used to compare the results from different patient subgroups. SPSS software, version 20 (SPSS, Chicago, IL, USA) was used to analyze statistics. In all statistics analyzed, the p values were two sided. The significance level was set at $p < 0.05$.

Results

Patients

Table 1 shows the characteristics of the patients and tumors. One hundred ninety-five patients were treated with the hypofractionated radiotherapy scheme. The proportion of risk classifications was low risk in 27 (13.8%) patients, intermediate risk in 70 (35.9%) patients, and high risk in 98 (50.3%) patients. All patients completed the planned radiotherapy schedule. The median follow-up period for the censored patients was 69 months [interquartile range (IQR), 59–85 months].

Table 1 Characteristics of the patients and tumors ($N = 195$)

Variable	No. of patients	Value(s) median (IQR)	Percent (%) of patients
Age (years)		74 (67–76)	
ADT (androgen deprivation therapy)			
Yes	174		89.2
No	21		10.8
T stage			
T1c–T2a	123		63.1
T2b	21		10.8
T2c–T3b	51		26.1
Gleason score			
4–6	47		24.1
7	86		44.1
8–10	62		31.8
Prostate-specific antigen (PSA) (ng/ml)		12.1 (6.6–28.1)	
≤0	114		58.5
10–20	41		21.0
20<	40		20.5
Risk distribution			
Low risk	27		13.8
Intermediate risk	70		35.9
High risk	98		50.3

Treatment outcomes

Thirteen (6.7%) patients experienced biochemical failure after a median of 40 months (IQR, 25–72 months): 3 and 10 patients had intermediate-risk and high-risk disease, respectively. No patient with low-risk disease experienced biochemical failure. Two biochemical failure patients developed clinical failure: 1 patient had bone metastases and 1 patient had pelvic lymph node metastases. No patient died of prostate cancer in this study. Four (2.1%) patients died of diseases other than the progression of prostate cancer, such as myelodysplastic syndrome, hilar cholangiocarcinoma, pancreatic carcinoma, and cholecystic carcinoma, respectively. For all patients, the 5-year bNED survival rate and the OS rates were 92.4% and 97.3%, respectively. The survival curves of bNED for all patients are shown in Fig. 1. Based on risk classifications, the 5-year bNED for patients with low-, intermediate-, and high-risk disease was 100%, 93.2%, and 89.8%, respectively (Fig. 2).

Acute and late toxicity, based on the RTOG/EORTC criteria

One hundred sixty-eight (65.1%) patients and 27 (34.9%) patients experienced grade 0–1 and grade 2 acute GU toxicity, respectively. No patient experienced grade 3 or higher

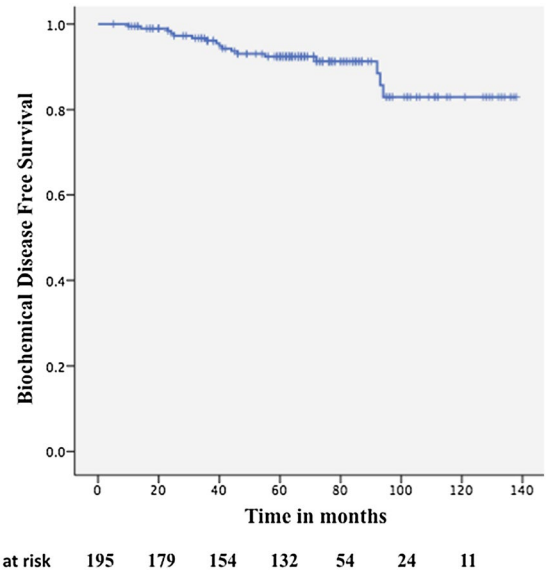

Fig. 1 Survival curve of biochemical evidence of disease for all patients

GU toxicity. One hundred ninety (97.4%) patients and 5 (2.6%) patients experienced grade 0–1 and grade 2 late GU toxicity, respectively. No patient had grade 3 or worse GU toxicity.

No patient experienced acute GI toxicity of grade 2 or higher. Only two (1%) patients experienced grade 2 late GI toxicity, which involved intermittent rectal bleeding. No patient experienced late GI toxicity of grade 3 or higher.

Patient-reported outcomes on EPIC

The average values of the EPIC scores were evaluated with the standard deviation at each measuring point. Figure 3 shows the longitudinal changes in the EPIC QOL scores for the general domains of urinary, bowel, sexual, and hormonal domains. The analysis of variance (ANOVA) revealed a significant difference among the average values of the general urinary domain at each time point (F value, 7.87; $p < 0.01$). The average score of the general urinary domain was significantly decreased 1 month after radiotherapy completion (compared to the baseline, $p < 0.01$). It returned to the baseline level at 3 months post radiotherapy (compared to the baseline, $p = 0.60$), and maintained its value thereafter. The average values of the general bowel domain indicated a similar trend with a significant difference in the ANOVA (F value, 4.57; $p < 0.01$). The average values significantly decreased at 1 month and 3 months (compared to the baseline: $p < 0.01$ and $p = 0.02$, respectively). Values returned to the baseline level at 6 months (no significant difference, compared to the baseline, $p = 0.18$), and thereafter were maintained. The change in the average score of the general

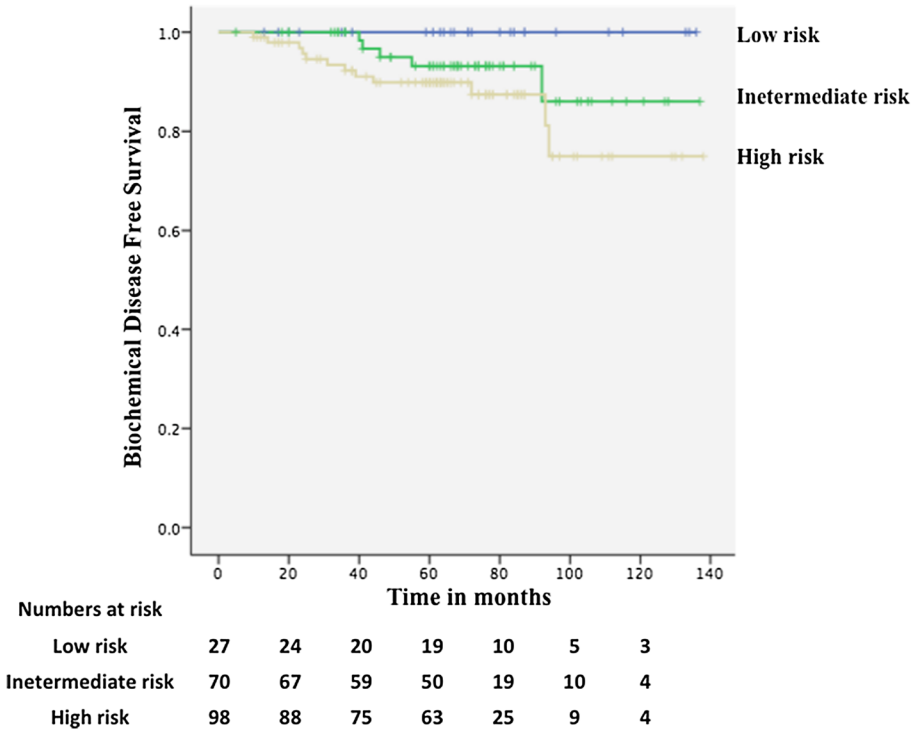

Fig. 2 Survival curve of biochemical evidence of disease in the patients by risk classification. *Blue line* low risk, *green line* intermediate risk, *yellow line* high risk

sexual and hormonal domain was not significantly different between these domains at each time point, based on the ANOVA (F value = 2.20 and F value = 1.45, respectively; $p = 0.05$ and $p = 0.21$, respectively).

Discussion

A lower alpha–beta ratio in prostate cancer than in the surrounding normal tissue suggests that hypofractionated radiotherapy using fewer and larger fractional doses could be more effective than the conventional fractionated radiotherapy protocol for this disease. We previously [21, 22] reported outcomes and toxicity of moderate hypofractionated radiation therapy of 69 Gy in 23 fractions of 3 Gy using the four-field technique. We therefore have included a new radiation protocol of IMRT (66 Gy in 22 fractions, 3 times per week) since May 2005.

In the current study, the OTT of radiotherapy (i.e., the hypofractionated scheme) was more than 7 weeks, which is similar to that of conventional radiotherapy. The PROs and clinician-reported outcomes were used for the toxicity evaluation.

Patel and colleagues [23] reported the clinical outcomes of hypofractionated three-dimensional radiation therapy of 66 Gy (22 fractions of 3 Gy, 5 fractions per week) for patients with low- and intermediate-risk prostate cancer, which was similar to our protocol. Other investigators have reported excellent outcomes for the 5-year bNED (97%) and the 8-year bNED (92%), with a median follow-up of 90 months; however, the grades were worse for late toxicity, based on the definition of the common terminology criteria for adverse events (CTCAE, version 3), at grade 2 or higher for GI toxicity (27%) and GU toxicity (33%). Kupelian et al. [24] investigated the long-term outcomes (median follow-up, 66 months) of hypofractionated IMRT (70 Gy at 2.5 Gy per fraction) for localized prostate cancer and reported a 5-year bNED of 88% for all patients, 97% for patients with low-risk disease, 93% for patients with intermediate-risk disease, and 75% for patients with high-risk disease.

Several prospective randomized phase III trials have recently been published, and four recently completed studies—the conventional or hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer (CHHiP) Trial [8], the PROstate fractionated irradiation trial (PROFIT) [9], the NRG 0415 Trial [10], and the hypofractionated irradiation for PROstate cancer (HYPRO) Trial [11])—compared hypofractionated radiotherapy with conventional radiotherapy for localized prostate cancer. The results demonstrated that hypofractionated radiotherapy was not inferior to conventional fractionated radiotherapy in effectiveness. However, in some of these trials, acute or late toxicity profiles were slightly worse, compared to those of conventional fractionation. Inferring the cause of disparity in the toxicity profiles is difficult because many factors differed among these trials, such as different dose fractionation and total doses, delivery schedule (daily or 3 days per week), and definition of the target.

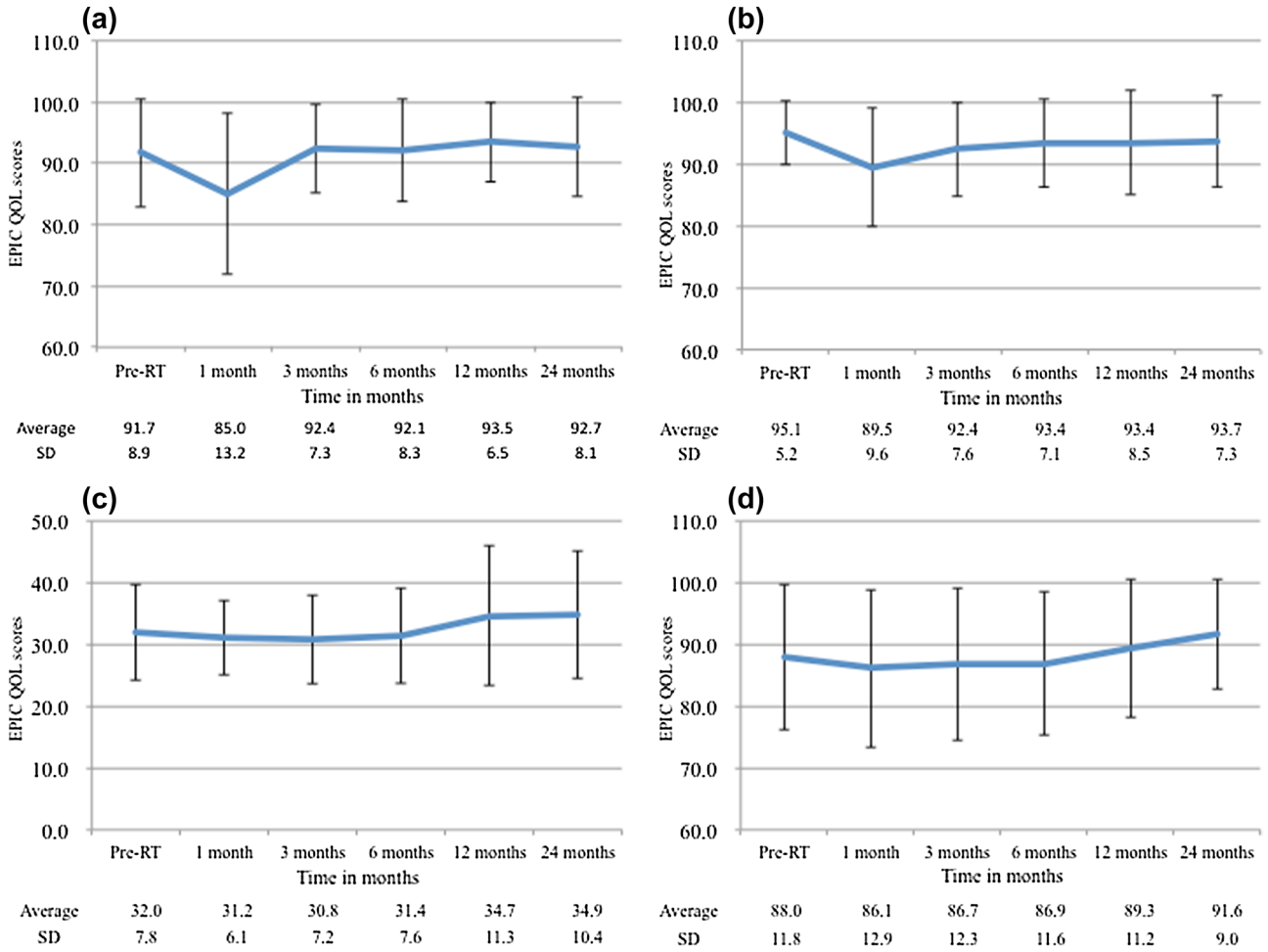

Fig. 3 Longitudinal changes in the EPIC QOL scores in the following general domains: urinary domain (**a**), bowel domain (**b**), sexual domain (**c**), hormonal domain (**d**). *EPIC* Expanded Prostate Cancer Index Composite, *QOL* quality of life

The bNED survival rate was satisfactory in the current study. The 5-year bNED was 95.0% in the overall population and remained above 90%, even for patients with high-risk disease. Compared to the hypofractionated arm in recent trials, the $EQD2_{1.5}$, which ranged from 73 to 90 Gy in the current study, could be regarded as a very high dose at 84.9 Gy in $EQD2_{1.5}$. This very high BED may have contributed to effective local tumor control, along with the combined effect of ADT. The favorable outcome also implies that maintaining the OTT with the 3-days-per-week schedule did not have a deleterious effect on treatment efficacy, irrespective of risk classification of disease, so long as a sufficient BED was prescribed. This finding is consistent with the findings reported in the HYPRO trial [11], which used the 3-days-per-week schedule with the prescribed dose of 64 Gy over 19 fractions (3.4 Gy per fraction).

With regard to clinician-reported toxicity, the hypofractionated arm in previous studies [25–28] showed an increased rate of acute or late GI/GU toxicity. According to the Quantitative Analysis on Normal Tissue Effects in the Clinic (QUANTEC) report, GI toxicity, especially the probability of rectal bleeding, is dose-volume dependent. However, there is no obvious threshold for the dose–volume relationship and the probability of GU toxicity. In the current study, severe acute or late GU/GI toxicity of grade 3 or higher was not observed. For GU toxicity, 34.9% of patients experienced grade 2 acute toxicity, which is consistent with the findings in previous reports (38–42%). Late GU toxicity was negligible: only 2.6% of patients had grade 2 GU toxicity, which reflected rapid recovery of GU symptoms after radiotherapy. No acute GI toxicity of grade 2 or higher occurred. Only 1% of patients experienced grade 2 late GI toxicity (e.g., rectal bleeding necessitating endoscopic laser ablation of the oozing vessels). The rarity in toxicity, except for the rate of grade 2 acute GU toxicity in the current study, is in distinct contrast to previous reports, including recently published landmark trials. A retrospective evaluation of toxicity tends to be difficult because of inherent

biases; however, there was no reported use of surgical intervention or record of severe rectal bleeding that necessitated a transfusion. The 3-days-per-week radiotherapy schedule, which maintained the OTT of the conventional fractionated scheme, may have contributed to the favorable toxicity profiles in this current study, even with a very high prescribed BED to the target.

The EPIC QOL scores in several urinary and bowel domains showed a transient decline after the completion of hypofractionated radiotherapy, although the patients recovered in a relatively short time and maintained their baseline score after recovery. According to Wilkins [29], who investigated PROs in the CHHiP Trial, the changes in bowel and urinary morbidity of the moderate hypofractionation scheme were small and similar to those among patients who were treated with the standard fractionation scheme up to 24 months after radiotherapy. The trend in the changes in the other EPIC main domains in their series was also similar to the changes in our study. The PROs in the hypofractionated arm in the PROFIT trial showed consistent results. The significantly favorable toxicity profile in the current study may be supported by these favorable PROs, which compensates for the lack of objectivity in evaluating treatment-related toxicity in retrospective analysis.

Conclusions

Our study provides valuable information regarding the efficacy and toxicity of moderately hypofractionated radiotherapy, but it has some limitations. First, it was a retrospective study and the patients' background was heterogeneous. Second, a follow-up period of 5 years is insufficient to evaluate tumor control and late toxicity for prostate cancer; therefore, the information in this study is insufficient to allow a definitive conclusion regarding long-term clinical outcomes and late toxicity profiles.

In treating localized prostate cancer, subtle variations in factors seem to contribute to different effects and toxicity. Therefore, data need to be accumulated from different treatment schemes concerning effectiveness and toxicity. It is important to report the results of this study using a unique treatment scheme. The current study indicated that moderately fractionated radiotherapy for localized prostate cancer, which delivers a total dose of 66 Gy in 22 fractions in 3 days per week, was effective and feasible. The PROs also supported the favorable provider-assessed toxicity profiles.

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Author contribution All authors have read and approved the final manuscript.

Compliance with ethical standards

Ethics approval and consent to participate The protocol of this study was approved by the institutional review board of Tokyo Women's Medical University in Tokyo, Japan (protocol number 637). All participants provided informed consent.

Conflict of interest No author has any conflict of interest.

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