Hypofractionated Intensity-modulated Radiotherapy for Intermediate- and High-risk Prostate Cancer: A Retrospective Study

NOBUTERU KUBO[1], HIDEMASA KAWAMURA[1], TAKAHIRO OIKE[1], HIRO SATO[1], MOTOTARO IWANAGA[1], TATSUJI MIZUKAMI[1], AKIKO ADACHI[1], HIROSHI MATSUI[2], KAZUTO ITO[3], KAZUHIRO SUZUKI[2] and TAKASHI NAKANO[1]

[1]*Department of Radiation Oncology, Gunma University Graduate School of Medicine, Gunma, Japan;*
[2]*Department of Urology, Gunma University Graduate School of Medicine, Gunma, Japan;*
[3]*Institute for Preventive Medicine, Kurosawa Hospital, Gunma, Japan*

Abstract. *Background/Aim: The aim of this study was to evaluate the efficacy and safety of hypofractionated intensity-modulated radiotherapy (IMRT) for intermediate- and high-risk prostate cancer. Patients and Methods: Seventy-five consecutive patients with intermediate- and high-risk prostate cancer treated with IMRT (63 Gy/21 fractions/7 weeks) between 2010 and 2013 were retrospectively analyzed. PSA relapse and adverse events were determined based on the Phoenix criteria and the Common Terminology Criteria for Adverse Events v4.0, respectively. Results: The 5-year PSA relapse-free rate, clinical relapse-free rate, and overall survival rate for all patients was 92.1%, 95.1%, and 92.9%, respectively. The incidence of late grade 2 gastrointestinal- and genitourinary-toxicity at 5 years was 1.3% and 17.1%, respectively. No grade 3 or greater toxicities were observed. Conclusion: These data indicate that hypofractionated IMRT (63 Gy in a total of 21 fractions with 3 fractions per week) is effective and safe for intermediate- and high-risk prostate cancer.*

In recent years, incidence for prostate cancer has witnessed an upsurge (1). Radiotherapy is one of the curative therapies for prostate cancer and radiation dose-escalation studies show that the high dose up to 80-81 Gy delivered by conventional fractionation schedule (*i.e*., 1.8-2 Gy per fraction, 5 fractions per week) is required for local control of prostate cancer (2). Although this conventionally fractionated radiotherapy shows favorable tumor local control, the long treatment course is a burden for the patients as well as for health economics.

The radiotherapy fractionation effect is often quantified using α/β value from the linear-quadratic (LQ) model. It is considered that prostate cancer cells have an α/β value of approximately 1.5 (3-6), which is lower than that of the rectum (7-9). This indicates that hypofractionated radiotherapy is effective for prostate cancer without increasing rectal toxicities. In fact, several studies have demonstrated feasibility of hypofractionated radiotherapy for prostate cancer (10-13). However, dose, fractionation and radiotherapy techniques vary among the studies, making it difficult to establish a standard treatment regimen. According to the linear-quadratic model with employing the α/β value of 1.5 for tumors, biological effect of a hypofractionated radiotherapy comprising 63 Gy delivered in 21 fractions (*i.e*., 3 Gy per fraction) is comparable to a conventionally fractionated radiotherapy comprising 80 Gy delivered in 40 fractions (*i.e*., 2 Gy per fraction). Therefore, the hypofractionated radiotherapy has the potential to be a clinically feasible regimen that contributes to reduce the burden for patients and for medical economy. To address this, we conducted a retrospective study to evaluate the efficacy and safety of the hypofractionated radiotherapy (63 Gy in 21 fractions, 3 fractions per week) for the patients with prostate cancer using intensity-modulated radiotherapy (IMRT).

Patients and Methods

This study was approved by the Institutional Review Board of Gunma University Hospital as an opt-out consent model (Number: 1308).

Table I. *Patient characteristics*.

Characteristics	All		Intermediate risk		High risk	
Number of patients	75		34		41	
Age in years (median, range)	70	(55-84)	68.5	(55-78)	71	(61-84)
Follow-up in months (median, range)	52	(16-79)	50.5	(16-74)	54	(24-79)
T stage						
T1c	21	(28%)	13	(38%)	8	(20%)
T2a	7	(9%)	6	(18%)	1	(2%)
T2b	11	(15%)	7	(21%)	4	(10%)
T2c	12	(16%)	8	(24%)	4	(10%)
T3a	17	(23%)	0	(0%)	17	(41%)
T3b	6	(8%)	0	(0%)	6	(15%)
T4	1	(1%)	0	(0%)	1	(2%)
Pretreatment PSA (ng/ml)						
<10	41	(55%)	26	(76%)	15	(37%)
10-20	21	(28%)	8	(24%)	13	(32%)
>20	13	(17%)	0	(0%)	13	(32%)
Gleason score						
5	1	(1%)	0	(0%)	1	(2%)
7	47	(63%)	34	(100%)	13	(32%)
8	12	(16%)	0	(0%)	12	(29%)
9	14	(19%)	0	(0%)	14	(34%)
10	1	(1%)	0	(0%)	1	(2%)
Duration of ADT (years)						
None	1	(1%)	1	(3%)	0	(0%)
<1	8	(11%)	7	(21%)	1	(2%)
1-2	16	(21%)	11	(32%)	5	(12%)
2-3	22	(29%)	10	(29%)	12	(29%)
>3	28	(37%)	5	(15%)	23	(56%)
Diabetes mellitus	11	(15%)	5	(15%)	6	(15%)
Anticoagulants usage	14	(19%)	8	(24%)	6	(15%)

PSA: Prostate-specific antigen; ADT: androgen deprivation therapy.

Patients. Seventy-five consecutive patients with intermediate- or high-risk prostate cancer who received hypofractionated IMRT at Gunma University Hospital (Gunma, Japan) from January 2010 to August 2013 were retrospectively enrolled to this study. Clinical stage was determined according to the 7th edition of the International Union Against Cancer (UICC) TNM staging system. All biopsies were reviewed by one urologist/pathologist. The risk for the disease was classified as follows; i) low risk: clinical stages T1c-T2b, a Gleason score of ≤6, and a pretreatment prostate-specific antigen (PSA) of <10 ng/ml, ii) intermediate risk: clinical stage T2c, a Gleason score of 7, or a pretreatment PSA of 10-20 ng/ml, and iii) high risk: clinical stage T3a-T4, a Gleason score ≥8, or a pretreatment PSA of >20 ng/ml.

Radiotherapy treatment. Pelvic-computed tomography (CT) was obtained at 2.5-mm thickness using an immobilization device. Magnetic resonance imaging (MRI) was performed on the same day as CT. CT-MRI image registration was accomplished using the Eclipse Planning System (Varian Medical Systems, Palo Alto, CA). The whole prostate was delineated as the clinical target volume (CTV), with whole- and proximal-seminal vesicle included in the CTV for the patients that suffered seminal vesicle invasion and for those who did not, respectively. The planning target volume (PTV)

was defined by adding margins to CTV; the margin was 7 mm in the anterior, lateral, superior, and inferior directions, while it was 4 mm in the posterior direction. The rectum was delineated from the rectosigmoid flexure to the anus. The treatment plan for IMRT involved a total of 63 Gy delivered in 21 fractions, with 3 fractions per week in a dose prescribed to 95% of PTV. This was generated upon satisfaction of the following criteria: i) V55 and V20 for the rectum is lower than 14% and 60%, respectively (where VX indicates the volume that receives irradiation for X Gy or higher) and ii) whole circumference of the rectum in any slice is not irradiated with more than 50% of the prescribed dose. IMRT was performed using the Varian Trilogy Linear Accelerator (Varian Medical Systems, Palo Alto, CA) using 7-field dynamic multi-leaf collimator with 10-MV photons. Pretreatment verification of the prostate position was conducted using a kilovoltage cone-beam CT during each treatment session.

Follow-up. The patients were followed up every 3 months for 2 years, and thereafter every 6 months. PSA relapse was determined according to the Phoenix consensus definition, *i.e.*, the nadir PSA value plus 2 ng/ml (14). Patients without biochemical relapse were censored at death or last follow-up. Clinical relapse was determined based on CT, MRI, and bone scintigraphy examination. Toxicity was
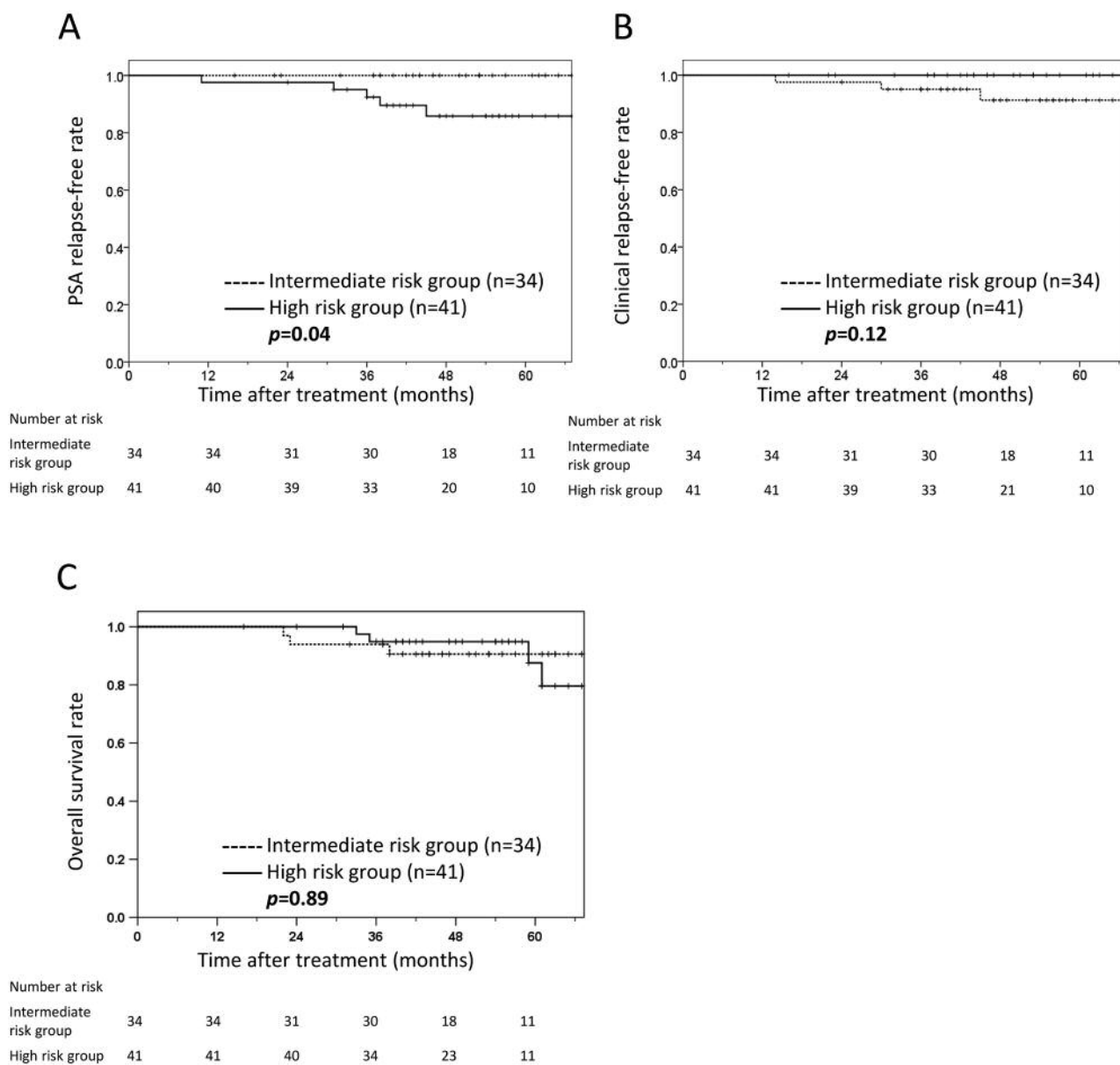
Figure 1. *The Kaplan–Meier estimates for PSA relapse-free rate (A), clinical relapse-free rate (B), and overall survival rate (C) for the intermediate- and high-risk group (dotted lines and solid lines, respectively). p-Values as assessed by log-rank test are shown.*

recorded based on the Common Terminology Criteria for Adverse Events v4.0. Acute toxicity was defined as the toxicity observed within 90 days after the initiation of radiotherapy, while late toxicity was defined as the toxicity observed thereafter.

Statistical analysis. PSA relapse-free rate, clinical relapse-free rate, and overall survival rate were estimated using the Kaplan–Meier method, and the differences in endpoints between subgroups were examined by log-rank test. The prognostic impact of clinical factors and that of dosimetric parameters were examined by Cox regression. The cutoff values for clinicopathological factors and dosimetric parameters were determined by receiver operator curve analysis using Youden index (15). All statistical analyses were performed using SPSS v21.0 (IBM, NY, USA). A *p*-value<0.05 was considered as statistically significant.

Results

Patient characteristics. The characteristics of the study cohort are summarized in Table I. The median follow-up period was 52 (16-79) months. Among 75 patients, 34 (45%)

and 41 (55%) were in the intermediate- and high-risk group, respectively. All patients, except one, were treated with neoadjuvant androgen-deprivation therapy (ADT).

Treatment outcomes. The 5-year PSA relapse-free rate for the intermediate risk group was significantly higher compared to that for the high risk group (100% *versus* 85.8%, *p*=0.04) (Figure 1A). Cox regression analysis showed that high pretreatment PSA was a significant predictive factor for PSA relapse-free rate (*p*=0.03, cutoff=32.2 ng/ml, hazard ratio=7.1), while age, T stage, Gleason score and duration of ADT were not (Table II). There were 3 patients with clinical relapse, two of which had bone metastases and one had local recurrence. The 5-year clinical relapse-free rate for the intermediate- and high-risk group was 100% and 91.3%, respectively, and there was no significant difference in the 5-year clinical relapse-free rate between the two groups (*p*=0.12) (Figure 1B). The 5-year overall survival rate for the intermediate- and high-risk group was 90.6% and 87.6%, respectively, and there was no significant difference in the 5-year overall survival rate between the two groups (*p*=0.89) (Figure 1C). Of note, only one out of seven deaths observed in this study was related to prostate cancer.

Adverse events. Regarding acute toxicity, incidence of grade 2 gastrointestinal and genitourinary toxicities was 0% and 20.0%, respectively, while no grade 3 or greater toxicities were observed (Table III).

Regarding late toxicity, the incidence of grade 2 gastrointestinal toxicity at 5 years was 1.3%, which translates to one case of rectal bleeding (Table III, Figure 2A). The incidence of grade 1 gastrointestinal toxicity at 5 years was 6.7%, which included three cases of rectal bleeding and two cases of fecal incontinence (Table III, Figure 2A). The incidence of grade 2 genitourinary toxicity at 5 years was 17.1% (Figure 2B), where the majority of patients reported urinary frequencies treated with α-blockers.

Cox regression analysis showed that V35-60 for the rectum have a significant predictive value for grade 1 or greater gastrointestinal toxicity (Table IV). Meanwhile, V5-60 for the bladder did not show a significant predictive value for grade 2 gastrointestinal toxicity (Table V).

Discussion

Feasibility of hypofractionated IMRT for prostate cancer has been examined in several studies. Pollack *et al.* have conducted a randomized control trial to compare a hypofractionated IMRT (70.2 Gy in 26 fractions, *i.e.*, 2.7 Gy per fraction) with a conventionally fractionated IMRT (76 Gy in 38 fractions, *i.e.*, 2 Gy per fraction). They found that there were no statistically significant differences in the incidence of PSA relapse-free rate and that of late toxicity

Table II. *Results of Cox regression analysis for predictive value of clinical factors for PSA relapse-free rate.*

Variable	Number	Hazard ratio	95% Confidence interval	*p*-Value
Age (years)				
<71.5	47	2.8	0.48-17.32	0.250
≥71.5	28			
T stage				
<T2c	39	75.2	0.06-102936.40	0.241
≥T2c	36			
Gleason score				
<9	60	5.8	0.97-34.79	0.054
≥9	15			
Pretreatment PSA (ng/ml)				
<32.2	67	7.1	1.16-43.85	0.034
≥32.2	8			
Duration of ADT (months)				
<32.5	40	4.1	0.46-36.90	0.206
≥32.5	35			

PSA: Prostate-specific antigen; ADT: androgen deprivation therapy.

between the two groups (16). Similarly, Dearnaley *et al.* have conducted a multi-institutional randomized study to compare a hypofractionated IMRT (60 Gy in 20 fractions or 57 Gy in 19 fractions, *i.e.*, 3 Gy per fraction) with a conventionally fractionated IMRT (74 Gy in 37 fractions, *i.e.*, 2 Gy per fraction). They found that the incidence of grade 2 or greater gastrointestinal toxicity was comparable among the three groups (11.9%, 11.3%, and 13.7%, respectively) and that the incidence of grade 2 or greater genitourinary toxicity was also comparable among the three groups (11.7%, 6.6%, and 9.1%, respectively) (10). Yet another group has compared a hypofractionated IMRT (72 Gy in 30 fractions, *i.e.*, 2.4 Gy per fraction) with a conventionally fractionated IMRT (75.6 Gy in 42 fractions, *i.e.*, 1.8 Gy per fraction) (17). They found that, during a follow-up of 6 years, there were no statistically significant differences between the two groups in terms of the incidence of late gastrointestinal and genitourinary toxicities. These data indicate that hypofractionated IMRT for prostate cancer is well tolerated, smiliar to conventionally fractionated treatment. On the other hand, a Dutch randomized non-inferiority phase III trial that compared a hypofractionated IMRT (64.6 Gy in 19 fractions, *i.e.*, 3.4 Gy per fraction) with a conventionally fractionated IMRT (78 Gy in 39 fractions, *i.e.*, 2 Gy per fraction), observed a high incidence of 3-year grade 2 or greater gastrointestinal- and genitourinary-toxicity (21.9% and 41.3%, respectively). Based on the toxicities, they concluded that their hypofractionated radiotherapy regimen is not feasible as a new standard of care for prostate cancer (18). In fact, among the studies discussed above, the
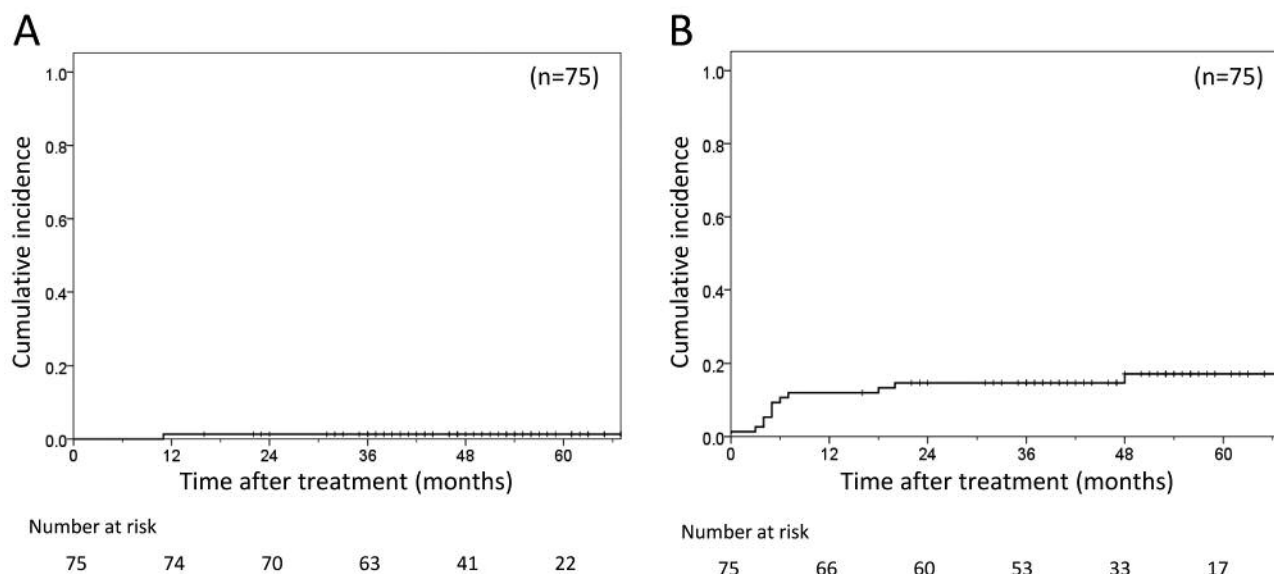
Figure 2. *(A) Cumulative incidence of grade-1 and -2 late gastrointestinal toxicity. (B) Cumulative incidence of grade 2 late genitourinary toxicity.*

Table III. *Gastrointestinal and genitourinary toxicities.*

Grade	Gastrointestinal toxicity				Genitourinary toxicity			
	0	1	2	≥3	0	1	2	≥3
Acute	74 (98.7%)	1 (1.3%)	0 (0%)	0 (0%)	24 (32.0%)	36 (48.0%)	15 (20.0%)	0 (0%)
Late (worst)	69 (92.0%)	5 (6.7%)	1 (1.3%)	0 (0%)	40 (53.3%)	23 (30.7%)	12 (16.0%)	0 (0%)
Last follow-up	72 (96.0%)	2 (2.7%)	1 (1.3%)	0 (0%)	48 (64.0%)	23 (30.7%)	4 (5.3%)	0 (0%)

hypofractionation regimen of the present study had the highest similarity to that of the Dutch study in terms of total dose (63 Gy *versus* 64.9 Gy), dose per fraction (3.4 Gy *versus* 3 Gy), and fraction per week (three in both studies). It is notable that, despite the similar hypofractionation regimens, the incidence of 3-year grade 2 or greater gastrointestinal- and genitourinary-toxicity observed in the present study was much lower compared to that in the Dutch study (1.3% and 21.9% for gastrointestinal toxicity, respectively; 14.7% and 41.3% for genitourinary toxicity, respectively). One reason of these differences might be that the total and fractional dose of the present study is lower compared to the Dutch study. Another reason might be the image-guided radiotherapy. It is reported that CT-based pretreatment verification of the prostate position contributes to lower gastrointestinal toxicities after radiotherapy for prostate cancer (19). In the present study, CT-based pretreatment verification of the prostate position was performed during each treatment session for all patients, whereas this pretreatment setup was not standardized in the Dutch study. Taken together, our data

indicate that a hypofractionated IMRT comprising 63 Gy in a total of 21 fractions with 3 fractions per week is tolerable with an application of CT-based pretreatment setup.

We have previously reported the result of hypofractionated radiotherapy for prostate cancer using conventional three-dimensional conformal radiotherapy techniques (20). In that study grade 2 or greater rectal bleeding was observed in 25% of the patients. In contrast, in the present study the incidence of grade 2 or greater rectal bleeding was much lower (1.3%) compared to the previous study. The low incidence of the gastrointestinal toxicity observed in the present study could be attributed to the favorable sparing of the rectum. In fact, no cases in the present study showed rectal V80, a significant risk factor for rectal bleeding (20), higher than 20%.

This study had certain limitations. First, this study was a retrospective monoinstitutional study. Second, the duration of ADT was not uniform among the participants. Third, the observation period was not sufficient to report long-term treatment outcomes. Therefore, further studies are warranted to validate the findings of this study in the general population.

Table IV. *Cox regression analysis for predictive values of clinical factors and dosimetric parameters for grade ≥1 gastrointestinal toxicity.*

Variable	Hazard ratio	95%Confidence interval	*p*-Value
Age (<65.5 *vs.* ≥65.5)	1.5	0.18-13.48	0.679
Diabetes mellitus (no *vs.* yes)	0.03	0.00-736.00	0.518
Anticoagulant therapy (no *vs.* yes)	0.9	0.10-7.36	0.890
Rectum V5 (<64.6% *vs.* ≥64.6%)	3.4	0.39-28.90	0.267
Rectum V10 (<56.4% *vs.* ≥56.4%)	5.7	0.67-48.98	0.112
Rectum V15 (<47.6% *vs.* ≥47.6%)	68.0	0.10-48639.11	0.208
Rectum V20 (<36.8% *vs.* ≥36.8%)	46.7	0.05-39907.31	0.264
Rectum V25 (<37.6% *vs.* ≥37.6%)	6.0	1.09-32.61	0.039
Rectum V30 (<22.3% *vs.* ≥22.3%)	50.8	0.06-39778.51	0.248
Rectum V35 (<25.0% *vs.* ≥25.0%)	8.3	1.52-45.68	0.014
Rectum V40 (<20.8% *vs.* ≥20.8%)	8.8	1.61-48.21	0.012
Rectum V45 (<16.9% *vs.* ≥16.9%)	8.3	1.52-45.68	0.014
Rectum V50 (<13.6% *vs.* ≥13.6%)	10.3	1.88-56.8	0.007
Rectum V55 (<9.9% *vs.* ≥9.9%)	10.3	1.88-56.8	0.007
Rectum V60 (<5.4% *vs.* ≥5.4%)	14.3	1.66-122.35	0.015

Table V. *Cox regression analysis for predictive values of clinical factors and dosimetric parameters for grade ≥2 genitourinary toxicity.*

Variable	Hazard ratio	95%Confidence interval	*p*-Value
Age (<69.5 *vs.* ≥69.5)	1.7	0.31-9.30	0.538
Diabetes mellitus (no *vs.* yes)	0.5	0.07-4.07	0.538
Anticoagulant therapy (no *vs.* yes)	1.5	0.42-5.69	0.519
Bladder V5 (<73.4% *vs.* ≥73.4%)	1.6	0.44-5.97	0.474
Bladder V10 (<62.6% *vs.* ≥62.6%)	1.6	0.44-6.05	0.463
Bladder V15 (<56.7% *vs.* ≥56.7%)	1.7	0.47-6.48	0.404
Bladder V20 (<52.6% *vs.* ≥52.6%)	2.0	0.53-7.31	0.309
Bladder V25 (<47.7% *vs.* ≥47.7%)	2.1	0.57-7.81	0.265
Bladder V30 (<39.5% *vs.* ≥39.5%)	1.7	0.47-6.39	0.413
Bladder V35 (<37.4% *vs.* ≥37.4%)	1.4	0.44-4.93	0.524
Bladder V40 (<32.8% *vs.* ≥32.8%)	1.6	0.47-5.19	0.469
Bladder V45 (<32.0% *vs.* ≥32.0%)	1.9	0.60-6.02	0.273
Bladder V50 (<27.6% *vs.* ≥27.6%)	2.0	0.64-6.43	0.228
Bladder V55 (<22.9% *vs.* ≥22.9%)	1.9	0.60-6.02	0.273
Bladder V60 (<17.6% *vs.* ≥17.6%)	1.9	0.60-6.02	0.273

In summary, IMRT for intermediate- and high-risk prostate cancer using a hypofractionated schedule of 63 Gy in 21 fractions with 3 fractions per week showed favorable 5-year outcomes without severe toxicity. These data highlight the potential of this treatment to contribute to the reduction of the clinical and economical burden for patients.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

NK and HK designed the study. HS, MI, and AA collected the data. NK and TO wrote the paper. HM, KI, KS, and TN revised the manuscript. All authors approved the final version of the manuscript.

References

1 Vital Statistics Japan (Ministry of Health, Labour and Welfare). Available from: https://ganjoho.jp/reg_stat/statistics/dl/index. html (last accessed January 29, 2018).

2 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology Prostate Cancer version 2. 2017. Available from: https://www.nccn.org/professionals/physician _gls/pdf/prostate.pdf (last accessed February 6, 2017).

3 Brenner DJ and Hall EJ: Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys *43*: 1095-1101, 1999. PMID: 10192361. DOI: 10.1016/S0360-3016(98)00438-6

4 Fowler J, Chappell R and Ritter M: Is alpha/beta for prostate tumors really low? Int J Radiat Oncol Biol Phys *50*: 1021-1031, 2001. PMID: 11429230. DOI: 10.1016/S0360-3016(01) 01607-8

5 Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD and Armour EP: 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, 2002. PMID: 11777617. DOI: 10.1016/S0360-3016(01)02664-5

6 Miralbell R, Roberts SA, Zubizarreta E and 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 *82*: e17-24, 2012. PMID: 21324610. DOI: 10.1016/j.ijrobp.2010.10.075

7 Marzi S, Saracino B, Petrongari MG, Arcangeli S, Gomellini S, Arcangeli G, Benassi M and Landoni V: Modeling of alpha/beta for late rectal toxicity from a randomized phase II study: conventional *versus* hypofractionated scheme for localized prostate cancer. J Exp Clin Cancer Res *28*: 117, 2009. PMID: 19689825. DOI: 10.1186/1756-9966-28-117

8 Tucker SL, Thames HD, Michalski JM, Bosch WR, Mohan R, Winter K, Cox JD, Purdy JA and Dong L: Estimation of α/β for late rectal toxicity based on RTOG 94-06. Int J Radiat Oncol Biol Phys *81*: 600-605, 2011. PMID: 21377288. DOI: 10.1016/j.ijrobp.2010.11.080

9 Brenner DJ: Fractionation and late rectal toxicity. Int J Radiat Oncol Biol Phys *60*: 1013-1015, 2004. PMID: 15519768. DOI: 10.1016/j.ijrobp.2004.04.014

10 Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, Graham J, Kirkbride P, Logue J, Malik Z, Money-Kyrle J, O'Sullivan JM, Panades M, Parker C, Patterson H, Scrase C, Staffurth J, Stockdale A, Tremlett J, Bidmead M, Mayles H, Naismith O, South C, Gao A, Cruickshank C, Hassan S, Pugh J, Griffin C and Hall E: Conventional *versus* hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol *17*: 1047-1060, 2016. PMID: 27339115. DOI: 10.1016/S1470-2045(16)30102-4

11 Incrocci L, Wortel RC, Alemayehu WG, Aluwini S, Schimmel E, Krol S, van der Toorn P-P, Jager H de, Heemsbergen W, Heijmen B and Pos F: Hypofractionated *versus* conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol *17*: 1061-1069, 2016. PMID: 27339116. DOI: 10.1016/S1470-2045(16)30070-5

12 Takakusagi Y, Kawamura H, Okamoto M, Kaminuma T, Kubo N, Mizukami T, Sato H, Onishi M, Ohtake N, Sekihara T and Nakano T: Long-term outcome of hypofractionated intensity-modulated radiotherapy using TomoTherapy for localized prostate cancer: A retrospective study. PLoS One *14*: e0211370, 2019. PMID: 30807581. DOI: 10.1371/journal.pone.0211370

13 Hashimoto Y, Motegi A, Akimoto T, Mitsuhashi N, Iizuka J, Tanabe K, Ishii Y, Kono S, Izumi S and Karasawa K: The 5-year outcomes of moderately hypofractionated radiotherapy (66 Gy in 22 fractions, 3 fractions per week) for localized prostate cancer: a retrospective study. Int J Clin Oncol *23*: 165-172, 2018. PMID: 28758177. DOI: 10.1007/s10147-017-1175-1

14 Roach M, Hanks G, Thames H, Schellhammer P, Shipley WU, Sokol GH and Sandler H: 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, 2006. PMID: 16798415. DOI: 10.1016/j.ijrobp.2006.04.029

15 Schisterman EF, Perkins NJ, Liu A and Bondell H: Optimal cut-point and its corresponding Youden Index to discriminate individuals using pooled blood samples. Epidemiology *16*: 73-81, 2005. PMID: 15613948. DOI: 10.1097/01.ede.0000147512.81966.ba

16 Pollack A, Walker G, Horwitz EM, Price R, Feigenberg S, Konski AA, Stoyanova R, Movsas B, Greenberg RE, Uzzo RG, Ma C and Buyyounouski MK: Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. J Clin Oncol *31*: 3860-3868, 2013. PMID: 24101042. DOI: 10.1200/JCO.2013.51.1972

17 Hoffman KE, Voong KR, Pugh TJ, Skinner H, Levy LB, Takiar V, Choi S, Du W, Frank SJ, Johnson J, Kanke J, Kudchadker RJ, Lee AK, Mahmood U, McGuire SE and Kuban DA: Risk of late toxicity in men receiving dose-escalated hypofractionated intensity modulated prostate radiation therapy: results from a randomized trial. Int J Radiat Oncol Biol Phys *88*: 1074-1084, 2014. PMID: 24661661. DOI: 10.1016/j.ijrobp.2014.01.015

18 Aluwini S, Pos F, Schimmel E, Krol S, van der Toorn PP, de Jager H, Alemayehu WG, Heemsbergen W, Heijmen B and Incrocci L: Hypofractionated *versus* conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial. Lancet Oncol *17*: 464-474, 2016. PMID: 26968359. DOI: 10.1016/S1470-2045(15)00567-7

19 de Crevoisier R, Bayar MA, Pommier P, Muracciole X, Pêne F, Dudouet P, Latorzeff I, Beckendorf V, Bachaud J-M, Laplanche A, Supiot S, Chauvet B, Nguyen T-D, Bossi A, Créhange G and Lagrange JL: Daily *versus* weekly prostate cancer image-guided radiotherapy: Phase 3 multicenter randomized trial. Int J Radiat Oncol Biol Phys, 2018. PMID: 30071296. DOI: 10.1016/j.ijrobp.2018.07.2006

20 Akimoto T, Muramatsu H, Takahashi M, Saito J-I, Kitamoto Y, Harashima K, Miyazawa Y, Yamada M, Ito K, Kurokawa K, Yamanaka H, Nakano T, Mitsuhashi N and Niibe H: Rectal bleeding after hypofractionated radiotherapy for prostate cancer: correlation between clinical and dosimetric parameters and the incidence of grade 2 or worse rectal bleeding. Int J Radiat Oncol Biol Phys *60*: 1033-1039, 2004. PMID: 15519772. DOI: 10.1016/j.ijrobp.2004.07.695