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Comparison of intensity-modulated radiotherapy with the 5-field technique, helical tomotherapy and volumetric modulated arc therapy for localized prostate cancer

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ABSTRACT

The outcomes of three methods of intensity-modulated radiation therapy (IMRT) for localized prostate cancer were evaluated. Between 2010 and 2018, 308 D'Amico intermediate- or high-risk patients were treated with 2.2 Gy daily fractions to a total dose of 74.8 Gy in combination with hormonal therapy. Overall, 165 patients were treated with 5-field IMRT using a sliding window technique, 66 were then treated with helical tomotherapy and 77 were treated with volumetric modulated arc therapy (VMAT). The median age of patients was 71 years. The median follow-up period was 75 months. Five-year overall survival (OS) and biochemical or clinical failure-free survival (FFS) rates were 95.5 and 91.6% in the 5-field IMRT group, 95.1 and 90.3% in the tomotherapy group and 93.0 and 88.6% in the VMAT group, respectively, with no significant differences among the three groups. The 5-year cumulative incidence of late grade ≥2 genitourinary and gastrointestinal toxicities were 7.3 and 6.2%, respectively, for all patients. Late grade ≥2 gastrointestinal toxicities were less frequent in patients undergoing VMAT (0%) than in patients undergoing 5-field IMRT (7.3%) and those undergoing tomotherapy (11%) ($P = 0.025$), and this finding appeared to be correlated with the better rectal DVH parameters in patients undergoing VMAT. Other toxicities did not differ significantly among the three groups, although bladder dose-volume parameters were slightly worse in the tomotherapy group than in the other groups. Despite differences in the IMRT delivery methods, X-ray energies and daily registration methods, all modalities may be used as IMRT for localized prostate cancer.

Keywords: prostate cancer; intensity-modulated radiotherapy (IMRT); tomotherapy; volumetric modulated arc therapy (VMAT); adaptive response

INTRODUCTION

Intensity-modulated radiotherapy (IMRT) is an established treatment for prostate cancer. The IMRT technique was introduced in the 1990s and involved the use of multiple static ports with a sliding window or step-and-shoot technique to modulate X-ray beams. Technological innovations yielded other methods for IMRT, namely, tomotherapy and volumetric modulated arc therapy (VMAT). Dosimetric comparisons of these modalities have been performed [1,2]; however, to the best of our knowledge, the clinical outcomes of these IMRT techniques have not yet been compared.

Since 2004, we have been performing IMRT for localized prostate cancer employing the three modalities of IMRT with various fractionation schedules [3, 4]. Between 2010 and 2018, we used 2.2 Gy daily fractions, and patients undergoing 5-field IMRT, tomotherapy and VMAT were treated with the same prescribed doses and dose constraints. Although the dose distribution may be more important than the treatment modality in determining the treatment quality, the latter may affect the treatment outcome, and we considered it meaningful to compare the treatment outcomes in patients treated with the three modalities.

The most significant difference among the three treatment modalities may be the beam delivery method. Five-field static IMRT is delivered with fixed beams with short intermissions between respective portals, and influences of such intermissions are not yet completely clarified [5]. With tomotherapy, doses are administered with a helical mode from cranial to caudal directions, so each part in the target is irradiated at a higher dose rate, although overall dose rates for the target do not differ greatly. In VMAT, rotational beams are delivered continuously. These differences are not reflected in dose distribution and dose volume histogram (DVH). In addition to differences in beam delivery methods, X-ray energies were 18 MV for 5-field IMRT, 6 MV for tomotherapy and 10 MV for VMAT. Regarding the daily verification of treatment positions, ultrasound was used in 5-field IMRT, while megavoltage and kilovoltage computed tomography (CT) was used in tomotherapy and VMAT, respectively. Therefore, there have been concerns that low-dose irradiation before treatment may cause a radioadaptive response, resulting in radioresistance in tumor cells [6, 7]. Furthermore, margins for the planning target volume (PTV) were reduced by 1 mm in all directions in 2014. Due to these differences, we herein compared the dosimetric characteristics and clinical outcomes of the three methods for IMRT.

MATERIALS AND METHODS

Patient characteristics

For IMRT of localized prostate cancer, we initially used 2.0 Gy daily fractions (74 Gy for low-risk patients and 78 Gy for intermediate- and high-risk patients); the daily dose was sequentially increased to 2.1 Gy (73.5 Gy for low risk and 77.7 Gy for intermediate and high risk) and then to 2.2 Gy (72.6 Gy for low risk and 74.8 Gy for intermediate and high risk) to shorten the treatment period [3, 4]. We now use 2.5 Gy per day. In 2010, we started to use 2.2-Gy daily fractions with the 5-field sliding window technique, and tomotherapy and VMAT were introduced in 2012 and 2015, respectively.

In the present study, patients with localized prostate cancer treated with IMRT using 2.2 Gy daily fractions according to our protocol between March 2010 and February 2018 were analyzed. Low-risk patients were excluded because the patient number was small ($n = 30$) and they were treated with a lower dose (72.6 Gy). Only adenocarcinoma patients were included in this study, and patients for whom androgen deprivation therapy (ADT) was not in accordance with our protocol were excluded. Specifically, patients treated with IMRT after more than 2 years of ADT and those treated with IMRT after more than 1 year of treatment-free follow-up following ADT were excluded. Risk classification was based on the D'Amico Risk Categories [8]. The UICC 8th edition was used for TNM classification, and clinical staging was conducted using ultrasonography, magnetic resonance imaging (MRI), CT and bone scintigraphy. The present study was approved by our Institutional Review Board (No. 60-20-0109) and informed consent was obtained from all patients.

IMRT and ADT

Planning procedures were common to the three modalities and were previously described in detail [3, 4, 9]. All patients were immobilized in a supine position with a whole-body vacuum bag system, and CT scans for planning were performed at a slice thickness of 3.2 mm. CT images were reconstructed at a thickness of 2 or 2.5 mm. Targets and organs at risk (OARs) were delineated on 3D radiation treatment planning systems (Eclipse Ver. 6.5, Varian Medical Systems, Palo Alto, CA, USA; Pinnacle^3 Ver. 9.0, Philips Medical System, Einthoven, The Netherlands; RayStation Ver. 4.5, Stockholm, Sweden) by referring to MRI images.

The clinical target volume (CTV) included the whole prostate and seminal vesicles (SV) depending on the T factor. CTV included one-third of SV for T1 stage, one-half of SV for T2, and whole SV for T3. PTV margins for CTV were defined as 8, 6, 8 and 7 mm in the anterior, posterior, craniocaudal and lateral directions, respectively, until June 2014 (Margin-1). They were reduced from July 2014 to 7, 5, 7 and 6 mm in the anterior, posterior, craniocaudal and lateral directions, respectively (Margin-2). All 5-field IMRT cases and 21 tomotherapy cases were treated using Margin-1, while 45 tomotherapy cases and all VMAT cases were treated using Margin-2. Dose constraints for targets and OARs were common to the three modalities, and were previously described [3, 9]; Supplementary Table 1. In all groups, the dose of 74.8 Gy in 34 fractions was prescribed for the Dmean of PTV. In 5-field IMRT, daily registration before treatment was performed using an optically guided 3D-ultrasound target localization system (SonArray, Zmed Inc., Ashland, MA, USA) as previously described [3]. Contours of the target, rectum and bladder delineated on planning CT were superimposed onto daily US images, and patient position was corrected whenever necessary. In tomotherapy and VMAT, the prostate position was adjusted before every treatment using megavoltage CT and kilovoltage CT, respectively. Five-field IMRT and VMAT were performed using 18- and 10-MV X rays, respectively, from linear accelerators. Tomotherapy was performed with TomoHD™ or Radixact™ (Accuray Inc., Sunnyvale, CA, USA).

In principle, patients in the high-risk and intermediate-risk groups received 6 months of neoadjuvant ADT before starting radiotherapy. In

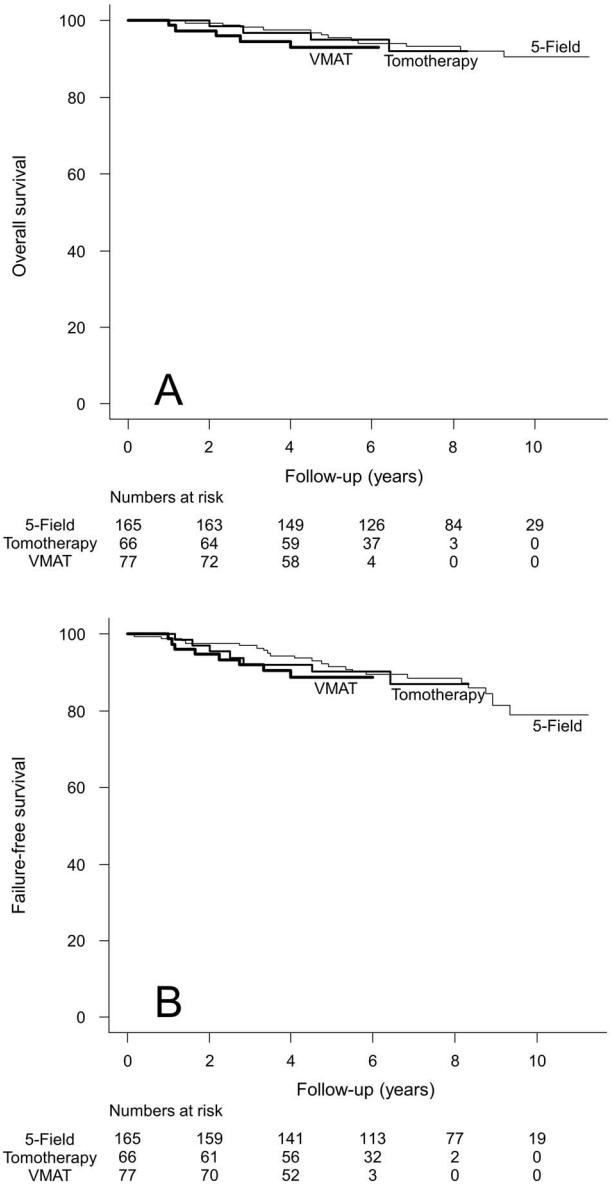

Fig. 1. OS (A) and biochemical or clinical FFS (B) curves after 5-field IMRT, tomotherapy and VMAT.

addition, high-risk patients received adjuvant ADT for 2 years, unless patients refused it or had intolerable adverse effects.

Follow-up and data collection

Follow-up evaluations were performed every 1–3 months for up to 1 year after irradiation, and every 3–6 months thereafter. Biochemical failure was defined according to the Phoenix definition of a nadir prostate-specific antigen (PSA) concentration plus 2 ng/ml [10]. Clinical failure was defined as the appearance of a new lesion or the recurrence of the primary lesion, regardless of PSA levels. Toxicities were evaluated with the Common Terminology Criteria for Adverse Events version 5.0. Late toxicities were defined as events occurring 3 months after the initiation of IMRT.

Statistical analysis

The student's *t*-test and one-way analysis of variance were used to compare continuous variables. The proportion of categorical variables was examined with the chi-squared test. The Bonferroni correction was applied to counteract the problems of multiple comparisons. OS and FFS rates were calculated from the start of IMRT by the Kaplan–Meier method, and differences between groups were examined using the Log-rank test. Differences in the cumulative incidence of late grade ≥ 2 toxicities between groups were examined by Gray's test, taking competing risks such as death into account. The Student's *t*-test was used to compare differences between groups in a DVH analysis. With the patient numbers enrolled in this study, an increase or decrease of 15–20% from a baseline 5-year FFS of 80–85% [3, 4] was considered detectable, with an alpha error of 5% and a beta error of 20% (https://nshi.jp/en/js/onesurvyr/). Also, an increase of 25–30% or decrease of 9–14% from a baseline incidence of Grade ≥ 2 toxicity of 10–15% [3, 4] appeared detectable. However, the patient numbers were considered sufficient to detect small differences ($< 1\%$) in DVH parameters. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [11]. All statistical analyses were 2-sided.

RESULTS

Patients and treatment

A total of 308 patients were analyzed; 165 were treated using 5-field IMRT between March 2010 and April 2014, 66 with tomotherapy between July 2012 and March 2017, and 77 with VMAT between May 2015 and February 2018. Until July 2012, 5-field IMRT was the sole method of IMRT in our institution. Between July 2012 and April 2014, 5-field IMRT or tomotherapy was used depending on machine availability and patient preferences. Between April 2014 and May 2015, tomotherapy was exclusively used, and from May 2015, VMAT became the main modality for IMRT for prostate cancer; however, tomotherapy was also used based on patient preferences. All patients completed planned IMRT. Patient characteristics are shown in Table 1. The median age of all patients was 71 years. Median follow-up periods were 75 months for all patients, 96 months in the 5-field group, 75 months in the tomotherapy group and 56 months in the VMAT group. Median follow-up periods in living patients were 78 months for all patients, 98 months in the 5-field group, 76 months in the tomotherapy group and 57 months in the VMAT group.

OS and FFS

Five-year OS and FFS rates for all patients were 94.7 and 90.5%, respectively. Figure 1A shows OS curves according to treatment modalities. Five-year OS rates were 95.5% in the 5-field IMRT group, 95.1% in the tomotherapy group and 93% in the VMAT group, with no significant differences ($P = 0.62$). One patient in the 5-field IMRT group died of prostate cancer at 28 months, and 20 died of other diseases. Five-year FFS rates were 91.6% in the 5-field IMRT group, 90.3% in the tomotherapy group and 88.6% in the VMAT group, with no significant differences (Fig. 1B; $P = 0.70$). One patient after 5-field IMRT and

Table 1. Patient and treatment characteristics

Group	All patients	5-Field	Tomotherapy	VMAT	*P*
No. of patients	308	165	66	77	
Age (years)	52–83	56–83	53–82	52–83	0.26
Median	71	71	73	73	
Initial PSA (ng/ml)	2.6–373.3	2.6–248.0	3.5–88.9	4.0–373.3	0.48
Median	10.8	10.8	11.0	10.6	
Risk	119/189	64/101	24/42	31/46	0.89
Intermediate/High					
T 1/2/3	65/160/83	37/80/48	17/32/17	11/48/18	0.26
Margin-1/Margin-2	186/122	165/0	21/45	0/77	< 0.001
ADT	306 (99%)	164 (99%)	65 (98%)	77 (100%)	0.53
Use of anticoagulants	55 (18%)	29 (18%)	10 (15%)	16 (21%)	0.68
Co-existing DM	54 (18%)	25 (15%)	11 (17%)	18 (23%)	0.29
Follow-up (months)	10–136	17–136	22–100	10–74	
Median	75	96	75	56	

ADT = androgen deprivation therapy, DM = diabetes mellitus. Margin-1: 8 mm in the anterior, 6 mm in the posterior, 8 mm in the craniocaudal and 7 mm in the lateral directions. Margin-2: 7 mm in the anterior, 5 mm in the posterior, 7 mm in the craniocaudal and 6 mm in the lateral directions.

Table 2. Acute grade ≥ 2 toxicities

	All patients	5-Field	Tomotherapy	VMAT	*P*
Genitourinary					
Urinary frequency	56 (18%)	30 (18%)	16 (24%)	10 (13%)	0.22
Urinary retention	4 (1.3%)	3 (1.8%)	0	1 (1.3%)	0.54
Total	59 (19%)[a]	33 (20%)	16 (24%)	10 (13%)[a]	0.22
Gastrointestinal					
Rectal hemorrhage	2 (0.7%)[b]	2 (1.2%)	0	0[b]	0.42

[a]One patient had urinary frequency and urinary retention. [b]Since one patient had undergone rectal surgery, 76 patients were evaluated in the VMAT group.

another after VMAT developed bone metastasis at low PSA levels at 64 and 13 months, respectively.

Five-year OS and FFS rates were 96.4 and 96.3% in the intermediate-risk group, and 93.6 and 86.7% in the high-risk group, respectively, with no significant difference in OS ($P = 0.53$) and significant differences in FFS (Supplementary Fig. 1; $P = 0.0035$). Figure 2 shows OS curves for the three modalities in the intermediate- and high-risk groups. In the intermediate-risk group, the 5-year OS was 96.7% for the 5-field IMRT group, 100% for the tomotherapy group and 93.4% for the VMAT group ($P = 0.54$). In the high-risk group, the 5-year OS was 94.7% after 5-field IMRT, 92.3% after tomotherapy and 92.6% after VMAT ($P = 0.86$). Figure 3 shows FFS curves for the three modalities in the two risk groups. In the intermediate-risk group, the 5-year FFS was 96.6% after 5-field IMRT, 100% after tomotherapy and 93.3% after VMAT ($P = 0.51$). In the high-risk group, the 5-year FFS was 88.4% after 5-field IMRT, 84.7% after tomotherapy and 85.2% after VMAT ($P = 0.86$).

Toxicity and DVH analysis

The incidence of acute grade 2 GU and GI toxicities were 19 and 0.7% for all patients, 20 and 1.2% for the 5-field IMRT group, 24 and 0% for the tomotherapy group and 13 and 0% for the VMAT group, respectively ($P = 0.22$ and 0.42, respectively; Table 2). No acute grade ≥ 3 toxicities were observed.

The 5-year cumulative incidence of late grade ≥ 2 GU and GI toxicities were 7.3 and 6.2% for all patients, 6.3 and 7.3% for the 5-field IMRT group, 8.2 and 11% for the tomotherapy group and 8.0 and 0% for the VMAT group, respectively. While there were no differences in the overall incidences of late grade ≥ 2 GU toxicities ($P = 0.60$), late grade ≥ 2 GI toxicities were less frequent in patients undergoing VMAT than in those treated with the other modalities ($P = 0.025$; Table 3, Fig. 4). Late grade ≥ 3 toxicities developed in four patients. In the 5-field IMRT group, grade 3 hematuria occurred at 53 months in one patient. In the VMAT group, grade 3 hematuria was observed at 53 months and grade 3 urethral stricture at 24 and 35 months, respectively, in two cases. Argon plasma coagulation was performed for one patient in the 5-field IMRT group, five in the tomotherapy group and none in the VMAT group.

Table 4 shows DVH parameters for the three modalities; 71.06 and 67.32 Gy are 95% and 90% of the prescribed dose (74.8 Gy), respectively, and 75.1, 57.7, 38.5 and 62.5 Gy are included in the dose constraint (Supplementary Table 1). Some rectal parameters, such as

Table 3. Late grade ≥ 2 toxicities

	All patients	5-Field	Tomotherapy	VMAT	*P*
Genitourinary					
Urinary frequency	10 (3.2%)	6 (3.6%)	3 (4.5%)	1 (1.3%)	0.60
Hematuria	6 (1.9%)	2 (1.2%)	1 (1.5%)	3 (3.9%)	0.029
Urinary retention	5 (1.6%)	1 (0.6%)	1 (1.5%)	3 (3.9%)	0.15
Urinary incontinence	7 (2.3%)	5 (3%)	1 (1.5%)	1 (1.3%)	0.86
Total	25 (8.1%)	13 (7.9%)[a]	6 (9.1%)	6 (7.8%)[b]	0.60
Gastrointestinal					
Rectal hemorrhage (Onset, median; range, months)	19 (15; 5–23) (6.2%)[c]	12 (15; 6–23) (7.3%)	7 (15; 5–22) (11%)	0[c]	0.025

[a]One patient had urinary frequency and urinary incontinence. [b]One patient had hematuria, urinary retention and urinary incontinence. [c]Since one patient had undergone rectal surgery, 76 patients were evaluated in the VMAT group.

Dmax, V75.1Gy, D1cc and D2cc, were worse in tomotherapy plans using Margin-1 than in 5-field plans (Margin-1 used), whereas others, including V57.7Gy and V38.5Gy, were better in tomotherapy plans. All rectal parameters, except for D5cc and D10cc, were better in VMAT plans (Margin-2 used) than in tomotherapy plans using Margin-2. All bladder parameters, except for V62.5Gy, were worse in tomotherapy plans using Margin-1 than in 5-field plans, and all bladder parameters were worse in tomotherapy plans using Margin-2 than in VMAT plans. When tomotherapy Margin-1 and Margin-2 plans were compared, bladder D1cc, D2cc and D5cc were worse in the Margin-1 group, but differences in the other parameters did not reach statistically significant levels. When 5-field IMRT and VMAT were compared, all rectal parameters were better in VMAT than 5-field plans, while bladder V75.1Gy and V38.5Gy were better in 5-field IMRT but bladder D10cc was better in VMAT.

DISCUSSION

OS and FFS in 308 patients with intermediate- or high-risk prostate cancer were similar to or better than those in previous studies [12–17]. These clinical outcomes did not significantly differ among the three treatment modalities. Although the patient numbers were not sufficient to detect small differences, the PTV dose constraints were common to the three modalities, and so this result may be reasonable. The differences in beam delivery and daily registration methods did not seem to greatly influence OS and FFS.

On the other hand, there was a difference in toxicities; late grade ≥ 2 GI toxicities were less frequent in the VMAT group. The difference was correlated with the DVH profiles; rectal DVH parameters were generally better in VMAT than in 5-field IMRT and tomotherapy. Since VMAT was most recently introduced in our institution, improvement in planning skills may be partly related to the improved DVH profiles. However, the differences in X-ray energy and margin sizes could be other reasons. Since the prostate is deep-seated, treatment with a higher energy is advantageous, particularly in patients with a large body size [9]; in the treatment plans of tomotherapy, which uses the lowest energy of 6 MV, the rectal and bladder DVH parameters were slightly worse than those of 5-field IMRT using 18 MV and VMAT using 10 MV. Smaller margin sizes used in VMAT may also be related to the improved rectal DVH parameters and decreased late grade ≥ 2 GI toxicities. Other groups are using narrower margins with promising outcomes [15, 18], and further reductions in the margins may be a topic of future investigations. Slightly higher incidences of GI toxicities in 5-field IMRT and tomotherapy may be resolved by using a hydrogel spacer, which we are now using. The differences in bladder DVH parameters did not seem to influence GU toxicities, since GU toxicities were less frequent than GI toxicities.

A concern associated with tomotherapy and VMAT is low-dose irradiation by MV- or KV-CT for daily registration. The radiation doses from CT scans were previously estimated to be 1–3 cGy [19, 20]. Based on recent findings, this level of low-dose irradiation may not induce carcinogenesis [7]. However, a radioadaptive response that induces radioresistance to subsequent high-dose irradiation has been reported [7, 21]. Previous studies showed that this radioadaptive response was more likely to occur after a few hours of low-dose irradiation [6, 22]; however, in tomotherapy and VMAT, intervals between CT and actual treatment are less than a few minutes, thus concerns regarding adaptive responses may be unfounded. The present results showed no significant differences in OS and FFS between 5-field IMRT (no CT before treatment) and tomotherapy or VMAT with CT before treatment. However, it is important to note that patient numbers in each group were not sufficiently large to detect slight differences between the groups. This issue warrants further study using a larger number of patients.

Our dose-fractionation schedule of 2.2 Gy per day is not a commonly used one. We started IMRT with a conventional 2-Gy daily fraction, and the daily dose was prudently increased step by step to 2.1 Gy and then 2.2 Gy to shorten the overall treatment time. In view of the lower α/β ratio reported for prostate cancer as compared to the ratios of the surrounding normal tissues [23], 2.2 Gy per day is considered biologically better than 2.0 Gy per day, but in this regard, still a higher dose per fraction should be better. So, we are now using a fraction of 2.5 Gy per day.

There are a few limitations in the present study. Although we evaluated 308 patients, patient numbers in the tomotherapy and VMAT groups were not sufficient to detect slight differences in clinical outcomes. Since we moved to the next hypofractionation protocol using

Table 4. Dose-volume parameters for patients treated with 34 fractions of 2.2 Gy

		5-Field ***n*** **= 165**	**Tomotherapy Margin-1** ***n*** **= 20** [a]	**Tomotherapy Margin-2** ***n*** **= 45**	**VMAT** ***n*** **= 77**	***P*** [b]	***P*** [c]	***P*** [d]	***P*** [e]
PTV	Dmax (Gy)	79.2 ± 1.6	79.2 ± 1.7	79.2 ± 1.3	79.8 ± 1.1	0.99	0.0092	0.0018	0.95
Rectum	Dmax (Gy)	75.3 ± 1.2	76.4 ± 2.0	76.2 ± 1.6	74.8 ± 0.52	< 0.001	< 0.001	< 0.001	0.70
	V75.1Gy (%)	0.017 ± 0.053	0.44 ± 0.75	0.45 ± 0.81	0.0009 ± 0.0059	< 0.001	< 0.001	0.0096	0.94
	V71.06Gy (%)	5.2 ± 1.8	5.0 ± 1.3	5.1 ± 1.6	3.6 ± 1.6	0.66	< 0.001	< 0.001	0.88
	V71.06Gy (cc)	2.8 ± 1.2	3.2 ± 1.5	2.8 ± 1.5	1.9 ± 1.2	0.12	< 0.001	< 0.001	0.27
	V67.32Gy (%)	10 ± 2.0	8.8 ± 1.4	8.8 ± 1.5	7.5 ± 1.9	0.0048	< 0.001	< 0.001	0.84
	V67.32Gy (cc)	5.4 ± 1.9	5.5 ± 2.1	4.7 ± 2.2	3.9 ± 1.7	0.85	0.026	< 0.001	0.18
	V57.7Gy (%)	17 ± 2.4	16 ± 1.9	16 ± 1.7	14 ± 2.3	0.001	< 0.001	< 0.001	0.21
	V38.5Gy (%)	34 ± 3.8	30 ± 3.6	31 ± 2.8	29 ± 3.4	< 0.001	< 0.001	< 0.001	0.16
	D1cc (Gy)	72.3 ± 0.54	73.2 ± 1.4	73.0 ± 1.5	71.8 ± 1.2	< 0.001	< 0.001	< 0.001	0.52
	D2cc (Gy)	71.5 ± 0.82	72.1 ± 1.4	71.3 ± 2.1	70.2 ± 1.8	0.0022	0.0041	< 0.001	0.11
	D5cc (Gy)	66.7 ± 3.3	66.7 ± 4.2	64.5 ± 5.3	63.0 ± 4.9	1.0	0.11	< 0.001	0.11
	D10cc (Gy)	53.7 ± 7.7	54.7 ± 8.7	50.8 ± 10	48.2 ± 8.8	0.60	0.14	< 0.001	0.14
Bladder	Dmax (Gy)	76.0 ± 1.5	77.5 ± 1.3	76.9 ± 1.6	75.8 ± 1.4	< 0.001	< 0.001	0.27	0.15
	V75.1Gy (%)	0.28 ± 0.67	3.7 ± 2.2	2.7 ± 2.6	0.68 ± 1.5	< 0.001	< 0.001	0.0051	0.16
	V62.5Gy (%)	16 ± 6.2	18 ± 5.4	18 ± 5.1	16 ± 5.5	0.16	0.0076	0.80	0.76
	V38.5Gy (%)	31 ± 12	40 ± 11	40 ± 11	35 ± 12	0.0043	0.028	0.022	0.93
	D1cc (Gy)	74.1 ± 1.1	76.1 ± 0.72	75.3 ± 1.2	74.4 ± 1.3	< 0.001	< 0.001	0.13	0.0096
	D2cc (Gy)	73.8 ± 0.95	75.8 ± 0.64	75.0 ± 1.1	74.0 ± 1.3	< 0.001	< 0.001	0.15	0.0064
	D5cc (Gy)	73.2 ± 0.77	75.1 ± 0.66	74.2 ± 1.3	73.0 ± 1.5	< 0.001	< 0.001	0.30	0.0063
	D10cc (Gy)	72.2 ± 1.3	73.1 ± 2.8	72.1 ± 2.6	70.5 ± 3.2	0.015	0.0061	< 0.001	0.17

Data are mean ± standard deviation.

[a] One patient whose planning data could not be retrieved was excluded. [b] Between 5-field IMRT and Tomotherapy Margin-1. [c] Between Tomotherapy Margin-2 and VMAT. [d] Between 5-field IMRT and VMAT. [e] Between Tomotherapy Margin-1 and Margin-2. Margin-1: 8 mm in the anterior, 6 mm in the posterior, 8 mm in the craniocaudal and 7 mm in the lateral directions. Margin-2: 7 mm in the anterior, 5 mm in the posterior, 7 mm in the craniocaudal and 6 mm in the lateral directions. 71.06 and 67.32 Gy are 95% and 90% of the prescribed dose (74.8 Gy), respectively. 75.1, 57.7, 38.5 and 62.5 Gy are included in the dose constraint (Supplementary Table 1).

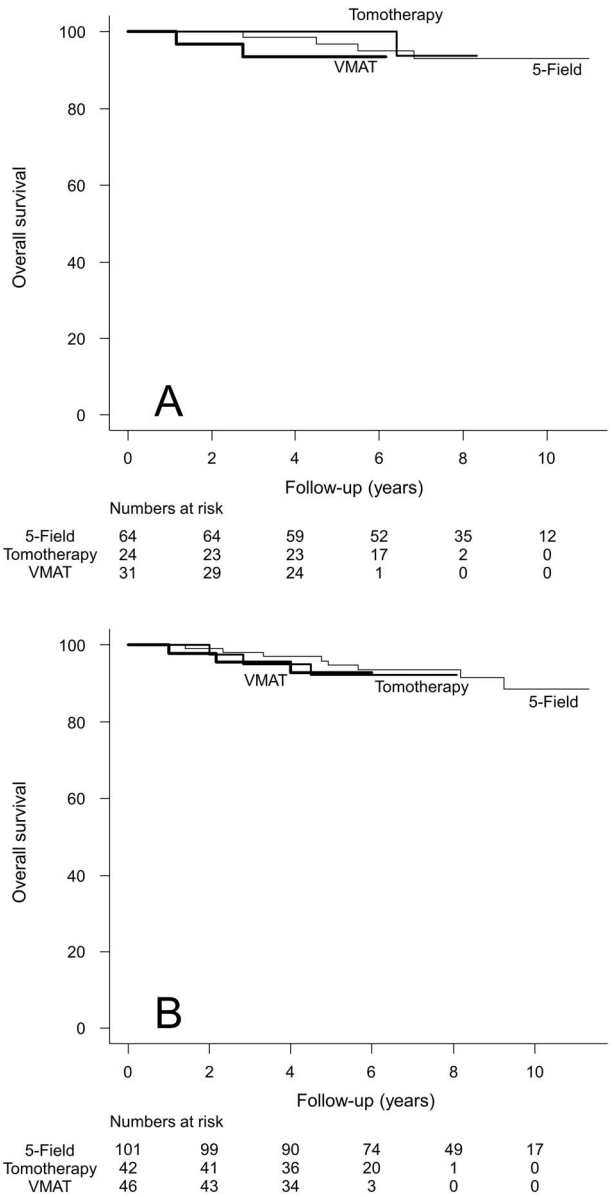

Fig. 2. OS curves after 5-field IMRT, tomotherapy and VMAT in intermediate- (A) and high-risk (B) patients.

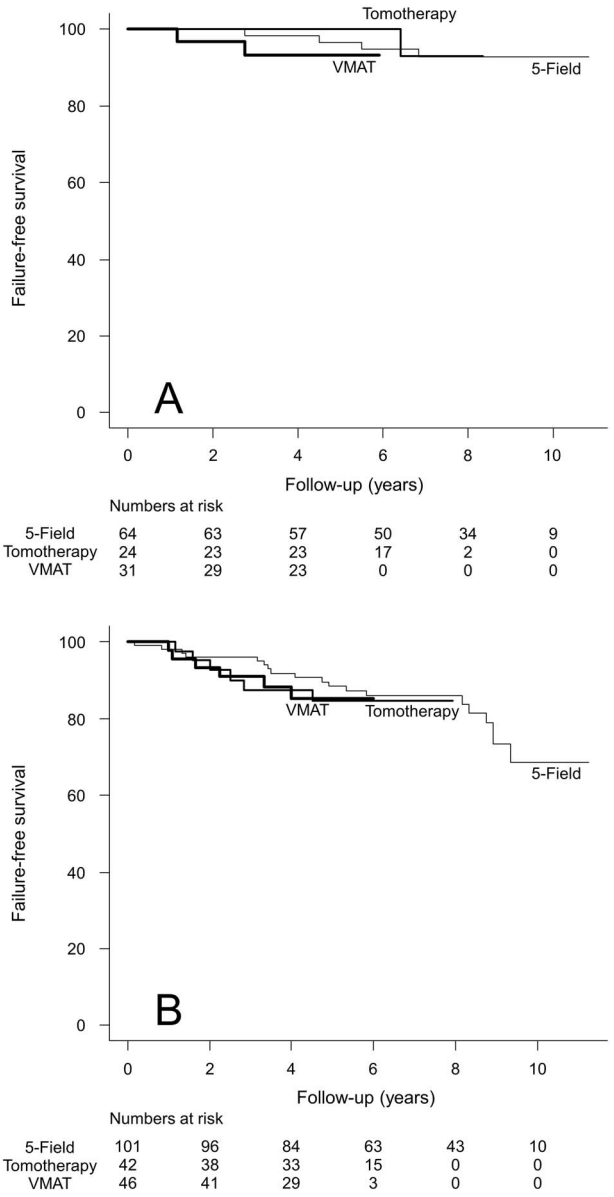

Fig. 3. Biochemical or clinical FFS curves after 5-field IMRT, tomotherapy and VMAT in intermediate- (A) and high-risk (B) patients.

2.5 Gy daily fractions in 2018, it was not possible to increase the numbers in these groups. To the best of our knowledge, the outcomes of the three IMRT modalities have not yet been compared; therefore, the present results may help patients to select a facility for the treatment of localized prostate cancer. Since another limitation is the imbalance in the follow-up period among the three groups, we will continue the follow-up of more recently treated patients. Third, DVH analyses could be influenced by the skills of treatment planning, so comparison should be better made in a planning study involving the same planners for the three modalities. Furthermore, no patients underwent the placement of a hydrogel spacer. However, the results of the present study may be useful for patients who cannot or refuse to undergo spacer placement.

In conclusion, the present results revealed that the three methods of IMRT for prostate cancer yielded similar clinical outcomes despite some differences in DVH parameters. All three methods are useful for the treatment of localized prostate cancer.

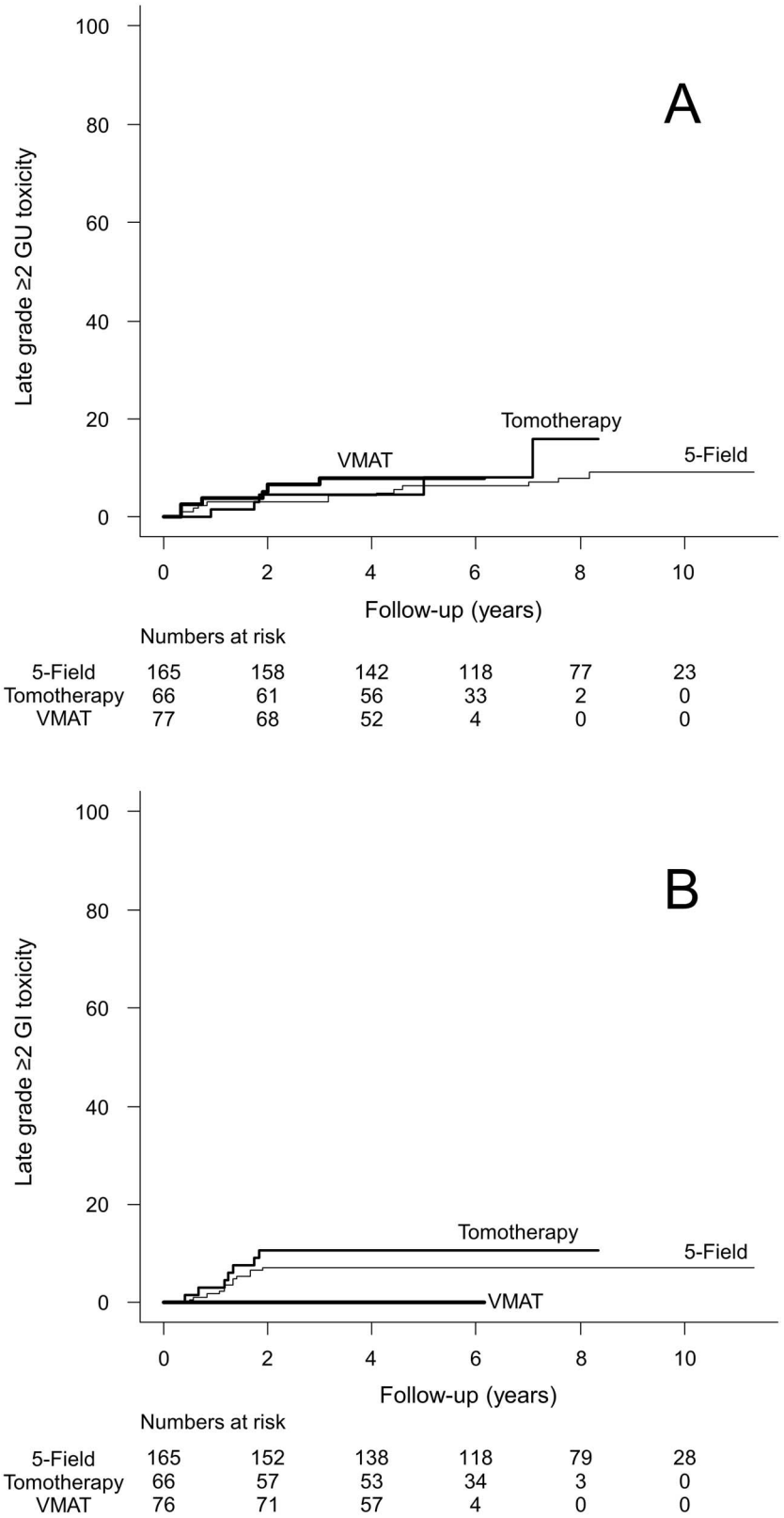

Fig. 4. Cumulative incidence of late grade ≥ 2 genitourinary (A) and gastrointestinal (B) toxicities. One patient who had had rectal surgery was excluded from analysis of GI toxicity.

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CONFLICT OF INTEREST

The authors have no conflicts to declare.

SUPPLEMENTARY DATA

Supplementary data is available at *RADRES Journal* online.

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