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Comparison of Late Toxicity After Whole-pelvis *Versus* Prostate-only VMAT for Prostate Cancer

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Abstract. *Background/Aim: To evaluate whether whole-pelvis (WP) volumetric modulated arc therapy (VMAT) is associated with increased late toxicity compared with prostate-only (PO) VMAT in patients with localized prostate cancer. Patients and Methods: Participants comprised 384 consecutive patients treated with definitive VMAT to 78 Gy in 39 fractions from July 2011 to August 2016. Of these, 183 patients received PO-VMAT and 201 patients received initial WP-VMAT to 46.8 Gy in 26 fractions using a simultaneous integrated boost technique. Gastrointestinal (GI) and genitourinary (GU) toxicities were prospectively scored using Common Terminology Criteria for Adverse Events version 4.0. Results: Median follow-up was 49 months (range=16-88 months) in the PO-VMAT group and 52 months (range=10-85 months) in the WP-VMAT group. Frequencies of Grade 3 late GI and GU toxicities were ≤3% across both groups. No patients experienced Grade 4+ toxicity. Cumulative incidences of Grade 2+ late GI and GU toxicities were similar between PO- and WP-VMAT groups (p=0.508 and p=0.838, respectively). Five-year cumulative incidences of Grade 2+ late GI and GU toxicities were 12.2% and 6.6% for the PO-VMAT group and 12.3% and 8.9% for the WP-VMAT group, respectively. Conclusion: WP-VMAT did not increase late GI and GU toxicities. This suggests that concerns about increasing toxicity profile are insufficient reason for omitting WPRT for patients with high-risk prostate cancer.*

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Radiation therapy (RT) is one of the main options available for the radical treatment of patients with high-risk prostate cancer. Whole-pelvic radiation therapy (WPRT) could theoretically improve the outcomes of patients with potential risk of lymph node metastasis by sterilizing microscopic disease. However, the use of WPRT in patients with high-risk prostate cancer remains controversial, since no survival benefit has yet been proven. In addition, arguments against the routine use of WPRT include that it may lead to additional toxicity compared with prostate-only RT (PORT). Currently, intensity modulated radiotherapy (IMRT) is generally used in the treatment of prostate cancer. Several studies have demonstrated that the dose reduction to organs at risks (OARs) provided by IMRT reduces gastrointestinal (GI) and genitourinary (GU) toxicities compared with 3DCRT (1-4). Similarly, IMRT improves target coverage and OAR sparing over 3DCRT when using WPRT (5-7). Accordingly, IMRT should be used when comparing toxicities between PORT and WPRT.

Four randomized trials have compared PORT and WPRT (8-11). Of these, multicentric phase II PIVOTAL trial (10) and single-center phase III POP-RT trial (11) used dose-escalated or hypofractionated IMRT. Both trials demonstrated acceptable toxicity profile in WPRT patients. However, the outcomes of these studies were inconsistent.

PIVOTAL trial reported no difference in late GI and GU toxicities at 24 months between PORT and WPRT (10). In contrast, POP-RT trial demonstrated that late grade ≥2 GU toxicities were higher in the WPRT arm than in the PORT arm, while late grade ≥2 GI toxicities were not different between the arms (11). In addition to this inconsistency, data in the literature comparing late toxicity between PO- and WP-IMRT are still limited. We therefore compared late GI and GU toxicities between dose-escalated PO- and WP-volumetric modulated arc therapy (VMAT) with daily cone-beam computed tomography (CBCT)-based image-guided RT (IGRT) for patients with localized prostate cancer.

Patients and Methods

This prospective study investigated 384 consecutive patients treated for clinically localized prostate cancer undergoing definitive VMAT using daily image guidance between July 2011 and August 2016. Of these, 183 patients were treated with PO-VMAT and 201 patients with WP-VMAT. Written informed consent was obtained from each parent before the start of treatment, and this study was approved (number: 201407-03) by the Tane General Hospital Ethics.

Treatment. All patients had biopsy-proven adenocarcinoma of the prostate. In accordance with our institutional protocol, patients classified as low or intermediate risk according to the 2009 National Comprehensive Cancer Network criteria were treated in the PO field. Patients with high risk were mainly treated in the WP field, but patients >80 years old or who did not wish to receive WPRT were treated in the PO field.

The details of treatment have been described previously (12). In summary, patients were instructed to have an empty bowel and a comfortably full bladder at the time of treatment planning and during treatment. All patients were treated to 78 Gy in 39 fractions of 2 Gy to the prostate planning target volume (PTV). Patients treated with WPRT received 46.8 Gy in 26 fractions of 1.8 Gy to the nodal PTV using a simultaneously integrated boost technique. VMAT plans were generated with a single arc for the PO fields and double arcs for the WP fields, using 10-MV photon beams. Daily IGRT was performed using ExacTrac (Brainlab AG, Feldkirchen, Germany) and CBCT.

Androgen-deprivation therapy (ADT) was recommended for intermediate-risk patients for 6 months, and for high-risk patients for 2 or 3 years. ADT was not recommended for low-risk patients, but ADT was administered according to the discretion of the treating physician. Neoadjuvant ADT was administered for at least 3 months.

Late toxicity assessment. Late GI and GU toxicities were prospectively scored for all patients according to the Common Terminology Criteria for Adverse Events version 4.0 adverse event scoring system. Patients were monitored at 3-month intervals for the first 2 years, and every 6 months thereafter. Late toxicities were defined as those occurring after 3 months from the end of RT. The endpoint was considered to be the occurrence of Grade 2+ late GI and GU toxicities.

Statistical analyses. Differences in baseline characteristics between the PO- and WP-VMAT groups were compared using unpaired Student's *t*-test for continuous variables and the χ^2 test or Fischer's exact test as appropriate. Dose-volume parameters were compared with the unpaired Student's *t*-test. Either the χ^2 test or Fischer's exact test was used to compare differences in the frequencies of maximum GI and GU toxicities. Cumulative incidences of Grade 2+ late GI and GU toxicities were estimated using the Kaplan–Meier method. The log-rank test was used to compare groups. Values of $p<0.05$ were considered statistically significant.

Table I. *Patient characteristics*.

Characteristic	PO-VMAT	WP-VMAT	*p*-Value
No. of patients	183	201	
Follow-up (months)			0.390
Median	49	52	
Range	16-88	10-85	
Age (years)			0.061
Median	73	72	
Range	49-84	50-79	
Gleason score			<0.001
4-6	58 (32%)	9 (4%)	
7	100 (55%)	52 (26%)	
8-10	25 (13%)	140 (70%)	
PSA (ng/ml)			<0.001
Median	9.1	27.0	
Range	3.9-409.0	4.0-445.0	
Clinical stage			<0.001
T1	64 (35%)	20 (10%)	
T2	109 (60%)	68 (34%)	
T3	10 (5%)	99 (49%)	
T4	0	14 (7%)	
NCCN risk group			<0.001
Low risk	34 (19%)	0	
Intermediate risk	116 (63%)	0	
High risk	33 (18%)	201 (100%)	
Androgen deprivation	123 (67%)	192 (96%)	<0.001
Diabetes	27 (15%)	40 (20%)	0.184
Anticoagulants	27 (15%)	32 (16%)	0.752

PO-VMAT: Prostate-only volumetric-modulated arc therapy; WP-VMAT: whole-pelvic volumetric-modulated arc therapy; PSA: prostate-specific antigen; NCCN: National Comprehensive Cancer Network.

Results

Median follow-up was 49 months (range=16-88 months) in the PO-VMAT group and 52 months (range=10-85 months) in the WP-VMAT group. Patient characteristics are shown in Table I. No significant differences in age or comorbidities were apparent between groups. However, as WPRT was used to treat high-risk prostate cancer, patients in the WP-VMAT group displayed significantly higher Gleason score, prostate-specific antigen levels, and clinical stages and received ADT more frequently.

All dose-volume constraints were met for all treatment plans with the exception of two cases: one in the PO-VMAT group with bladder V_{70Gy} (percentage structure volume receiving ≥70

Table II. *Dosimetric comparison of prostate-only volumetric-modulated arc therapy (PO-VMAT) and whole-pelvic volumetric-modulated arc therapy (WP-VMAT).*

Parameter		PO-VMAT (mean±SD)	WP-VMAT (mean±SD)	*p*-Value*
Prostate PTV				
Volume	[ml]	113±35	102±27	<0.001
$D_{95\%}$	[Gy]	75.9±0.4	76.3±0.5	<0.001
D_{mean}	[Gy]	78	78	-
$D_{2\%}$	[Gy]	79.7±0.2	79.4±0.2	<0.001
Nodal PTV				
Volume	[ml]	-	829±140	-
$D_{95\%}$	[Gy]	-	44.7±0.3	-
D_{mean}	[Gy]	-	46.8±0.3	-
Rectum				
Volume	[ml]	62±19	62±18	0.891
D_{mean}	[Gy]	25.2±5.8	39.8±3.4	<0.001
$D_{2\%}$	[Gy]	77.2±2.6	77.0±1.1	0.340
V_{70Gy}	[%]	9.9±3.5	11.0±3.8	0.003
V_{50Gy}	[%]	20.2±6.1	26.0±6.5	<0.001
V_{30Gy}	[%]	32.6±10.2	65.5±11.4	<0.001
Bladder				
Volume	[ml]	197±84	219±87	0.014
D_{mean}	[Gy]	25.0±9.2	43.3±5.4	<0.001
$D_{2\%}$	[Gy]	78.2±1.0	78.0±0.8	0.075
V_{70Gy}	[%]	11.0±5.7	10.5±5.0	0.412
V_{50Gy}	[%]	19.5±9.8	27.3±10.2	<0.001
V_{30Gy}	[%]	32.8±15.4	80.4±11.6	<0.001
Bowel bag				
$D_{2\%}$	[Gy]	3.1±3.7	47.9±2.0	<0.001
V_{45Gy}	[ml]	0.2±1.0	94.5±44.8	<0.001

PTV: Planning target volume; $D_{n\%}$: minimal dose to n% of the structure; V_{nGy}: percentage or absolute structure volume receiving ≥n Gy. *Unpaired Student's *t*-test.

Table III. *Comparison of late maximum gastrointestinal (GI) and genitourinary (GU) toxicity grades between prostate-only volumetric-modulated arc therapy (PO-VMAT) (n=175) and whole-pelvic volumetric-modulated arc therapy (WP-VMAT) (n=196).*

	GI		GU	
	PO-VMAT	WP-VMAT	PO-VMAT	WP-VMAT
Toxicity				
Grade 0	105 (57%)	106 (53%)	91 (50%)	99 (49%)
Grade 1	60 (33%)	72 (36%)	78 (43%)	87 (43%)
Grade 2	18 (10%)	21 (10%)	8 (4%)	10 (5%)
Grade 3	0	2 (1%)	6 (3%)	5 (3%)
p-Value	0.477		0.960	

Gy) of 29.1%; and the other in the WP-VMAT group with rectal V_{50Gy} of 64.2%. Mean values for dose-volume parameters of the targets and OARs are shown in Table II. Absolute differences in prostate PTV dose-volume parameters between PO- and WP-VMAT groups were very small. Similarly, whether significant differences existed between groups, the absolute differences in rectal and bladder V_{70Gy} were only 1.1% and 0.5%, respectively. In contrast, rectal and bladder mean doses, as V_{30Gy} and V_{50Gy}, respectively, were significantly higher in the WP-VMAT group.

Maximal late GI and GU toxicities are summarized in Table III. No significant differences in late GI and GU toxicities were seen between the PO- and WP-VMAT groups. Grade 2+ late GI toxicities were recorded in 18 patients (10%) and 23 patients (11%) in the PO- and WP-VMAT groups, respectively. Two patients (1%) receiving WP-VMAT experienced Grade 3 rectal bleeding. Fecal incontinence developed in 15 patients (8%) in the PO-VMAT group and 28 patients (14%) in the WP-VMAT group. Of these 43 patients, 34 patients experienced mild incontinence and did not require the use of sanitary pads, whereas 3 patients (2%) in the PO-VMAT group and 6 patients (3%) in the WP-VMAT group had Grade 2 incontinence requiring sporadic use of sanitary pads. No significant difference in late fecal incontinence was seen between groups (p=0.204). With respect to late GU toxicity, 14 patients (7%) and 15 patients (8%) developed Grade 2+ toxicity in the PO- and WP-VMAT groups, respectively. Grade 3 late GU toxicities were seen in 6 patients (3%) in the PO-VMAT group, as hematuria (n=5) and urinary retention (n=1). Five patients (3%) in the WP-VMAT group reported grade 3 urinary retention. No patients experienced Grade 4+ toxicity. Kaplan–Meier curves for actuarial incidence of Grade 2+ late GI and GU toxicities are illustrated in Figure 1. No significant differences in cumulative incidences of Grade 2+ late GI and GU toxicities were seen between the PO- and WP-VMAT groups. The 5-year cumulative incidences of Grade 2+ late GI and GU toxicities were 12.2% (95%CI=6.5-18.0%) and 6.6% (95%CI=2.8-10.3%) for the PO-VMAT group and 12.3% (95%CI=7.7-16.9%) and 8.9% (95%CI=4.2-13.5%) for the WP-VMAT group, respectively.

Discussion

Late toxicity outcomes comparing PORT and WPRT using current radiation technology available from literature remain limited. In the present study, late GI and GU toxicities after PO- and WP-VMAT with daily CBCT-based IGRT were prospectively compared in 384 patients with localized prostate cancer. With a median follow-up of 49 months, patients treated with WP-VMAT had a favorable toxicity profile and no significant differences in late GI or GU toxicities were apparent between PO- and WP-VMAT groups.

Earlier randomized phase III studies that compared PORT with WPRT using conventional or 3D-CRT techniques for patients with localized prostate cancer have reported conflicting results with regard to late toxicities (8, 9). A subset analysis of the RTOG 9413 trial showed that a larger

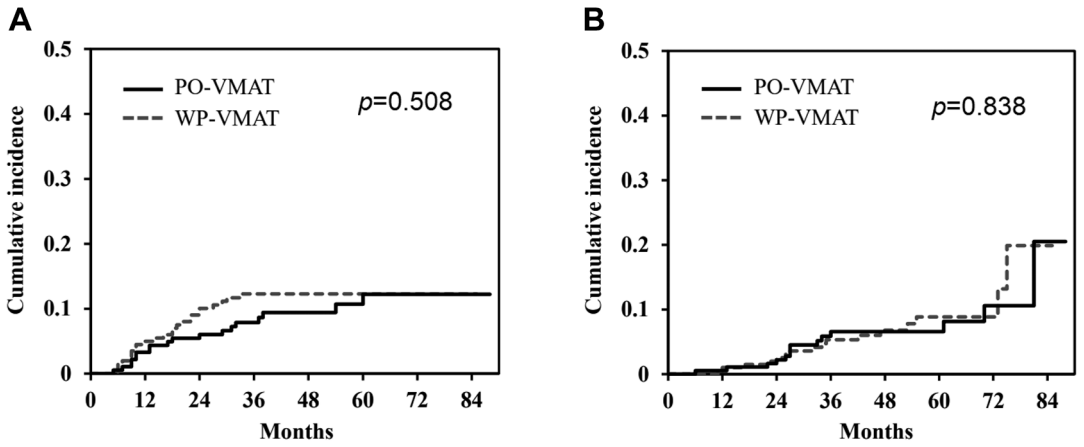

Figure 1. *Kaplan–Meier curves of grade 2+ late (A) gastrointestinal toxicity and (B) genitourinary toxicity. PO-VMAT: Prostate-only volumetric modulated arc therapy; WP-VMAT: whole-pelvic volumetric modulated arc therapy.*

field size resulted in a significant increase in Grade 3+ late GI toxicity, but no difference in Grade 3+ late GU toxicity among patients treated to the PO, mini-pelvis, and WP fields (8). Similarly, meta-analysis of 2,432 patients with high-risk prostate cancer enrolled into trials RTOG 9202, 9406, and 9413 concluded that patients who received combined WPRT and long-term hormonal therapy were more likely to develop a Grade 2+ GI toxicity than those who received PORT (13). On the other hand, the GETUG-01 trial demonstrated that frequencies of late GI and GU toxicities did not differ significantly between PORT and WPRT groups (9). However, the upper field border of the WP field was around S1/S2 in the GETUG-01 trial, whereas the superior limit was placed at the level of the L5/S1 interspace in the RTOG 9413 trial. Further, in these studies, dose escalation to the prostate beyond 70 Gy was not applied, except in the RTOG 9406 trial.

IMRT is one of the most widely used delivery modalities for the definitive treatment of localized prostate cancer. However, only limited data exist comparing late toxicity between PORT and WPRT, in the setting of dose-escalated IMRT. Guckenberger et al. (14) compared 75 patients treated with PO-IMRT and 25 patients treated with WP-IMRT. At a median follow-up of 26 months, no significant differences were identified regarding late GI and GU toxicities. In a retrospective study of 60 patients, Deville et al. (15) showed no difference in Grade 2+ late GI toxicity (6% *vs*. 6%) or Grade 2+ late GU toxicity (16% *vs*. 20%) with a median follow-up of 24 months, when PO-IMRT was compared with WP-IMRT. PIVOTAL, phase II randomized trial, evaluated the toxicity profile of high-dose pelvic lymph node IMRT (10). Although the primary endpoint of PIVOTAL trial was acute G1 RTOG toxicity at 18 weeks from the start of RT, this trial reported late toxicity up to 2 years as a secondary analysis, where the 2-year cumulative proportions of Grade 2+ late GI and GU toxicities were 16.9% and 5.1% for the PO-IMRT group and 24.0% and 5.6% for the WP-IMRT group, respectively. However, in these studies, the follow-up period was short to adequately evaluate late toxicity. The recently published randomized phase III POP-RT trial reported the toxicity of WPRT compared to PORT using moderately hypofractionated IG-IMRT (11). With a median follow-up of 68 months, cumulative grade 2+ GI toxicity was similar for WPRT and PORT (8.2% *vs*. 4.5%, p=0.28). However, unlike our results, cumulative grade 2+ GU toxicity was significantly higher with WPRT (20.0% *vs*. 8.9%, p=0.02). Possible explanations for this difference are due to the use of hypofractionation and a higher pelvic dose (50 Gy in 25 fractions in the POP-RT trial versus 46.8 Gy in 26 fractions in this study) in the POP-RT trial.

Differences in DVH parameters for the rectum and bladder at the low- and intermediate-dose levels did not translate into statistically significant differences in late GI or GU toxicities. Late rectal toxicity other than rectal syndrome, such as fecal incontinence and increased fecal frequency, is reportedly associated with the volume of rectum receiving ≥60 Gy (16). In contrast, rectal syndrome has been considered to be related to intermediate doses to larger volumes of the rectum (17, 18). In this study, results of DVH analysis revealed that rectal V_{50Gy} was significantly higher in the WP-VMAT group. However, counter to our expectations, no difference in the frequency of late fecal incontinence was seen between groups. One possible reason is that the mean rectal V_{50Gy} of 26% in the WP-VMAT group was sufficiently lower than the usual dose-volume constraint of rectal V_{50Gy} <50%. As for the bladder, the correlation between late GU toxicity and bladder DVH parameters has been less clear (19). Some studies have

demonstrated bladder neck dose as predictive of late GU toxicity (20). Data from the POP-RT trial implied that bladder volume exposed to a mid-range dose of 30-40 Gy contributed to an increase in Grade 2+ late GU toxicity observed with WP-IMRT (21). However, the bladder neck is usually included in the high-dose area around the prostate and is likely to receive a similar dose, whichever field size is used. In addition, bladder volume is not constant during RT and bladder DVH parameters obtained from the planning CT image are therefore unlikely to represent the true dose distribution to the bladder during the course of treatment.

The strengths of this study include the prospective, albeit not randomized, data collection, the use of contemporary VMAT with daily CBCT-based image guidance in a consistent manner, and the considerable number of patients and follow-up period. However, some limitations to this study must be considered. First, this study was conducted at a single institution, which may limit its generalizability. Second, the proportion of patients who received ADT differed between groups. Whether ADT increases the risk of late toxicity remains a controversial issue in the literature (22, 23). However, we could not assess the impact of WPRT on late toxicity in the case of VMAT monotherapy. Third, median follow-up in this study was 49 months, which still may not be long enough to evaluate late GU toxicity.

In conclusion, our study demonstrated that frequencies of late GI and GU toxicities did not differ significantly between PORT and WPRT when using VMAT with daily IGRT. This suggests that concerns about an increasing toxicity profile are not sufficient reason for omitting WPRT for patients with high-risk prostate cancer.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study. The Authors are responsible for the content and writing of the paper.

Authors' Contributions

RO and KI conceived the idea of the study. RO, KI, TN, YH, RT, HM and SM contributed to data collection. KK and RK developed the statistical analysis plan and conducted statistical analyses. KI drafted the original manuscript. TT supervised the conduct of this study. All Authors reviewed the manuscript draft and revised it critically on intellectual content. All Authors approved the final version of the manuscript to be published.

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