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Moderate hypofractionated volumetric modulated Arc therapy with daily image guidance for patients with localized prostate cancer

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► ***Original article***

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ABSTRACT

Background: Technical advances have allowed the delivery of a higher dose to the tumor volumes, while reducing the dose to nearby organs at risk. Laboratory and clinical evidence suggest that hypofractionation might raise the therapeutic effect. We report our outcomes of moderately hypofractionated schedules with volumetric modulated arc radiotherapy (VMAT) on biochemical failure (BCF) free survival and toxicities in patients with localized prostate cancer. ***Materials and Methods:*** Between 2013 and 2017, 58 patients were treated using the VMAT technique with daily image guided radiotherapy (IGRT). 3 (5.2%), 32 (55.2%), and 23 (39.7%) of patients had low, intermediate, or high risk disease, respectively. A prescription dose of 70 Gy in 2.5 Gy daily for 28 fractions was used. BCF-free survival was evaluated using 2005 Phoenix criteria and estimated using the Kaplan–Meier method. Radiotherapy-related toxicity was scored according to the Common Terminology Criteria for Adverse Events 4.0 criteria. ***Results:*** The median follow-up was 37.3 months (range 18.8-82.1). Overall 4 year BCF-free survival were 94.0%. For low-intermediate and high risk patients, the 4 year BCF-free survival were 100% and 83.3%, respectively (p=0.027). Pretreatment prostate -specific antigen (p=0.016) and Gleason score (p=0.007) were significant predictors of BCF-fee survival. The incidence of late grade 2 gastrointestinal and genitourinary toxicity was 8.6% and 13.8%, respectively. No grade 3 or greater toxicities were observed. ***Conclusions:*** Outcoms after moderately hypofractionated VMAT-IGRT were encouraging. Moderate hypofractionation was effective and safe for the treatment of localized prostate cancer.

Keywords: *Prostate cancer, Moderate hypofractionation, Volumetric modulated Arc radiotherapy, PSA, Image guidance radiotherapy.*

INTRODUCTION

Prostate cancer is the highest prevalent malignancy among adult men [1]. Conventional fraction size external beam radiation therapy (EBRT) has been considered as a standard treatment in prostate cancer. Although the conventional fractionated EBRT shows good treatment results, long treatment period and the resulting economic costs are a problem [2,3].

Recently, hypofractionation radiation therapy has been evaluated as a strategy of EBRT in prostate cancer [4]. The hypofractionation schedule came from the hypothesis that prostate carcinoma tissue shows low α/β ratio of 1.5 Gy (0.9-2.2 G) which is smaller than even nearby normal tissue such as rectum [5]. Therefore, fewer and larger than conventional fractions with a lower total dose may improve the therapeutic ratio with decreasing rectal toxicity[5]. Numbers of clinical trials have showed effectiveness of hypofractionated schedulle radiotherapy for prostate cancer compared with conventionally fractionated treatment [6-9].

By the development of physics and mechanics, volumetric modulated arc therapy (VMAT) has become common radiation dose delivery method using linear accelerator [10,11]. When treated with VMAT, the radiation dose enters the target volume

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through a continuously changing field generated by a multileaf collimator (MLC) in multiple photon arcs [10]. VMAT has been found to be similar or superior for target volume coverage and nearby rectal saving compared with intensity modulated radiotherapy (IMRT) [12].

In recent years, IMRT is changing to VMAT in the radiotherapy of prostate due to its shorter treatment time [13]. Moderate hypofractionated radiotherapy in prostate cancer using IMRT has been reported in many studies, but only few trials were carried out with VMAT with daily image guidance radiotherapy (IGRT). We report our clinical outcomes of moderately hypofractionated schedules with VMAT with daily IGRT on biochemical failure (BCF) free survival and detailed described toxicities in localized prostate cancer patients.

MATERIALS AND METHODS

Fifty-eight patients with localized prostate adenocarcinoma who received moderately hypofractionated VMAT from 2012 and 2017 were retrospectively analyzed. This research was approved by the Ethical Committee for Clinical Trials of our institution (Approved number: 2019-03-019). All patients were classified into low, intermediate and high risk groups based on National Comprehensive Cancer Network (NCCN) clinical guidelines in oncology, Prostate cancer, version 2.2019 [14].

VMAT treatment planning and delivery

For treatment and simulation, patients were allowed to lie down in the supine with knee and ankle devices. Planning CT (16 Slice big bore Virtual Simulator, GE, USA) scans in 2.5 mm thickness was performed with a whole-body vacuum cushion for immobilization. All patients were educated to void their bladder at least 2 hours before the start of treatment and simulation. The patients were also educated to empty their rectum through daily defecation.

Clinical target volume (CTV) of low risk group patients was limited to the prostate alone, but CTV of intermediate and high risk group patients included the prostate and both proximal seminal vesicles (if not involved). If the seminal vesicle is involved, CTV covered the entire prostate and ipsilater whole seminal vesicle. Planning target volume (PTV) was made 0.5 cm wide on the CTV but backwards widened only 0.3 cm to decrease rectal dose. Contouring of the nearby normal tissue in accordance with the Radiation Therapy Oncology Group (RTOG) pelvic normal tissue contouring guidelines.

All patients were irradiated with 70 Gy in 28 daily fractions of 2.5 Gy in a dose prescribed to 95% of PTV. The entire patients received 2 arcs VMAT with 6 MV photon beam using Varian Linear Accelerator Clinac 2300 Ix (Varian Medical System, Palo Alto, Ca, USA). To oragns at risk (OAR), bladder, recum, femoral heads and bowel, the following constraints were applied: for bladder V_{70Gy}<10%, V_{60Gy}<25% and V_{50Gy}<35%, for rectum V_{70Gy}<10%, V_{60Gy}<25% and V_{50Gy}<35%, for femoral heads V_{40Gy}<5% and for bowel constraints was prescribed to reduce the dose as low as possible. In all patients, Aria 8.11. (Varian Medical System, Palo Alto, CA, USA) was used to plan VMAT. Before radiotherapy, for image guidance purpose, daily cone beam (CB) CT was conducted. We co-registered planning CT and CB CT images based on soft tissue. Position correction was made every day with no action threshold using self-acting table movement. Androgen deprivation therapy (ADT) was applied to 29.3% of the patients. Only a few patients with high risk received ADT for 12-24 months.

Follow-up and Statistical analysis

Patients were seen once per week during treatment and followed every three months during the first 2 years and then every six months. Prostate-specific antigen (PSA) test and Physical examination were carried out at every follow-up visit. The phoenix consensus definition became the criterion for BCF [15]. Treatment-related toxicity was scored based on the Common Terminology Criteria for Adverse Events (CTCAE) 4.0 criteria. To correctly evaluate the toxicity, the pre-existing symptoms before radiotherapy were excluded. Toxicity was scored according to severity at the time of visit. Acute toxicity was recorded during treatment and within 3 months after treatment, while the toxicity observed after were was defined as that

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late toxicity.

Overall survival (OS) rate and BCF-free survival were calculated by the Kaplan–Meier method, and the significance of the differences in OS and BCF-free survival between subgroups were evaluated by log-rank test. Cox regression was used to determine the prognostic impact of clinical factors and that of dosimetric parameters. The IBM SPSS software, version 19.0 (SPSS, Inc., IBM, Chicago, IL, USA) was used to run statistical analysis.

RESULTS

The median follow-up was 37.3±1.84 months (range, 18.8-82.1 months). The median age of the population of study was 71.5±1.82 years (range, 56-83 years). Among 58 patients, 3 (5.2%), 32 (55.2%) and 23 (39.6%) were in the low, intermediate and high risk group, respectively. Patients' pretreatment characteristics are listed in table 1.

Table 1. Patient characteristics (n=58).

Characteristics		n (% or range)
Median age (years)		71.5±1.82 (56-83)
ECOG scale	0	33 (56.9%)
	1	25 (43.1%)
T stage	T1-T2a	9 (15.5%)
	T2b-T2c	39 (67.3%)
	≥T3	10 (17.2%)
Pretreatment PSA (ng/mL)	Median	9.68±1.72 (4.04-64.96)
	<10	30 (51.7%)
	10-20	20 (34.5%)
	≥20	8 (13.8%)
Gleason Score	≤6	11 (19.0%)
	7	21 (53.4%)
	≥8	16 (27.6%)
ADT	No	41 (70.7%)
	Yes	17 (29.3%)
NCCN Risk group	Low	3 (5.2%)
	Intermediate	32 (55.2%)
	High	23 (39.7%)

Abbreviations; ECOG: Eastern Cooperative Oncology Group; ADT: Adndrogen deprivation therapy; PSA: Prostate-specific antigen; NCCN: National Comprehensive Cancer Network;

Survival and relapse

The 4 year OS rate and BCF-free survival for the whole cohort was 97.4% and 94.0%, respectively (figure 1). The 4 year BCF-free survival rate for the low-intermediate risk group was significantly higher compared to that for the high risk group (100% versus 83.3%, p=0.027) (figure 2). Three patients experienced BCF in only high risk group. The 4 year OS rate for the low-intermediate risk group and high risk group were 100% and 91.7%, respectively, and there was no statistically significant difference (p=0.134). On univariate analysis, Gleason score (p=0.007) and pretreatment PSA (p=0.016) were significant predictive factors for BCF-free survival, while age and T stage were not (table 2). There were no significant differences for the above factors on multivariate analysis.

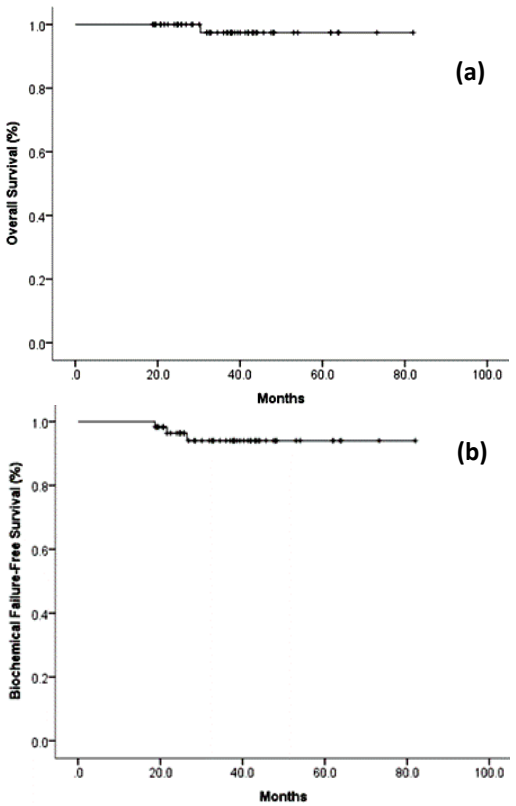

Figure 1. The overall survival rates **(a)** and biochemical failure -free survival rates **(b)** in all patients.

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Table 2. Results of Cox regression univariated analysis of predictive value of clinical factors for biochemical failure-free survival rate.

Variable	HR	95% CI	p-value
Age (<72 vs ≥72)	0.013	0.000-149.432	0.364
T stage (<T2c vs ≥T2c)	0.689	0.062-7.633	0.761
Pretreatment PSA (<20 vs ≥20)	11.138	1.126-127.870	0.016
Gleason score (<9 vs ≥9)	13.068	1.164-146.731	0.007
HR: Hazard Ratio; CI: Confidence Interval; PSA: Prostate-specific antigen			

Toxicities

All patients underwent all planned treatment without interruption. Acute grade 1 and 2 gastrointestinal (GI) toxicities were 8.6% and 5.2%, respectively, and acute grade 1 and 2 genitourinary (GU) toxicities were 63.8% and 24.1%, respectively (table 3). No acute toxicities ≥ grade 3 occurred. Most of acute toxicity started over 4 weeks. Most common GU toxicity was urinary frequency (70.7%). Common GI toxicities were rectal tenesmus (5.2%) and proctitis (5.2%). The grade 2 late GI toxicity was 8.6% with the highest peak at 1 year and ≥ grade 3 toxicity was not reported. Five patients experienced rectal bleeding. Two patients improved after minor laser cauterization and three improved without any treatment. Grade 2 late GU toxicity was at 13.8% with the highest peak at 2 years and no ≥ grade 3 toxicity (table 4). The majority of patients reported urinary frequencies which were usually controlled by α-blockers.

Table 3. Acute Toxicity and specific symptoms.

Symptoms	Grade 1	Grade 2	Grade 3
Gastrointestinal			
Tenesmus	3 (5.2%)	-	-
Hemorrhage	-	2 (3.4%)	-
Proctitis	2 (3.4%)	1 (1.7%)	-
Sum	5 (8.6%)	3 (5.2%)	-
Genitourinary			
Urinary obstruction	2 (3.4%)	1 (1.7%)	-
Urinary frequency	28 (43.1%)	13 (22.4%)	-
Urinary incontinence	2 (3.4%)	-	-
Urinary tract pain	2 (3.4%)	-	-
Urgency	3 (5.2%)	-	-
Sum	37 (63.8%)	14 (24.1%)	-

Table 4. Late toxicity according to follow-up period.

Grade		6 M (n=58)	12 M (n=58)	24 M (n=50)	36 M (n=28)	Worst in follow-up period
1	GI	3 (5.2%)	2 (3.4%)	-	-	5 (8.6%)
	GU	28 (48.3%)	19 (32.8%)	14 (28.0%)	2 (7.1%)	28 (48.3%)
2	GI	3 (5.2%)	4 (6.9%)	2 (4.0%)	1 (3.6%)	5 (8.6%)
	GU	5 (8.6%)	6 (10.3%)	8 (16.0%)	4 (14.3%)	8 (13.8%)
GI: Gastrointestinal; GU: Genitourinary; M: Months.						

Dosimetric findings

Dosimetric results are summarized in table 5. The median value of mean PTV dose was 72.3 Gy with median value of $V_{95\%}$ resulting in 98.9%. Concerning OARs, for all 41 patients, the median value of mean rectal dose was 35.3 Gy, median rectal volume receiving 40, 50, 60 and 70 Gy was 38.8%, 25.2%, 14.5% and 1.8%, respectively. Median value of mean bladder dose was 32.2 Gy, median bladder volume receiving 40, 50, 60 and 70 Gy was 36.9%, 25.7% 15.9% and 6.7%, respectively. There was no statistical correlation between acute GI/GU toxicities and dosimetric parameters.

Table 5. Summary of the dosimetric data analysis for the PTV and Organ at Risk.

Parameter		Median±SD	Range
PTV	Mean (Gy)	72.3±0.97	71.5 - 73.4
	$D_{2\%}$ (Gy)	79.8±12.5	67.5 - 76.7
	$D_{98\%}$ (Gy)	68.2±1.7	65.7 - 68.9
	$V_{95\%}$ (%)	98.9±1.7	97.6 - 99.4
	$V_{115\%}$ (%)	0.7±0.45	0.4 - 1.5
Rectum	Mean (Gy)	35.3±5.1	29.8 - 38.2
	V_{40Gy} (%)	38.8±8.6	30.2 - 42.9
	V_{50Gy} (%)	25.2±4.9	20.0 - 29.2
	V_{60Gy} (%)	14.5±2.7	11.7 - 15.9
	V_{70Gy} (%)	1.8±1.2	1.6 - 1.9
Bladder	Mean (Gy)	32.2±11.7	28.2 - 42.8
	V_{40Gy} (%)	36.9±15.7	30.1 - 52.1
	V_{50Gy} (%)	25.7±13.7	19.0 - 39.2
	V_{60Gy} (%)	15.9±8.4	12.1 - 24.2
	V_{70Gy} (%)	6.7±4.3	2.4 - 9.5

DISCUSSION

Numerous studies have demonstrated that escalated-dose radiotherapy for localized

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prostate cancer improves biochemical control [2,3,16,17]. Nevertheless, high-dose escalation radiation therapy up to 75.6-81.0 cGy by conventional fractionation increases the overall treatment time thus health care cost increase. Recently, several reports showed that hypofractionated radiation schedule might provide similar excellent outcome compared with dose escalated conventionally fractionated radiation therapy. Dearnaley D *et al.* presented a randomized trial comparing conventional (74 Gy in 37 fractions) and two hypofractionated (60 Gy in 20 and 57 Gy in 19) radiotherapy in localized prostate cancer [16]. The 5 years BCF-free survival was 88.3% in the 74 Gy group, 90.6% in the 60 Gy group, and 85.9% in the 57 Gy group. 60 Gy group was not inferior to 74 Gy group (p=0.0018). The estimated 5 year cumulative incidence of grade ≥ 2 GI and GU toxicities were 13.7% and 9.1% in the 74 Gy group, 11.9% and 11.7% in the 60 Gy group, 11.3% and 6.6% in the 57 Gy group, respectively. Late toxicities were similar between the hypofractionated groups and the conventional group [8]. Catton CN *et al.* also compared hypofractionation (60 Gy in 20 fractions) and conventional fractionation (78 Gy in 39 fractions). The BCF-free survival at 5 year was 85% in both arms and there were no significant differences between both arms for grade ≥ 3 late toxicity[18]. Hoffman KE *et al.* reported a randomized trial testing the hypothesis that moderately hypofractionated IMRT (HIMRT) (72 Gy in 2.4 Gy fractions) improves prostate cancer treatment outcome compared with conventionally fractionated IMRT (CIMRT) (75.6 Gy in 1.8 Gy fractions) for localized prostate cancer patients. The failure rate at 8 year was 10.7% with HIMRT and 15.4% with CIMRT. There was no difference in OS (P =0.39). The cumulative incidence of grade ≥2 GI and GU toxicity was 5.0% and 16.4% in conventional fractionation and 12.6% and 15.1% in hypofractionation (p=0.08 and p=0.84) [19].

Direct comparisons are not appropriate, but in comparison with the aforementioned randomized studies, the BCF-free survival of this study was similar but the acute and late grade ≥2 GI and GU toxicities were slightly lower. The low rate of GI and GU toxicity reported in this study might be derived from the better saving of the bladder and rectum. These favorable toxicities might be caused by the smaller margin expansion of PTV from CTV with a consequently lower bladder and rectal radiation exposure. Moreover, VMAT technique with daily CB CT IGRT might improve the toxicities. CT-based pretreatment varification of prostate position is reported to decrease the GI toxicities after radiation therapy for prostate cancer. De Crevoisier R *et al.* compared the efficacy and safety of daily versus weekly IGRT for patients with prostate cancer. Acute rectal bleeding was significantly lower in the daily IGRT group (6%) than in the weekly group (11%) (P=0.014). In the daily group, late rectal toxicity was significantly lower (P = .027)[20].

Recently, VMAT is a widely used radiation therapy technique for prostate cancer[10]. VMAT uses a large number of beam directions form an arc trajectory and delivers doses dynamically during rotation of the gantry, differently compared to IMRT[21]. VMAT has been proved to be equal or better for target coverage and nearby normal tissue saving compared with IMRT in prostate cancer radiation therapy[12]. Quan EM *et al.* reported a comparative study of the plan quality between IMRT and VMAT for the treatment of prostate cancer. For the same PTV coverage, the VMAT plans had significantly better plan quality in terms of rectum sparing than IMRT plans (p<0.0001)[21]. Zhang P *et al*. also evaluated VMAT plans compared with the standard IMRT plans in prostate cancer. The VMAT resulted improved rectal sparing, with a reduction of 1.5% in normal tissue complication probability [12]. Mellon EA et al. compared VMAT with step-and-shoot IMRT in prostate cancer patients. VMAT reduced median beam-on time from 4.3 to 3.4 minutes (P=0.03). There was no statistically significant difference in PTV volumes between the VMAT and step-and-shoot IMRT groups (P=0.76), but VMAT showed more homogeneous dose distributions (P=0 .003) [22]. However, there are no studies comparing VMAT and IMRT for outcomes and adverse effects. Anyway, in this study, we used the VMAT to

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dose delivery to target volume in all patients.

This study had some limitations. This study was retrospective. The observation period was not enough to report long-term treatment outcomes. Additionally, the duration of ADT was not constant between the participants.

In summary, VMAT-IGRT for localized prostate cancer using a hypofractionated schedule of 70 Gy in 28 fractions showed favorable outcomes without grade ≥3 toxicity. These data highlight the potential of this treatment to contribute to the reduction of the clinical and economical burden for patients with localized prostate cancer. More long-term follow up might be needed to achieve mature data.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Conflicts of interest*: *Declared none.

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