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Early toxicity of moderate hypofractionated volumetric modulated Arc radiotherapy for localized prostate cancer

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► ***Original article***

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ABSTRACT

Background*:** Based on the radiation biology model of prostate cancer, hypofractionated radiotherapy can improve the treatment outcomes without increasing toxicity. Although hypofractionated radiotherapy is implemented over a short period of time, it is more convenient and cheaper compared with conventional fractionated treatment. The aim of this study was to investigate the early toxicity of moderate hypofractionated schedules with volumetric modulate arc radiotherapy (VMAT) for localized prostate. ***Materials and Methods*:** Between 2014-2017, 41 patients were treated using the volumetric modulated arc radiotherapy (VMAT) technique with image guided radiotherapy. The target volume for low risk patient (2.4%) was the prostate alone, and that for intermediate (43.9%) and high risk patients (53.7%) was prostate and two thirds of the seminal vesicles. A prescription dose of 70 Gy in 2.5 Gy daily for 28 treatment was used. Radiotherapy-related toxicity was scored according to the Common Terminology Criteria for Adverse Events 4.0 criteria. ***Results: Early genitourinary (GU) toxicity was recorded for grades 0, 1, 2 and 3 in 7 (17.1%), 25 (61.0%), 9 (21.9%) and 0 patients, respectively. Most common GU toxicities were urinary frequency and urgency. Early gastrointestinal (GI) toxicity was observed for grade 0, 1 and 2 in 35 (85.4%), 6 (14.6%) and 0 patients, respectively. Most common GI toxicity was rectal discomfort but interventional therapy was not indicated. ***Conclusion:*** The moderate hypofractionated VMAT radiation therapy with precise dose delivery technique appeared safe with low early toxicity. Longer follow up is needed to assess late toxicity and tumor control probability.

Keywords: *Prostate cancer, acute toxicity, hypofractionation, volumetric modulated arc therapy, radiotherapy.*

INTRODUCTION

Prostate cancer is now one of the most common malignant diseases of male in the United States and Western countries [1]. Conventional fractionated radiotherapy, which is performed five times a week for eight weeks, is long-lasting treatment in radiation oncology practice and it is considered as standard treatment option in prostate cancer patients. Nevertheless, over the last few years, hypofractionation schedule has been adopted as a strategy of external beam radiation therapy (EBRT) in prostate cancer [2]. Numbers of clinical trials showed the non-inferiority of hypofractionated accelerated radiotherapy compared with conventionally fractionated radiotherapy of prostate cancer [3-6]. Although most tumors are thought to have a high α/β (>10 Gy) ratio, radiobiologic experiments have suggested that prostate cancer tissue has an α/β ratio of 1.5 Gy (0.9~2.2 Gy) and that is lower than even the surrounding normal tissue [7]. Based on the radiation biology model, hypofractionated radiation therapy may improve the treatment without increasing

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toxicity [8].

In parallel advances in physics, engineering and computing have been channelled into the development of volumetric-modulated arc therapy (VMAT). VMAT, which is a relatively new radiotherapy technique delivering radiation dose using continuous dynamic modulation of the dose rate, field aperture, gantry angle and speed in the treatment of prostate, has been reported to be equal or better for target coverage and normal tissue sparing compared with conventional fractionationated intensity modulated radiotherapy (IMRT) [9].

Moderate hypofractionated schedule uses relatively lower doses per fraction, usually 2.5–4 Gy, compared with ultra-hypofractionated. Due to the phenomenon of repopulation, we assume that partial reduction of early effects may be achieved by moderate hypofractionation. The aim of this study was to investigate the early toxicity of moderate hypofractionated schedules with VMAT for localized prostate cancer.

MATERIALS AND METHODS

Patients

Between January 2014 and January 2017, 41 patients with localized, histologically confirmed prostate adenocarcinoma were treated with volumetric modulated arc therapy with Rapidarc (Varian Medical Systems, Palo Alto, CA, USA). The study was approved by the Ethical Committee for Clinical Trials of our institution (registration number 2017-07-016) and the retrospective data was collected in our institutional database

Patients were stratified into three risk groups according to NCCN clinical guidelines in oncology, Prostate cancer, version 2.2017 [10].

VMAT treatment planning and delivery

For simulation and treatment, patients were placed in the supine position with their hands placed on the anterior chest. A whole-body vacuum cushion was used for immobilization. Planning CT (16 Slice big bore Virtual Simulator, GE, USA) scans in 2.5 mm thickness were obtained from the lower abdomen to the pelvis. All patients were instructed to empty their rectum through daily defecation. The patients were instructed to void their bladder at least 2 hours before the simulation and treatment.

The target volume was delineated on CT images. In low risk patients, clinical target volume (CTV) included the prostate alone, while in intermediate and high risk patients included the prostate and both proximal seminal vesicles (if not involved). If the seminal vesicle is involved, CTV was defined as the entire prostate and whole seminal vesicle. Planning target volume (PTV) was generated by adding anisotropic 0.5 cm margin to the CTV apart from posteriorly, where 0.3 cm margin was added (to decrease prostate-rectal interface dose). Contouring of the organs at risk followed the RTOG pelvic normal tissue contouring guidelines. The rectum was outlined from the level of ischial tuberosities to rectosigmoid flexure. The whole bladder was contoured; femoral heads were delineated to the level of ischial tuberosities.

All patients were treated using two arcs VMAT plan with 6 MV photons. The entire patients were treated to a total dose of 70 Gy in 28 daily fractions (2.5 Gy/fraction) over 51/2-6 weeks. Dose-volume constraints for organs at risk are summarized in table 2. For all patients, VMAT technique was planned with Aria 8.11. The dose was delivered by Clinac iX (Varian). Rapidarc (Varian Medical Systems, Palo Alto, CA, USA) is a form of conventional gantry-based linac volumetric arc therapy that incorporates variable gantry motion and dose rate with continuously moving multi-leaves collimators [11]. During therapy, daily cone beam CT was performed for image guidance purpose. Cone beam CT and planning CT images were co-registered based on soft tissue. Position correction was made every day with no action threshold using self-acting table movement.

Androgen deprivation therapy

Approximately 41.5% of the patients received androgen deprivation therapy (ADT). ADT consisted of a combination of antiandrogen and luteinizing hormone-releasing hormone agonist. The patients in the low and intermediate risk group were not treated with ADT, and those in

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the high-risk group received long-term ADT for 2–3 years.

Follow-up and Statistical analysis

Patients were scheduled to be seen weekly during radiotherapy and followed up after treatment at 1 month after the end of treatment, every 3 months for the first 2 years, and every 6 months thereafter. Physical examination and PSA assay were performed at each visit.

Radiotherapy-related toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.0 criteria. Toxicity was recorded on the basis of severity at the time of follow-up, regardless of the duration of symptoms. The pre-existing symptoms before treatment were excluded to correctly evaluate the toxicity. Acute toxicity was scored weekly during radiotherapy, and 1 and 3 months after completion of the treatment. Patients who needed any kind of drug support were classified as grade 2.

In this study, descriptive statistics (average, median, frequency) were used.

RESULTS

Moderate hypofractionated schedules with VMAT was completed in all 41 patients. All patients completed the treatment without any interruption. Forty-one patients with a median 13.2 months (range, 8-32 months) follow-up were analyzed. The median age was 72 years (range, 56-79 years). Patients' characteristics are summarized in table 1. All patents had at least 8 months of follow-up to observe the early side effects. Dosimetric results for all 41 patients are summarized in table 2. In particular, for PTV the ob-jectives were on averaged achieved, with median value of V95% resulting in 98.8%. Con-cerning OARs, for all 41 patients, the median value of mean rectum dose was 34.1 Gy, median rectal volume receiving 40, 50, 60 and 70 Gy was 38.4%, 24.5%, 14.3% and 1.7%, re-spectively. Median value of mean blad-der dose was 31.8 Gy, median bladder volume receiving 40, 50, 60 and 70 Gy was 36.5%, 25.0% 15.8% and 6.7%, respectively.

Table 1. Patient's characteristics

		Low and intermediate risk	High risk	All
Number of patients		19	22	41
Median age		70	73	72 (56-79)
Median of follow-up (months)		12.4	13.5	13.2
ECOG scale				
	0	12 (63.2%)	12 (54.5%)	24 (58.5%)
	1	7 (36.8%)	10 (45.5%)	17 (41.5%)
T stage				
	T1-T2a	4 (21.1%)	2 (9.0%)	6 (14.6%)
	T2b-T2c	15 (78.9%)	10 (45.5%)	25 (61.0%)
	T3-	0	10 (45.5%)	10 (24.4%)
Pretreatment PSA (ng/mL)				
	Median	10.45	21.32	11.86
	≤10	9 (47.4%)	7 (31.9%)	16 (39.0%)
	>10	10 (52.6%)	15 (68.1%)	25 (61.0%)
Gleason score				
	≤6	7 (36.8%)	0	7 (17.1%)
	7	12 (63.2%)	7 (31.9%)	19 (46.3%)
	≥8	0	15 (68.1%)	15 (36.6%)
Hormone therapy		3 (15.8%)	14 (63.6%)	17 (41.5%)

ECOG=Eastern Cooperative Oncology Group

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Table 2. Summary of the dosimetric data analysis for the PTV and Organ at Risk.

Parameter		Mean±SD	Range
PTV	Mean (Gy)	72.7±0.93	71.5 - 73.1
	$D_{2\%}$ (Gy)	79.4±11.1	68.7 - 75.7
	$D_{98\%}$ (Gy)	67.9±1.5	66.3 - 68.7
	$V_{95\%}$ (%)	98.8±1.4	98.4 - 99.1
	$V_{115\%}$ (%)	0.7±0.43	0.4 - 1.4
Rectum	Mean (Gy)	34.1±4.6	29.8 - 37.8
	V_{40Gy} (%)	38.4±8.4	30.2 - 42.3
	V_{50Gy} (%)	24.5±4.6	20.0 - 28.6
	V_{60Gy} (%)	14.3±2.9	11.7 - 15.6
	V_{70Gy} (%)	1.7±1.0	1.6 - 1.8
Bladder	Mean (Gy)	31.8±11.4	28.5 - 42.4
	V_{40Gy} (%)	36.5±15.4	30.5 - 51.3
	V_{50Gy} (%)	25.0±13.1	19.3 - 38.9
	V_{60Gy} (%)	15.8±8.1	12.4 - 23.9
	V_{70Gy} (%)	6.7±4.1	2.5 - 9.4

Low and intermediate risk patients

19 patients with low and intermediate risk cancer underwent therapy. 3 (15.8%) of these were treated with hormonal therapy administered by a urologist. Early genitourinary (GU) toxicities were recorded for grades 0, 1, 2 and 3 in 3 (15.8%), 14 (73.7%), 2 (10.5%) and 0, respectively. Early gastrointestinal (GI) toxicities were observed for grades 0, 1, 2 and 3 in 17 (89.5%), 2 (10.5%), 0 and 0, respectively.

High risk patients

22 patients with high risk underwent therapy. 14 (63.6%) of these were treated with neoadjuvant and concomitant hormonal therapy. Early GU toxicities were recorded for grades 0, 1, 2 and 3 in 4 (18.2%), 11 (50.0%), 7 (31.8%) and 0 patients, respectively. Early GI toxicities were observed for grades 0, 1 and 2 in 18 (18.8%), 4 (18.2%) and 0 patients, respectively.

Cumulative results of all patients

All of the patients remain locally controlled with no evidence of biochemical relapse during follow-up periods. 17 (41.5%) were administered with ADT as well. Early GU toxicities were recorded for grades 0, 1, 2 and 3 in 7 (17.1%), 25 (61.0%), 9 (21.9%) and 0 patients, respectively. Common GU toxicities were urinary frequency and urgency. Early GI toxicities were observed for grade 0, 1 and 2 in 35 (85.4%), 6 (14.6%) and 0 patients, respectively. Most common GI toxicity was rectal discomfort but intervention was not indicated. All patients tolerated the treatment well without any severe acute toxicity of grade 3 or 4. No interruptions of the treatment for toxicity were recorded.

The results are summarized in table 3 and figure 1.

Table 3. Distribution of early gastrointestinal and genitourinary toxicities.

		Low and intermediate risk	High risk	All
Genitourinary toxicity				
Patients, n (%)	Grade 0	3 (15.8%)	4 (18.2%)	7 (17.1%)
	Grade 1	14 (73.7%)	11 (50.0%)	25 (61.0%)
	Grade 2	2 (10.5%)	7 (31.8%)	9 (21.9%)
	Grade 3	0	0	0
Gastrointestinal toxicity				
Patients, n (%)	Grade 0	17 (89.5%)	18 (81.8%)	35 (85.4%)
	Grade 1	2 (10.5%)	4 (18.2%)	6 (14.6%)
	Grade 2	0	0	0
	Grade 3	0	0	0

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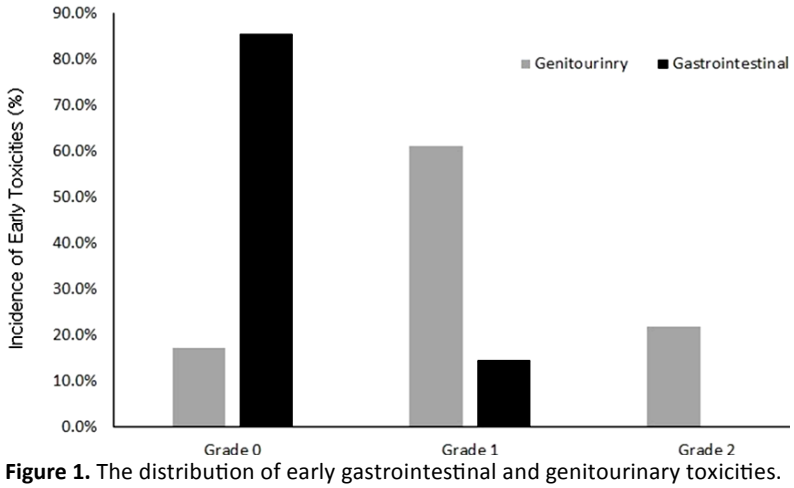


Figure 1. The distribution of early gastrointestinal and genitourinary toxicities.

DISCUSSION

Numerous phase III trials on escalated-dose radiotherapy for localized prostate cancer compared with conventional fraction radiotherapy have been demonstrated to improve biochemical control [11-15]. NCCN recommends that the dose of 75.6-79.2 Gy for the low-risk group and the dose of up to 81.0 Gy for the intermediate-risk or high-risk group in conventional fractions should be used to improve biochemical control [16]. However, high-dose up to 75.6-81.0 Gy by conventional fractionation increases the overall treatment time to 8-9 weeks and health care costs.

Recent reports showed that hypofractionated schedule could provide similar excellent control as other conventional radiation modalities. Prostate cancer has a low estimated α/β ratio of approximately 1.5 Gy; however, for normal tissue adjacent to the prostate, such as the bladder and rectum the α/β ratio was assumed to be 3-5 Gy [17-20]. Arcangeli *et al.* published a report comparing 80 Gy (2 Gy/fraction) versus 62 Gy (3.1 Gy/fraction) and showed that hypofractionated schedule is superior to the conventional fractionation in terms of freedom from biochemical failure rate with equivalent toxicity [21]. Pollack et al. actualized the data of their randomized study which compared regimens 76 Gy (2.0 Gy/fraction) versus 70.2 Gy (2.7 Gy/fraction). No significant difference was found in toxicity and in biochemical control [22].

Krupa *et al.* [23] assessed 158 patients treated using the RapidArc technique with Image-guided radiotherapy (IGRT). The target volume for low risk patients was the prostate alone with a prescribed dose of 20x3.0 Gy (EQD2=77 Gy). Targets volumes for intermediate and high risk patients were prostate and two thirds of the seminal vesicles with a prescribed dose 21-22×3.0/2.1 Gy. Early GU toxicities were observed for grades 0, 1, 2, 3 and 4 in 73 (46%), 60 (38%), 22 (14%), 0 and 3 (2%), respectively; early GI toxicities were recorded for grades 0, 1, 2 and 3 in 119 (75%), 37 (23%), and 2 (1%) patients, respectively. Tramacere *et al.* [24] treated 97 patients with a schedule of 62 Gy in 20 fractions over 5 weeks, maximum ≥G2 late GU and GI toxicities occurred in 8% and 11% patients, respectively.

Jereczek-Fossa *et al.* [25] compared acute toxicity of prostate cancer image-guided hypofractionated radiotherapy with conventional fraction without image-guidance. 179 cT1-T2N0M0 prostate cancer patients were treated within the prospective study with 70.2 Gy/26 fractions using IGRT in comparison with 174 patients who were treated to 80 Gy/40 fractions. Acute toxicity in the hypo-IGRT cohort included rectal (G1: 29.1%; G2: 11.2%; G3: 1.1%) and urinary events (G1: 33.5%; G2: 39.1%; G3: 5%). Acute toxicity in the non-IGRT patients included rectal (G1: 16.1%; G2: 6.3%) and urinary events (G1: 36.2%; G2: 20.7%; G3: 0.6%). The incidence of mild (G1-2) rectal and bladder complications was significantly higher for hypo-IGRT ($P = 0.0014$ and $P < 0.0001$,

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respectively). The acute toxicity rates were low and similar in both study groups with some increase in mild acute urinary injury in the hypo -IGRT patients

Aluwini *et al.* reported results of phase III randomized study, which examine whether patients with hypofractionated schedule experience differences in acute GI and GU adverse effects. 391 patients received 2.0 Gy * 29 fractions, five fractions per week and 403 patients received 3.4 Gy * 19 fractions, three fractions per week. Early GU toxicity worse than G2 was 58% versus 61% (P = 0.43) and GI toxicity 31% versus 42% (P = 0.0015) for conventional fractionation versus hypofraction-ation respectively. Hypofractionated radiotherapy was not non-inferior to standard fractionated radiotherapy in terms of early GU and GI toxicity for men with intermediate-risk and high-risk prostate cancer [26].

Trials using hypofractionated schedules showed overall low early toxicity. Most of them used image guidance technique and small CTV-PTV margins or special immobilization techniques. These studies are summarized in table 4. These studies are difficult to compare due to different dose delivery techniques, dose per fraction, etc. Most studies showed mild early toxicity.

Our study achieved low level of early toxicity, compared with above studies. This can be explained by choice of precise dose delivery by VMAT technique with daily cone beam image guidance.

Important limitations of the current study are that the clinical outcome and late toxicity are not reported. It is clear that late side effects might increase according to the increase of dose per fraction and it is a key point of the current approach based on a moderate hypofractionation schedule on prostate and seminal vesicles. However, the endpoint of the current report was to prove the feasibility and early toxicity by this approach. Another limitation is that data were collected in a retrospective fashion. A prospective trial would reduce any potential bias.

As shown in the results. The early toxicity profile assessed by moderate hypofractionated VMAT was shown to be safe and similar to the other series of published moderate hypofractionation studies. Longer follow-up is needed to collect data for late toxicities and clinical outcome assessment on these different issues.

Table 4. Gastrointestinal and genitourinary toxicity results compared to other series.

Reference	Patients (n)	Fractions (n)	Fraction dose (Gy)	Total dose (Gy)	Technique	Treatment time (weeks)	Acute GI ≥ G2 (%)	Acute GU ≥G2 (%)
Lukka *et al.*[3]	466	20	2.62	52.5	2D	4	4%	9%
Alumini *et al.*[26]	410	19	2.7	70.2	IMRT	6.5	42%	61%
Jereczek-Fossa *et al.*[25]	179	26	2.7	70.2	3D Arc	5.2	12.3%	44.1%
Krupa *et al.*[23]	158	20-22	3.0	60-66	VMAT	5	24%	16%
Tramacere *et al.*[24]	97	20	3.1	62.0	IMRT	5	15%	25%
Viani *et al.*[27]	112	23	3.0	69.0	3D CRT	4.6	20.5%	24.2%
Arcangeli *et al.*[21]	168	20	3.1	62.0	3D CRT	4	35%	40%
Alongi *et al.*[28]	40	5	7.0	35.0	VMAT	2	10%	40%
Current study	41	28	2.5	70.0	VMAT	5.5	14.6%	21.9%

2D=2 dimentional, IMRT=intensity-modulated radiotherapy, 3D Arc=3 dimentional arc therapy, VMAT=volumetric modulated arc therapy, 3D CRT=3 dimentional conformal radiotherapy

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