A Dosimetric Comparison between Conventional Fractionated and Hypofractionated Image-guided Radiation Therapies for Localized Prostate Cancer

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Abstract

Background: Image-guided radiation therapy (IGRT) is the preferred method for curative treatment of localized prostate cancer, which could improve disease outcome and reduce normal tissue toxicity reaction. IGRT using cone-beam computed tomography (CBCT) in combination with volumetric-modulated arc therapy (VMAT) potentially allows smaller treatment margins and dose escalation to the prostate. The aim of this study was to compare the difference of dosimetric diffusion in conventional IGRT using 7-field, step-and-shoot intensity-modulated radiation therapy (IMRT) and hypofractionated IGRT using VMAT for patients with localized prostate cancer.

Methods: We studied 24 patients who received 78 Gy in 39 daily fractions or 70 Gy in 28 daily fractions to their prostate with/without the seminal vesicles using IMRT ($n = 12$) or VMAT ($n = 12$) for prostate cancer between November 2013 and October 2015. Image guidance was performed using kilovoltage CBCT scans equipped on the linear accelerator. Offline planning was performed using the daily treatment images registered with simulation computed tomography (CT) images. A total of 212 IMRT plans in conventional cohort and 292 VMAT plans in hypofractionated cohort were enrolled in the study. Dose distributions were recalculated on CBCT images registered with the planning CT scanner.

Results: Compared with 7-field, step-and-shoot IMRT, VMAT plans resulted in improved planning target volume (PTV) D95% (7663.17 ± 69.57 cGy vs. 7789.17 ± 131.76 cGy, $P < 0.001$). VMAT reduced the rectal D25 ($P < 0.001$), D35 ($P < 0.001$), and D50 ($P < 0.001$), bladder V50 ($P < 0.001$), D25 ($P = 0.002$), D35 ($P = 0.028$), and D50 ($P = 0.029$). However, VMAT did not statistically significantly reduce the rectal V50, compared with 7-field, step-and-shoot IMRT (25.02 ± 5.54% vs. 27.43 ± 8.79%, $P = 0.087$).

Conclusions: To deliver the hypofractionated radiotherapy in prostate cancer, VMAT significantly increased PTV D95% dose and decreased the dose of radiation delivered to adjacent normal tissues comparing to 7-field, step-and-shoot IMRT. Daily online image-guidance and better management of bladder and rectum could make a more precise treatment delivery.

Key words: Hypofractionated Radiotherapy; Image-guided Radiotherapy; Prostate Cancer; Treatment Planning; Volumetric-modulated Arc Therapy

INTRODUCTION

Prostate cancer is the most common cancer in older males. Radiation therapy (RT) is frequently used in the curative treatment of localized prostate cancer. Dose-escalated RT has been shown in multiple randomized trials to improve biochemical disease-free survival. According to the international guidelines, external beam RT (EBRT) is now considered a standard of care and a curative therapeutic modality for patients with prostate cancer. Techniques continue to evolve that maximize the dose of radiation delivered to the prostate while sparing organs at risk. Intensity-modulated RT (IMRT) has replaced three-dimensional (3D) conformal RT as the most common

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method of RT for prostate cancer because it produces more conformal dose distributions that can escalate prescribed dose and reduce normal tissue toxicity. The most common method for IMRT delivery for prostate cancer involves 7–9, fixed gantry positions with computer-generated, sliding-window multi-leaf collimator (MLC) positions to modulate the dose to the prostate. This is commonly referred to as conventional "step-and-shoot" IMRT. Volumetric-modulated arc therapy (VMAT) is an innovative form of IMRT optimization that allows the radiation dose to be efficiently delivered using a dynamic modulated arc. The VMAT simultaneously coordinates gantry rotation, MLC motion, and dose rate modulation, and facilitating highly conformal treatment with better normal tissue sparing. Multiple groups have observed that VMAT reduced beam-on time and the amount of radiation delivered (monitor units [MUs]) relative to 7- to 9-field, step-and-shoot IMRT.[1-4]

A conventional EBRT course with radical intent usually needs 38–40 fractions up to a total nominal dose of 76–80 Gy, lasting 7–9 weeks. This conventional fractionation approach is best compromised between efficacy and safety of treatment, particularly in terms of late rectal complications. The α/β ratio represents the radiobiological parameter explaining how normal and cancer tissues would respond to different radiation schedules. Despite the uncertainty, several reviews consistently estimated an average α/β ratio of approximately 1.5–2 Gy for prostate cancer versus 3 Gy for rectal late effects suggesting that prostate cancer cells, being slowly proliferated, have high sensitivity to dose per fraction. A low α/β ratio is the characteristic of tumors particularly sensitive to high dose per fraction. In this sense, hypofractionation (from mild to extreme) could improve the therapeutic index of radiotherapy in prostate cancer, with optimal local control rates and lower side effects to surrounding late-responding healthy tissues, including the rectal wall.

Image-guided RT (IGRT) is the preferred method for curative treatment of localized prostate cancer and is associated with improved outcome and reduced toxicity.[5] IGRT using cone-beam computed tomography (CBCT) in combination with conformal RT techniques such as IMRT or VMAT potentially allows smaller treatment margins and dose escalation to the prostate. Combining IGRT and IMRT/VMAT allows to overcome one of the major limitations of delivering higher total dose and/or high dose per fraction. In this clinical and technological background, it became possible to take advantage of hypofractionation and its increased therapeutic ratio.

To practice hypofractionation at the Department of Radiation Oncology, Beijing Hospital, a transition from 7-field, step-and-shoot IMRT to VMAT for clinically localized prostate cancer began in November 2013. To conduct a dosimetric comparison of these two techniques, we retrospectively generated two cohorts of patients matched for planning target volumes (PTVs) and total dose.

METHODS

Patients

We studied 24 patients with clinically localized prostate cancer treated with IGRT selected from more than 300 patients in Department of Radiation Oncology, Beijing Hospital between November 2013 and October 2015. We identified 12 patients received 78 Gy in 39 fractions delivered using IMRT and 12 patients received 70 Gy in 28 fractions delivered using VMAT to prostate with/without seminal vesicles (SVs). Patients' characteristics and treatment parameters are summarized in Tables 1 and 2. The age ranged from 72 to 90 years (average age: 79.2 years) in conventional cohort and from 74 to 81 years (average age: 77.5 years) in

Table 1: Characteristics of 24 localized prostate cancer patients in this study, *n*

Characteristics	Conventional cohort (*n* = 12)	Hypofractionated cohort (*n* = 12)
AJCC clinical stage		
I	4	4
II	4	6
III	4	2
Recurrence risk group		
Low	2	0
Intermediate	4	6
High	6	6
T-stage		
T1	2	0
T2	6	8
T3	4	4
Gleason score		
2–6	4	4
7	6	4
8–10	2	4
Highest pretreatment PSA		
<10 ng/ml	2	0
10–20 ng/ml	6	8
>20 ng/ml	4	4

AJCC: American Joint Committee on Cancer; PSA: Prostate specific antigen.

Table 2: Treatment parameters for 24 localized prostate cancer patients in this study

Parameters	Conventional cohort (*n* = 12)	Hypofractionated cohort (*n* = 12)
PTV margins, mm	7/5	5/4
Treatment plans	IG-IMRT	IG-VMAT
Beam fields	7-fixed-fields	2 arcs
Techniques	Step-and-shot	Gantry rotation
Fraction	2 Gy*39f	2.5 Gy*28f
CBCT delivery	Every other day (daily on the first and last week)	Daily
Treatment time, min	3–7	2–4
CBCT images	200 slices	280 slices

PTV: Planning target volume; CBCT: Cone-beam computed tomography; IMRT: Intensity modulated radiation therapy; VMAT: Volumetric-modulated arc therapy; IG: Image-guided.

hypofractionated cohort. This study was approved by the Local Ethics Committee of Beijing Hospital.

Simulation and bladder and rectum preparation

All patients underwent computed tomography (CT)-based treatment planning in the supine position with their bodies immobilized by a custom vacuum immobilization device. In conventional cohort, the rectum was empty, and before simulation, 500–1000 ml water mixed with/without nonionic contrast was drunk to fill the bladder. In hypofractionated cohort, a comfortably full bladder and empty rectum were prepared at the time of simulation. All patients had undergone 5-mm slice thickness CT using Philips Brilliance Big Bore CT-Simulator (Philips Healthcare System, Cleveland, OH, USA).

Treatment plans

The CT data were digitally transferred to an Eclipse™ (Varian Medical Systems, Palo Alto, CA, USA) workstation for target and critical structure delineation. Target and critical structure delineation were undertaken following standard departmental protocols derived from the CHHiP trial protocol. In conventional cohort, prostate and SV clinical target volume 1 (CTV1), covering the prostate and the entire SVs for high-risk patients, the bilateral proximal SVs for intermediate patients, and prostate-only CTV (CTV2), covering the prostate alone, were contoured on the planning CT images. PTV for 66 Gy (PTV1) was defined as CTV1 with a margin of 5 mm posterior and 7 mm in other directions. The PTV for 12 Gy (PTV2) was created using a 3D, isotropic, 5-mm margin around the prostate. In hypofractionated cohort, CTV delineation was the same with conventional CTV1. A 5-mm margin was grown isotropically (4 mm posterior) from CTV to form PTV.

Treatment plans were generated using IMRT or VMAT techniques. All IMRT plans consisted of seven coplanar fields. Plans were calculated with Eclipse™ 11.0 Treatment Planning System (Varian Medical Systems) using AAA algorithm and a sliding-window MLC delivery technique. VMAT plans consisted of two 360° arcs. Gantry speed, MLC leaf position, and dose rate varied continuously during VMAT delivery. The 6 MV photon energies were generated for both IMRT and VMAT techniques. IMRT plans were designed to a planned total prescription dose at the isocenter of 78 Gy in 39 fractions (66 Gy in 33 fractions to PTV1 with a boost of 12 Gy to PTV2). All VMAT treatments were planned to be delivered of 70 Gy in 28 fractions. Two plans were generated and each was normalized to deliver 95% of PTV receiving at least 78 Gy and 70 Gy, respectively. Dose constraints for the rectum and bladder were based on recommendations of RT oncology group. Step-and-shoot IMRT plans were delivered using Varian Clinac®-iX (Varian Medical Systems). VMAT plans were created for delivery on Varian linear accelerator TrueBeam® (Varian Medical Systems).

Treatment delivery

At each daily treatment, patients prepared their rectum and bladder same as simulation, and the skin-marked isocenter was aligned with laser guidance in the supine position. Daily image guidance was performed using kilovoltage CBCT scans equipped on the linear accelerator. A pretreatment CBCT (pre-CBCT) image was taken. Planning CT and CBCT images were automatically matched using deformable image registration software and then checked manually before a visual inspection to ensure that the PTV encompassed the prostate and SVs. In hypofractionated cohort, if the rectum was not empty, the patient was asked to empty their bowels before treatment and the CBCT was repeated. In conventional cohort, if the rectum encroached by 50%, across the diameter of the CTV outline, the radiation oncologists attempted to match to the target, only asking the patient to reempty their bowels if no good match could be achieved. Precision of the online targeting and correction process was determined to be 3 mm. Thus, only pretreatment displacements >3 mm were corrected before starting treatment. Once a satisfactory match was achieved, if a single nonconformance of 3 mm was recorded on any direction, isocenter shifts were calculated and applied, even reposition was conducted by the treating radiographer before treatment delivery. Then, the treatment plan was delivered after online CBCT imaging and position correction. A total of 24 pretreatment planning CT images, 200 pre-CBCT images in conventional cohort, and 280 pre-CBCT images in hypofractionated cohort were enrolled in the study.

Offline replanning

Offline daily localization data were available. CTV, rectum, and bladder were delineated on all CBCT images. CTV-to-PTV margins were created. If on three directions during treatment nonconformance was >3 mm, in these cases prompt remedial action were taken. Dose distributions would be directly evaluated on CBCT images registered with simulation CT images. If pretreatment displacements within 3 mm, isocenter positions were not corrected, then after incorporating these setup errors into planning the position, offline planning is performed for patients who did not underwent correction of displacements before treatment using the daily treatment images obtained registered with simulation CT images. Dose distributions were recalculated on CBCT images registered with the planning CT scanner.

VMAT was compared with 7-field, step-and-shoot IMRT in prostate cancer patients treated with a consistent PTV to a uniform total RT dose. IMRT plans were designed to a planned total dose at the isocenter of 78 Gy in 39 fractions (66 Gy in 33 fractions to PTV1 with a boost of 12 Gy to PTV2). VMAT plans were planned to be delivered of 70 Gy in 28 fractions ($\alpha/\beta = 2$, EQD2 = 78 Gy). A total of 212 IMRT plans and 292 VMAT plans were gained.

Plan evaluation

Dose-volume metrics of the prostate, rectum, and bladder were calculated from the relevant histograms. The dose-volume parameters included the PTV relative doses of the 95% volumes and doses constraints to the rectum, bladder was determined, including rectal V50, D25, D35, and D50, bladder V50, D25, D35, and D50.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive data are presented as mean ± standard deviation (SD). The statistical significance of the difference between each pair of planning and replanning in the conventional IMRT/hypofractionated VMAT treatment techniques was tested using the paired *t*-test. The independent-sample *t*-test was used to determine statistical differences between volumes and doses in IMRT versus VMAT plans in independent patient groups. The Pearson *R* value was calculated to determine the strength of correlations between the dose-volume parameters of target volumes and organ at risks (OARs). All *P* values were two-sided, and *P* < 0.05 was considered statistically significant.

RESULTS

In conventional cohort, there were no statistically significant differences between the pretreatment planning and replanning groups with respect to PTV D95%, rectal volume, bladder volume, and rectal V50, D25, D35, and D50, bladder V50, D25, and D50 [Table 3].

In hypofractionated cohort, there were no statistically significant differences between the pretreatment planning and replanning groups with respect to rectal volume, bladder volume and rectal V50, D25, D35, and D50, bladder V50, D25, D35, and D50 [Table 4]. There was statistically significant difference between two groups with regard to PTV D95% (*P* = 0.013), but the dose variation was not more than 1%.

There were statistically significant differences between the step-and-shoot IMRT and VMAT (α/β = 2, EQD2 = 78 Gy) cohorts with respect to PTV D95%. There were also significant differences between two cohorts with regard to rectal volume, bladder volume and rectal D25, D35, and D50, bladder V50, D25, D35, and D50. However, the rectal V50 was similar in two cohorts [Table 5]. Compared with 7-field, step-and-shoot IMRT, VMAT plans resulted in improved PTV D95% (*P* < 0.001). There were less rectal and bladder volumes in VMAT cohort. VMAT reduced the rectal volume, bladder volume and rectal D25, D35, and D50, and bladder V50, D25, D35, and D50. However, VMAT did not significantly reduce the rectal V50 compared with the step-and-shoot IMRT (*P* = 0.087).

A significant correlation between the bladder and rectal volume and dose was observed. There were statistically correlations between the PTV D95% with bladder and rectum doses, especially in hypofractionated cohort with many dose-volume parameters of rectum. There were few correlations between the PTV D95% with bladder and rectum volumes except in the step-and-shoot IMRT cohort. It was indicated that there were some space to promote in the management of bladder and rectum in this cohort [Tables 6 and 7].

Table 3: Conventional fractionated dose-volume parameters of PTV and OARs for the pretreatment planning and replanning (mean ± SD)

Items	Pretreatment planning	Replanning	t	P
PTV D95% (cGy)	7741.67 ± 106.12	7663.17 ± 69.57	1.309	0.248
BV (cm)	209.65 ± 168.18	202.02 ± 67.32	0.144	0.891
RV (cm)	71.44 ± 27.73	71.99 ± 12.88	−0.044	0.966
BV50 (%)	51.81 ± 16.76	49.70 ± 16.41	2.245	0.075
RV50 (%)	24.48 ± 7.73	25.02 ± 5.54	−0.368	0.728
BD25 (cGy)	5407 ± 2011	5280 ± 2028	2.095	0.090
BD35 (cGy)	4356 ± 2170	4197 ± 2096	3.277	0.022
BD50 (cGy)	3270 ± 1890	3148 ± 1795	1.772	0.137
RD25 (cGy)	6039 ± 349	6178 ± 714	−0.655	0.542
RD35(cGy)	5149 ± 653	5227 ± 711	−1.122	0.313
RD50 (cGy)	3920 ± 171	4111 ± 569	−0.987	0.369

OAR: Organ at risk; SD: Standard deviation; BV: Bladder volume; RV: Rectal volume; BD: Bladder dose; RD: Rectal dose; PTV: Planning target volume.

Table 4: Hypofractionated dose-volume parameters of PTV and OARs for the pretreatment planning and replanning (mean ± SD)

Items	Pretreatment planning	Replanning	t	P
PTV D95% (cGy)	6984.17 ± 21.25	6924.67 ± 57.75	3.790	0.013
BV (cm)	139.83 ± 42.95	126.97 ± 27.41	0.838	0.440
RV (cm)	50.97 ± 13.50	61.92 ± 6.35	−2.396	0.062
BV50 (%)	26.12 ± 8.70	22.57 ± 14.04	0.484	0.649
RV50 (%)	28.67 ± 5.66	27.43 ± 8.79	0.362	0.732
BD25 (cGy)	4770 ± 457	4195 ± 1375	0.850	0.434
BD35 (cGy)	3836 ± 330	3428 ± 1363	0.682	0.526
BD50 (cGy)	2703 ± 469	2507 ± 1230	0.410	0.699
RD25 (cGy)	5046 ± 888	5013 ± 1091	0.096	0.927
RD35(cGy)	4222 ± 790	4226 ± 866	−0.012	0.991
RD50 (cGy)	3423 ± 551	3261 ± 473	0.812	0.454

OAR: Organ at risk; SD: Standard deviation; BV: Bladder volume; RV: Rectal volume; BD: Bladder dose; RD: Rectal dose; PTV: Planning target volume.

Table 5: Dose-volume parameters of PTV and OARs for hypofractionated patients (α/β = 2, EQD2 = 78 Gy) and conventional patients (mean ± SD)

Items	Hypofractionated cohort (n = 12)	Conventional cohort (n = 12)	t	P
PTV D95% (cGy)	7789.17 ± 131.76	7663.17 ± 69.57	−4.779	<0.001
BV (cm)	126.97 ± 27.41	202.02 ± 67.32	7.266	<0.001
RV (cm)	61.92 ± 6.35	71.99 ± 12.88	3.613	<0.001
BV50 (%)	22.57 ± 14.04	49.70 ± 16.41	13.668	<0.001
RV50 (%)	27.43 ± 8.79	25.02 ± 5.54	−1.720	0.087
BD25 (cGy)	4584 ± 1718	5280 ± 2028	3.153	0.002
BD35 (cGy)	3730 ± 1724	4197 ± 2096	2.185	0.028
BD50 (cGy)	2703 ± 1623	3148 ± 1795	2.203	0.029
RD25 (cGy)	5617 ± 1480	6178 ± 714	4.303	<0.001
RD35 (cGy)	4728 ± 1173	5227 ± 711	4.201	<0.001
RD50 (cGy)	3622 ± 741	4111 ± 569	5.823	<0.001

OAR: Organ at risk; SD: Standard deviation; BV: Bladder volume; RV: Rectal volume; BD: Bladder dose; RD: Rectal dose; PTV: Planning target volume.

Table 6: Correlations between dose-volume parameters for the 200 conventional replannings (*P*)

Items	PTV 95%	BV	BV50	BD25	BD35	BD50	RV	RV50	RD25	RD35	RD50
PTV 95%	/	0.033	0.764	0.029	0.136	0.137	0.205	0.230	0.002	0.369	0.076
BV	0.033	/	0.542	0.003	0.000	0.000	0.002	0.011	0.000	0.000	0.000
BV50	0.029	0.003	/	0.110	0.132	0.129	0.086	0.091	0.474	0.055	0.004
BD25	0.137	0.000	0.098	/	0.129	0.000	0.000	0.000	0.000	0.000	0.000
BD35	0.205	0.002	0.026	0.086	/	0.000	0.000	0.000	0.000	0.000	0.002
BD50	0.230	0.011	0.015	0.091	0.001	/	0.000	0.000	0.000	0.001	0.040
RV	0.764	0.542	0.110	0.010	0.098	0.026	/	0.015	0.030	0.598	0.623
RV50	0.136	0.000	0.010	0.132	0.000	0.000	0.001	/	0.745	0.235	0.557
RD25	0.002	0.000	0.030	0.474	0.745	0.000	0.000	0.000	/	0.000	0.000
RD35	0.369	0.000	0.598	0.055	0.235	0.000	0.000	0.001	0.000	/	0.000
RD50	0.076	0.000	0.623	0.004	0.557	0.000	0.002	0.040	0.000	0.000	/

BV: Bladder volume; RV: Rectal volume; PTV: Planning target volume; BD: Bladder dose; RD: Rectal dose.

Table 7: Correlations between dose-volume parameters for the 280 hypofractionated replannings (*P*)

Items	PTV 95%	BV	BV50	BD25	BD35	BD50	RV	RV50	RD25	RD35	RD50
PTV 95%	/	0.300	0.457	0.110	0.243	0.441	0.227	0.000	0.004	0.003	0.075
BV	0.300	/	0.000	0.000	0.000	0.000	0.660	0.509	0.809	0.633	0.219
BV50	0.457	0.000	/	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.256
BD25	0.110	0.000	0.000	/	0.000	0.000	0.000	0.000	0.000	0.000	0.095
BD35	0.243	0.000	0.000	0.000	/	0.000	0.000	0.000	0.000	0.000	0.220
BD50	0.441	0.000	0.000	0.000	0.000	/	0.000	0.001	0.000	0.001	0.714
RV	0.227	0.660	0.000	0.000	0.000	0.000	/	0.878	0.269	0.138	0.000
RV50	0.000	0.509	0.001	0.000	0.000	0.001	0.878	/	0.000	0.000	0.000
RD25	0.004	0.809	0.000	0.000	0.000	0.000	0.269	0.0000	/	0.000	0.000
RD35	0.003	0.633	0.000	0.000	0.000	0.001	0.138	0.000	0.000	/	0.000
RD50	0.075	0.219	0.256	0.095	0.220	0.714	0.000	0.000	0.000	0.000	/

BV: Bladder volume; RV: Rectal volume; PTV: Planning target volume; BD: Bladder dose; RD: Rectal dose.

DISCUSSION

There are three parts of target volume variation in prostate radiotherapy: interfraction deviation, interfraction deformation, and intrafraction deviation. Interfraction deviation is decided by the setup errors and the surrounding normal organs filling. The setup errors are made of systematic and random setup errors (RSEs). These data allow an assessment of patient positioning accuracy and precision while tracking the imaging frequency. Kupelian et al.[6] compared different image-guidance strategies in the alignment of prostate cancer patients. As expected, systematic errors were effectively reduced with imaging. However, the random errors were unaffected. Even when image guidance was performed every other day with a running mean of the previous displacements. This suggested that localizations must be performed daily in the setup of prostate cancer patients during a course of external beam radiotherapy.

Without the CBCT guidance, the influence of the normal organs nearby referred to the vesical and rectal filling which can result in the prostate motion on a vertical direction. Schallenkamp et al.[7] studied twenty prostate cancer patients treated using three or four intraprostatic gold fiducial markers. Daily pretherapy and through-treatment electronic portal images were obtained for each of four treatment fields. He found margins were 5.1 mm, 7.3 mm, and 5.0 mm in the superiorinferior, anteroposterior, and rightleft axes before localization and 2.7 mm, 2.9 mm, and 2.8 mm after localization, respectively. There are significant motions on AP direction. There were proofs that the rectal filling did the great deal in the prostate motion, especially on vertical direction. Ghilezan et al.[8] found that a prostate displacement of <3 mm (90%) can be expected for 20 min after the moment of initial imaging for patients with an empty rectum. This was not the case for patients presenting with full rectum. A full rectal state was invariably associated with mobile gas pockets responsible for the elevated levels of prostate motion. de Crevoisier et al.[9] found strong evidence that rectal distension on the treatment planning CT scan decreased the probability of biochemical control, local control, and rectal toxicity in patients who were treated without daily image-guided (IG) prostate localization, presumably because of geographic misses. Therefore, an empty rectum was warranted at the time of simulation. These results also emphasized the need for IGRT to improve local control in irradiating prostate cancer. IGRT has been widely used to improve targeting accuracy for prostate cancer treatment. In the current standard of clinical practice, daily online IGRT is used to correct interfaction translational target displacement. After online repositioning, the prostate is expected to be in the planned position.

However, recent evidence indicated that prostate deformation over a course of fractionated prostate radiotherapy may not be insignificant and may need to be accounted for in the planning margin design. A consequence of these results was that use of highly reduced planning margins must be viewed with caution. In our hypofractionated cohort, a more strict rectal management was conducted. Mayyas et al.[10] found that prostate deformation was assumed to be a secondary correction and was typically ignored in the PTV margin calculations. This assumption needs to be tested, especially when planning margins are reduced with daily image-guidance. The results showed that deformation of the prostate was most significant in the anterior direction. Deformation of the SVs was most significant in the posterior direction. Prostate deformation was found to be poorly correlated with rotation.

Intrafractional deviation is preferred to the movement of the prostate during prostate cancer radiotherapy. The phenomena such as motions of the pelvis, contractions of the muscles, movements of breathing, and gastrointestinal peristalses are the common reasons. Budiharto et al.[11] drew the conclusions that the RSEs was the main contributor to intrafractional motion. This RSE after online prostate localization and patient repositioning in the posterior direction emphasized the need to speed up the marker match procedure. Furthermore, prostate IMRT treatment should be administered as fast as possible to ensure that the pretreatment repositioning efforts were not erased by intrafractional prostate motion. The pre-CBCT images contained interfraction patient position and organ variations whereas the posttreatment CBCT images contained residual variations from the daily correction. The shortage of our study was that post-CBCT was not repeated. To induce intarfraction deviation, an optimized workflow with the use of faster treatment techniques, VMAT, is warranted.

There was evidence that definitive IG-IMRT for prostate cancer was well tolerated and also identified dose thresholds for the absolute volume of anterior rectal wall, above which patients were at greater risk of early and late complications. Peterson et al.[12] found that rectal adverse events (AEs) were a major concern with definitive RT treatment for prostate cancer. The anterior rectal wall was at the greatest risk of injury as it lied closest to the target volume and received the highest dose of RT. They enrolled a total of 111 consecutive patients with Stage T1c to T3aN0M0 prostate cancer who underwent IG-IMRT. Early AEs occurred in most patients (88%); however, relatively few of them (13%) were Grade 2. At 5 years, the cumulative incidence of late rectal AEs was 37%, with only 5% being Grade 2. Gauthier et al.[13] studied twenty patients and drew the conclusions that with FM-kV, the prescription dose could be increased by 2.1 Gy while keeping the same level of late rectal toxicity as with the traditional setup. Use of FM-kV was an efficient way of lowering the proportion of patients not fulfilling radiation therapy oncology group rectal and bladder dose-volume constraints. Results of the normal tissue complication probability analysis suggested that the PTV margin reduction allowed by FM-kV should decrease the rate of late rectal toxicities or may allow moderate dose escalation.

To compute the magnitude of a PTV-margin that allows the CTV receive the prescribed dose with a clinically acceptable and specified probability, statistics of all uncertainties in the treatment process chain should be known. Geometrical uncertainties in RT include both treatment preparation variations and execution uncertainties. They both can be systematic such as equipment maladjustments, planning setup uncertainties, and target volume delineation or random such as treatment setup uncertainties, inter- and intra-fraction organ motion. Langsenlehner et al.[14] noted that with daily online correction and repositioning based on implanted fiducials, a significant reduction of PTV margins can be achieved. The use of an optimized workflow with faster treatment techniques such as VMAT could allow for a further decrease, especially in hypofractionated cohort.

IGRT using CBCT imaging in combination with conformal RT techniques such as IMRT or VMAT potentially allows smaller treatment margins and escalates dose to the prostate. Rudat et al.[15] found that a relevant combined patient setup and prostate motion population random error of 4–5 mm was observed. Compared to daily IGRT, image guidance every other day required an expansion of the CTV–PTV margin of 8.1 mm, 6.6 mm, and 4.1 mm in the longitudinal, vertical, and lateral directions, thereby, increasing the PTV by approximately 30–40%. No Grade 3 or 4 acute radiation reactions were observed with daily IG-IMRT. Thus, a high dose with surprisingly low acute toxicity can be applied with daily IG-IMRT using implanted fiducial prostate markers. Daily image guidance was clearly superior to image guidance every other fraction concerning adequate target coverage with minimal margins. Oehler et al.[16] gave indications that for IGRT, CBCT, or kV/kV-image pairs with fiducial markers were interchangeable in respect of accuracy. Especially for hypofractionated RT, PTV margins can be kept in the range of 5 mm or below if stringent daily IGRT, ideally including prostate tracking, was applied. Palma et al.[17] reported that the most favorable equivalent uniform doses and lowest doses to organs at risk were achieved with variable dose rate VMAT, which was statistically significantly better than 5-field, step-and-shoot IMRT for rectal and femoral head dosimetric endpoints and better than constant dose-rate VMAT for most bladder and rectal endpoints.

Several recent studies have evaluated the use of VMAT delivery methods in prostate cancer. VMAT involves gantry rotation around the prostate using 14 arcs while the X-ray beam is on. Compared with IMRT, the potential advantages of VMAT include a large reduction in MU required to deliver a given fraction size and a concomitant reduction in treatment time. With decreased beam-on time, the intrafraction motion during irradiation is reduced, thus improving confidence that the delivered dose distribution agrees with the plan and with better normal tissue sparing. Fontenot et al.[18] reported that for prostate patients treated for SV involvement,

single-arc VMAT plans were delivered in 1.4 ± 0.1 min (vs. 9.5 ± 2.4 min for fixed-beam IMRT, $P < 0.01$) and required approximately 20% fewer MUs ($P = 0.01$). They drew the conclusion that single-arc VMAT plans were dosimetrically equivalent to fixed-beam IMRT plans with significantly improved delivery efficiency. Mellon et al.[19] compared variable dose rate VMAT with 7-field, step-and-shoot IMRT in prostate cancer patients treated with a consistent PTV to a uniform total RT dose. He studied 32 patients who received 8100 cGy in 45 daily fractions to their prostate and proximal 1 cm of the SVs using variable dose rate VMAT ($n = 22$) or 7-field, step-and-shoot IMRT ($n = 10$) for intermediate-risk or high-risk prostate cancer between July 2010 and April 2013. In 90% of patients, VMAT was delivered with two-arc. The results showed VMAT reduced median radiation beam-on time from 4.3 to 3.4 min ($P = 0.03$). There was no statistically significant difference in PTV volumes between the VMAT and step-and-shoot IMRT groups ($P = 0.76$). VMAT dose distributions were more homogeneous ($P = 0.003$). There was no difference between groups with regard to rectal V60, V65, V70, V75, bladder V65, V70, V75, V80, or femoral heads V33. They drew the conclusions that two-arc VMAT resulted in shorter beam-on times and more homogenous dose distributions than 7-field, step-and-shoot IMRT for prostate cancer. Onal et al.[20,21] found that VMAT was advantageous in sparing OARs and required less MU than IMRT. Additionally, no dosimetric advantage of higher energy was observed. They also selected 12 intermediate risk prostate cancer patients treated with prostate and SV radiotherapy to compare single-arc VMAT and 7-field IMRT treatment plans. For all patients, the prescribed dose was 78 Gy delivered in 39 fractions. The results showed the normal tissue surrounding the target was lower in VMAT plans compared with IMRT plans. VMAT plans achieved lower doses to all OARs for nearly all dosimetric endpoints. VMAT plans achieved 9.4%, 9.0% and 7.0% relative decrease in MUs required for RT delivery, for 6, 10 and 15 MV energy levels, respectively. The target volume and OAR dosimetric values did not differ significantly between 6, 10 and 15 MV photon energies. VMAT plans were found to be dosimetrically equivalent to IMRT plans for prostate cancer patients, with better rectum and bladder sparing and fewer MUs required.

Compared with IMRT, there were more advantages of VMAT to deliver hypofractionated radiotherapy in prostate cancer. Gladwish et al.[22] studied a total of 150 image pairs obtained from thirty patients who underwent extreme hypofractionated radiotherapy to a dose of 40 Gy in five fractions on standard linear accelerators. They found the prostatic displacement over the course of hypofractionated radiotherapy, delivered via VMAT, continued to be small. This suggested that the margins utilized in standard fixed-angle hypofractionated IMRT are adequate. An inherent benefit of VMAT is shorter treatment times, which becomes progressively more significant as the use and degree of hypofractionation increases. A secondary benefit of shortening treatment times may be to limit the organ motion uncertainty that would otherwise be associated with this hypofractionation. It showed that the use of VMAT in extreme hypofractionation may limit prostatic motion uncertainties that would be associated with longer treatment times.

In conclusion, to deliver the hypofractionated radiotherapy in prostate cancer, VMAT statistically significantly decreased beam-on time relative to 7-field, step-and-shoot IMRT. Decreased radiation beam-on time improves one's confidence that the dose distribution was being delivered as planned. A shorter beam-on time may allow one to reduce margins on the CTV, thereby decreasing the dose of radiation delivered to adjacent normal tissues. VMAT plans also had an increased PTV D95% dose and more homogeneous dose distributions. Better management of bladder and rectum, daily online image-guidance will make a more precision treatment.

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Conflicts of interest

There are no conflicts of interest.

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