Frequency and Predisposing Factors for Interfractional Rectal Displacement Requiring Repeated Precaution in Prostate Cancer Patients Treated with Image-Guided Intensity-Modulated Radiation Therapy

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Abstract. *Aim: To investigate the frequency and characteristics of interfractional rectal displacement in patients with prostate cancer treated with image-guided intensity-modulated radiation therapy (IG-IMRT) using helical tomotherapy. Patients and Methods: Data for a total of 256 patients were analyzed. Megavoltage computed tomography (MVCT) images were acquired before radiation therapy and interfractional rectal displacement was assessed with soft-tissue matching by comparing treatment planning images within 9,445 fractions. Anterior rectal region displacement larger than 5 mm, requiring repeated precaution, was defined as the action level of rectal displacement (ARD). Results: ARD was identified in 676 (7.2%) out of 9,445 fractions and at least once in 75% (190/256) of patients. Univariate analysis identified three predisposing factors for ARD: body mass index (BMI), rectal volume and prostate volume. Multivariate logistic regression analysis revealed that lower BMI and large rectal volume were statistically significant predictors of ARD. The highest incidence of ARD (13.6% and 9.1%) was found during the initial two weeks of treatment (first five and next five fractions), after which the incidence decreased to 5.96% (p<0.0001). Conclusion: ARD was identified in 7.9% of fractions and in 74.8% of patients and was most likely to occur in patients with a low BMI and/or large rectal volume. ARD occurred predominantly during the initial two weeks of treatment and became less likely over time.*

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Radiation therapy is one of the most widely used treatments for localized prostate cancer. With the development of radiation techniques, such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), it is possible to deliver higher prescribed doses with few serious adverse reactions (1). This process enables the delivery of accurate radiation therapy with a reduction in the size of the set-up margin and, therefore, a smaller planned target volume (PTV) (2). Helical tomotherapy is a form of IMRT with the ability to acquire megavoltage computed tomography (MVCT) images of a patient in the treatment position before therapy. This precise positioning using CT images allows not only for correct bone position (bone matching) used in conventional radiation therapy and suitable for bone lesions (2) but also for the visualization and identification of the position of organs, such as the prostate, rectum and bladder (soft-tissue matching). In our Unit, we identified interfractional rectal displacement using repeated MVCT before treatment and correct patient positioning using couch adjustment, a process known as image-guided IMRT (IG-IMRT) (3-6). However, we sometimes encountered considerable rectal displacement, which is sometimes impossible to correct using couch adjustment. We define this degree of displacement as the action level of rectal displacement (ARD). In these cases, the patient gets up from the couch and is instructed to drink water to fill the bladder and/or to void the rectum. A rectal enema is prescribed in several cases. The aim of the present study was to analyze the characteristics and predisposing factors for ARD, because ARD may not only cause treatment failure and/or toxicities but also be a bothersome phenomenon both for medical staff and patients.

Patients and Methods

Patients and patients' management. We investigated 256 male patients with prostate cancer who received IG–IMRT using helical tomotherapy (HI-ART TomoTherapy Inc., Madison, WI, USA) between 2009 and 2013. The patients were aged between 48 and 86 years (median=72 years). The patients' characteristics are presented in Table I. Details of the treatment have been described elsewhere (3, 4). In brief, vacuum cushions (Blue Bag, Medical Intelligence, Schwabmûenchen, Germany) were used to immobilize the patients in the supine position. Kilovoltage CT planning images were acquired for each patient (2-mm slice thickness), including a minimum of 5 cm above and below the level of the PTV (Aquilion 64; Toshiba Medical Systems Inc., Tokyo, Japan). The prostate gland and seminal vesicles were contoured as the clinical target volume (CTV) with the aid of fused magnetic resonance imaging (MRI) images. The primary PTV was defined by margins of 3 mm posteriorly and 5 mm in all other dimensions around the prostate gland and seminal vesicles (4). The prescribed dose was 72 Gy in 36 fractions for patients in the low-risk group and 74 Gy in 37 fractions for patients in other risk groups, set as D95 (*i.e.*, 95% of the PTV received the prescribed dose). The bladder and rectum (contoured from anal verge to rectosigmoid junction) were defined as risk organs and the major constraints during inverse planning were that no more than 35% of the rectal volume and no more than 50% of the bladder volume would receive 40 Gy of radiation. Patients were routinely instructed to empty the rectum, but not the bladder, 1 h before treatment. Patients took magnesium oxide (1 g/day) and dimethicone (80 mg 3 times a day, a total of 240 mg/day) 7 days prior to planning CT until the completion of treatment. If necessary, the dosage was altered according to patient response. MVCT images (3.5 MV) were acquired through PTV before treatment delivery, with a minimum slice thickness of 4 mm and a field of view of 35 cm. The first MVCT images were taken and autofused with the kilovoltage CT treatment planning images, and the superior–inferior, anterior–posterior and right–left shifts were then calculated using automatic image fusion for bone matching. The fused images were manually inspected for prostate soft-tissue matching and verified and corrected by two clinicians (rotational corrections were not implemented at the time of this study). Patients were then shifted into the calculated position by adjusting the couch. We defined ARD if most anterior rectal region moved larger than 5 mm and could not be corrected using couch adjustment (Figure 1). In these cases the patient was asked to get up from the couch and to void the rectum. If necessary, a rectal enema was used to dislodge large-volume rectal stool and/or rectal gas. A second set of MVCT images were acquired to verify that the prostate shift had been corrected. If ARD persisted, further correction was implemented. The total time between image acquisition and treatment delivery was typically less than 10 min. However, if ARD occurred, the time delay could be in the range of hours. We investigated the frequency and characteristics and predisposing factors for ARD.

Statistical analysis. All statistical analyses were performed using the Stat-view 5.0 statistical software (SAS Institute, Inc., Cary, NC, USA). The percentage values were analyzed using the χ^2 test and means were compared using the Student's *t*-test. Variables that had *p*-values <0.10 were tested further in multivariable analysis using a logistic regression model. All analyses used the conventional $p<0.05$ level of significance.

Table I. *Patients' characteristics.*

Variables		No. or median (range)
Age	(years)	72 (48-86)
Height	(m)	1.65 (1.5-1.85)
Body weight	(kg)	62 (42-95)
Body mass index	(kg/m^2)	23.3 (14.9-30.5)
Dose / fractions	74 Gy/37 fractions	229
	72 Gy/36 fractions	27
T category	T1:T2:T3a:T3b:T4:NA	79:108:50:13:3:3
Planned target volume (PTV)	(cm^3)	84.3 (31.6-217.6)
Prostate volume	(cm^3)	39.9 (15.5-136.)
Bladder volume	(cm^3)	158.9 (45.2-488.8)
Rectal volume	(cm^3)	40.9 (19.5-198.3)

Results

We treated 256 patients with 72 Gy/36 fractions (27 patients) or 74 Gy/37 fractions (229 patients). In total, 9,445 fractions and 10,279 MVCT images were analyzed for deviations of the prostate using soft-tissue matching. ARD occurred in 676 fractions (7.2%) out of 9,445 fractions (median, 2 ARD fractions in a patient; range, 1-15 ARD fractions in a patient). During the treatment course with 36-37 fractionations, 54 patients experienced 1 ARD, 27 two ARD, 35 three ARD, 24 four ARD and 51 five or more ARD during the treatment course. 75% (190/256) of patients experienced ARD at least once.

The highest incidence of ARD (13.6% and 9.1%) was found during the initial two weeks of treatment (first five and next five fractions), after which the incidence decreased to 5.96% (Table II) ($p<0.0001$). 137 patients (54%) showed ARD twice or more during treatment fractions. The predisposing factors for ARD are presented in Table III. Univariate analysis identified three predisposing factors for ARD: body mass index (BMI), rectal volume and prostate volume. The 191 patients with ARD had lower BMI (22.9±2.79 kg/m^2), larger prostate volume (44.9±18.7 cm^3) and larger rectal volume (44.8±16.5 cm^3) than their 65 counterparts (BMI 23.7±2.5 kg/m^2, prostate volume 39.5±13.5 cm^3 and rectal volume 37.9±10.9 cm^3). Multivariate logistic regression analysis revealed that BMI (odds ratio (OR)=0.404, 95% Confidential interval (95% CI)=0.201-0.815, p=0.0113) and rectal volume (OR)=3.458, 95% CI=1.949-6.468, p=0.0001) were identified as statistically significant predisposing factors for ARD (Table IV).

We examined the background characteristics of 51 patients with particularly high frequent occurrence of ARD (≥5 fractions during 36–37 fractions: 20%). BMI (OR=0.300, 95% CI=0.158-0.572, p=0.0003) and rectal volume (OR=2.553, 95% CI=1.297-5.065, p=0.0068) were identified as predisposing factors causing frequent occurrence of ARD.

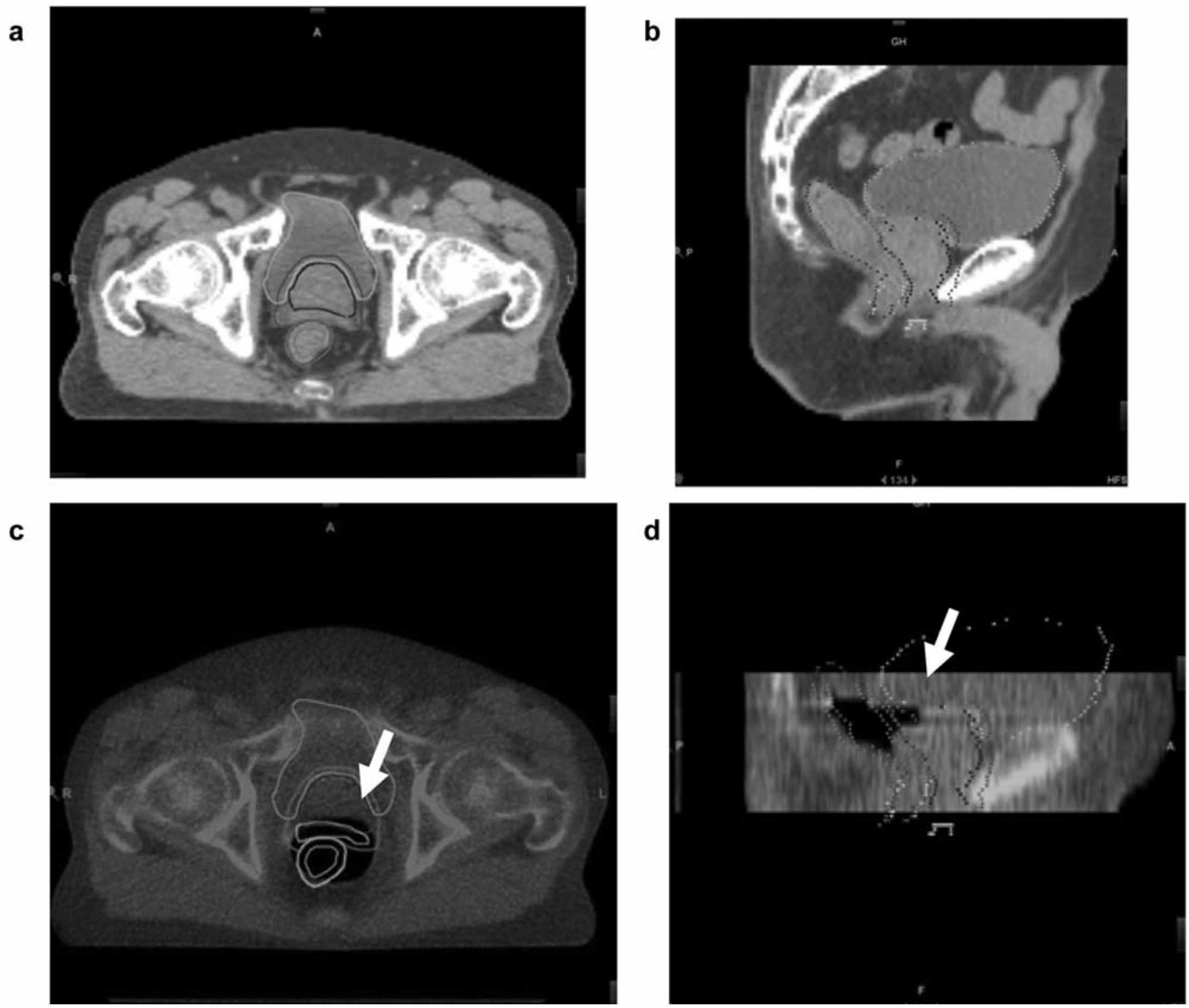

Figure 1. *Scheme of action level of rectal dislocation (ARD) required rectal voiding. a) Axial planning CT images (kVCT) and contour of organ at risks, b) saggital planning CT images (kVCT) and contour of organ at risks, c) axial MVCT image. At the first MVCT scan, this patient's rectum, showed large volumes of gas. Note displacement of rectal contour ≥5 mm compared to previous planning CT images. Arrow indicates rectal gas expansion into PTV, d) Sagittal MVCT image. Arrows indicate rectal gas expansion.*

Discussion

The use of IGRT facilitates precise target location from bone-structure matching to soft-tissue matching. This is particularly important in radiotherapy of prostate cancer because the position of the prostate gland varies with the filling and emptying of the bladder and rectum (7). Several correctional strategies, including implanted fiducials (8) and online three-dimensional CT imaging (9), have been developed and clinically implemented. Prostate matching was not possible in the bone matching era as a result of the lack of soft-tissue contrast in portal images (10-13). Previous studies have revealed that bone matching required PTV margins of 4.7-10.5 mm, 7.4-12 mm and 1.4-4.4 mm in the AP, SI, and LR dimensions, respectively (14-15). Soft tissue matching IG–IMRT enables the use of smaller PTV margins compared to bone matching IMRT (4-6). Several authors, including a researcher from our Institution (4) have assessed intrafractional prostate motion and reported that a 3-5 mm intrafractional margin was adequate for prostate dose coverage, except for seminal vesicle dose coverage (5, 6, 14, 15).

Table II. *Occurrence of action level of rectal displacement (ARD) according to treatment time course.*

	Number of ARD	Total fraction number	(%)	*p*-Value
Initial week (1-5 fractions)	174	1280	13.6%	<0.0001
Second week (6-10 fractions)	116	1280	9.1%	
Third week (11 fractions)-	386	6885	5.6%	

Table III. *Risk factor for action level of prostate displacement (ARD).*

		ARD (–) (n=65)	ARD (+) (n=191)	*p*-Value
Age	(years)	72±6	72±6	0.73
Height	(m)	1.65±0.05	1.65±0.06	0.35
Body weight	(kg)	64.4±6.87	62.6±9.37	0.25
Body mass index	(kg/m^2)	23.7±2.50	22.9±2.79	0.035
Dose/fractions	74 Gy/37 fractions	62	167	0.1
	72 Gy/36 fractions	3	24	
T category	T:;T2:T3:T4:NA	20:31:13:0:1	59:77:50:3:2	0.65
Prostate volume	(cm^3)	39.5±13.5	44.9±18.7	0.0327
Planned target volume (PTV)	(cm^3)	83.9±26.4	95.8±48.2	0.06
Bladder volume	(cm^3)	174±70.8	187±133	0.45
Rectal volume	(cm^3)	39.9±10.9	44.8±16.5	0.0021

The mean and standard deviation (SD).

Table IV. *Results of multivariate logistic regression model for action level of rectal displacement (ARD).*

Variable		Multivariate analysis (*p*-value)	
		ARD (n=191)	ARD ≥5 fractions (n=52)
Body mass index (kg/m^2)	<22 *vs*. 22-	0.0113 OR: 0.404 95%CI: 0.201-0.815	0.0003 OR:0.300 CI:0.158-0.572
Prostate volume (cm^3)	<40 *vs*. 40-	0.2049	0.3402
Planning target volume (PTV) (cm^3)	<94 *vs*. 94-	0.0683	0.4066
Rectal volume (cm^3)	<40 *vs*. 40-	0.0001 OR: 3.458 CI: 1.949-6.468	0.0068 OR: 2.563 CI: 1.297-5.065

OR, Odds ratio; 95%CI, 95% confidential interval.

On the other hand, MVCT occasionally revealed irregular rectal morphological changes (*e.g.*, partial rectal expansion; Figure 1), which was sometimes impossible to correct using couch adjustment. Our results demonstrated that patients with large rectal volume and/or low BMI were more likely to show rectal displacement. Large rectal volume identified on planning CT images has previously been reported as a predisposing factor for rectal bleeding or prostate-specific antigen (PSA) failure (16, 17). This could be partly explained by our finding that larger rectal volume correlated with frequent prostate displacement during radiotherapy. Stasi *et al*. also pointed out the importance of rectal volume control before and during radiotherapy (18). In the present study, a lean body (low BMI) was also identified as an important predisposing factor for ARD. To our knowledge, this is the first documentation of this finding in the literature. The increased occurrence of the ARD in patients with low BMI may be because lean patients have a small amount of abdominal muscles and/or supporting tissue, allowing for free movement of organs if not adequately corrected during preparation for treatment. It is plausible that ARD occurs more frequently during the first week of treatment and then decreases, because patients get used to the process of radiotherapy over time. Patients are tense and anxious during the first week but, as they become accustomed to radiotherapy, the muscles tend to become more relaxed.

There are several limitations to the present study. At first, this is a single-institutional retrospective analysis with limited experiences for soft-tissue matching IG-IMRT. Next, we did not use several procedures that have been reported to reduce rectal movement, such as hydrogel spacers (20) or rectal enemas (18, 21). This is probably the reason we initially experienced a few rectal bleeding cases after enema in patients with hemorrhoid; however, it is not totally justified. At last, we could not assess real time rectal movement during irradiation. These problems were left for further research.

In conclusion, ARD occurred most frequently during the initial two weeks of treatment and became less likely over time. Particular caution is required for patients with low BMI/or larger rectal volume.

Conflicts of Interest

The Authors state no conflicts of interest.

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