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Evaluation of image-matching and prostate movement angle using anatomical characteristics obtained from planning computed tomography

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ABSTRACT

Introduction: Setup errors and prostate movement may be associated with individual patient anatomy and internal physiological conditions. We evaluated image-matching and angle of prostate movement during prostate radiotherapy using anatomical characteristics.
Methods: We included 103 patients who underwent prostate volumetric-modulated arc therapy. Body mass index (BMI) and the volumes of the lesser pelvic cavity, bladder, rectum, and prostate were measured using planning computed tomography. Patients were divided into small- and large-value groups according to the median value of each anatomical characteristic. The medians and standard deviations of bone setup errors and inter- and intra-fraction prostate movements were calculated in the anterior–posterior (AP), left–right (LR), and superior–inferior (SI) directions using pelvic bone and fiducial markers with the ExacTrac X-ray system. Prostate movement angles were calculated from the approximation equation of correlation between the AP and SI direction for both groups (rectum volume, bladder capacity).
Results: The average setup errors in the LR direction exhibited a moderate positively correlation ($r = 0.43$) with lesser pelvic cavity volume in the small-value group, and a moderate negative correlation ($r = -0.45$) in the large-value group, as determined by BMI and lesser pelvic cavity volume. Intra-fraction prostate movement angles were tilted 6.7° in the AP direction in the large rectal volume group and 3.1° in the SI direction in the large bladder volume group.
Conclusions: Image-matching and prostate movement angles differed between groups stratified according to patient anatomical characteristics, suggesting the potential utility of anisotropic margins and careful patient setup.
Implications for practice: Evaluating patient-specific anatomical characteristics before radiotherapy planning may help estimate susceptibility to setup errors and facilitate the definition of anisotropic margins based on individual prostate movement angle information.
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Introduction

Prostate cancer can be treated using several modalities, including robot-assisted surgery, iodine-125 brachytherapy, and external beam radiotherapy, the latter of which requires daily management of the patient's internal organs.[1–5] In high-precision radiotherapy for prostate cancer, image-guided radiotherapy is essential for identifying setup errors and mitigating the impact of intra- and inter-fraction prostate movement throughout the treatment course.[6,7]

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Patients undergoing radiotherapy exhibit a range of body types,[8,9] which may influence setup errors, as well as the spatial relationship between the bone and target.[8] In patients with obesity, accurate patient setup can be challenging because of mobile surface anatomy and differences in prostate movement due to the influence of visceral fat density.[8,10] Patient-specific robust treatment planning can improve treatment accuracy without requiring expensive equipment.[11,12] Although robust radiotherapy can improve target dose coverage by increasing the radiation dose in the direction of target movement,[11] uncertainties in managing movement in the irradiation direction may result in over- or underdosage. Therefore, accurate information regarding individual patient prostate movement is increasingly important.[13]

The prostate is known to move during treatment because of bowel movements and anal sphincter contractions, even during volumetric-modulated arc therapy, which involves only a short irradiation time.[14,15] The position of organs surrounding the prostate varies daily because of multiple factors, including bladder and rectal volumes, resulting in discrepancies between the planned and delivered radiation doses.[13,16] Therefore, estimating patient-specific prostate movements before treatment planning may facilitate the development of more robust treatment plans.

Pretreatment planning computed tomography (CT) images provide information regarding the condition of a patient's internal organs and may enable accurate estimation of individual patient setup errors and prostate movement during treatment.[4,10,17] We previously evaluated the relationship between prostate movement and patient-specific anatomical characteristics, and Tanaka et al. reported that the lesser pelvic cavity and prostate volumes were associated with prostate movement.[10,15] Although previous studies have examined the relationships between patient-specific anatomical characteristics and the direction and magnitude of prostate movement, few have objectively evaluated prostate movement angles and image-matching accuracy based on the anatomical characteristics of individual patients.

This study aimed to evaluate the relationship between patient-specific anatomical characteristics, stratified into small- and large-value groups, and image-matching accuracy during prostate radiotherapy. We conducted a median split of anatomical data, including pelvis size, body mass index (BMI), fat volume, and rectal volume using treatment planning CT images. Subsequently, we evaluated the relationship between the bony and prostate matching results, as well as the angle of prostate movement during treatment. The patient-specific anatomical characteristics and image-matching evaluated in this study may help identify potential setup problems before treatment based on individual anatomical characteristics. Furthermore, the evaluation of prostate movement angles may contribute to robust radiotherapy planning. This includes using a gimbal mechanism for aligning the prostate movement angles and defining anisotropic margins.

Methods

Patients and equipment

We included 103 patients who underwent prostate volumetric-modulated arc therapy with the placement of a 2-mm diameter fiducial marker. The median age was 74.0 (range, 57–82) years, median height was 166 cm (range, 150.0–180.0 cm), and median weight was 64.8 kg (range, 41.5–115.0 kg). All patients were consecutive cases, and none were excluded. This study was approved by the Institutional Review Board. The sample size for this retrospective study was determined based on feasibility and included patients enrolled during the period approved by the Institutional Review Board. Additionally, we previously evaluated the relationship between a single factor and prostate movement in the same patient population. However, the present study focused on the relationships between multiple factors[15] and prostate movement and movement angles.

Radiotherapy planning CT scans were obtained using an Aquilion LB scanner (Canon Medical, Tochigi, Japan), and digital reconstructed radiographs were generated using a radiation treatment planning system (TPS; Eclipse, version 16; Varian Medical Systems, Palo Alto, CA, USA). Radiotherapy was performed using a Novalis STX linear accelerator (Varian Medical Systems), and image registration was performed using the ExacTrac X-ray system (BrainLAB AG, Feldkirchen, Germany). A total dose of 74–78 Gy in 37–39 fractions (37 fractions, n = 3; 39 fractions, n = 100) was administered. Image registration was performed using the ExacTrac X-ray system based on bony anatomy and fiducial markers before and after treatment, respectively. Patient immobilization was achieved using knee immobilization and foot support, and patients were instructed to maintain a full bladder during treatment. The mean irradiation time for the evaluation of intra-fraction prostate movement was 85.7 s (range, 71.5–150.0 s).

Calculation of setup errors, and inter- and intra-fraction prostate movement

Setup errors in the anterior–posterior (AP), superior–inferior (SI), and left–right (LR) directions, as well as the three-dimensional (3D) distance, were calculated using pelvic bony matching with six degrees of freedom on the ExacTrac X-ray system after patient positioning based on skin markers. Inter-fraction prostate movement was calculated as the difference in each direction, and the 3D distance between the pelvic bone and prostate using fiducial marker matching with three-axis translation using the ExacTrac X-ray system. Intra-fraction prostate movements were calculated using fiducial marker matching results obtained before and after radiotherapy. The 3D distances were calculated using the following formula:

$$3D\ distance = \sqrt{(AP)^2 + (LR)^2 + (SI)^2} \quad (1)$$

The median values and standard deviations (SDs) of the setup errors and inter- and intra-fraction prostate movements were calculated for the distances in the AP, SI, and LR directions, and for the 3D distance.

Calculation of anatomical characteristics

The BMI of the patients was obtained from the hospital information system at the start of radiotherapy. The volumes of the following anatomical characteristics and regions were calculated from planning CT images after contouring using the TPS: lesser pelvic cavity, pelvic cavity, pelvic cavity surrounding the prostate, subcutaneous adipose tissue, visceral fat of the lesser pelvic cavity, prostate, bladder, and rectum. The prostate, bladder, and rectal volumes were contoured by an oncologist, whereas the remaining structures were contoured by a therapeutic radiographer using the TPS. The lesser pelvic cavity was contoured from the pelvic inlet, with the sacral promontory serving as the superior boundary, to include the entire lesser pelvic cavity. Fat volume was calculated by determining the range of CT numbers from −50 to −500 HU using the TPS, excluding organ structures from the lesser pelvis cavity volume. Subcutaneous adipose tissue thickness was measured from the skin to the underlying muscle of the bone using axial planning CT images of the symphysis pubis, as previously described.[10,18] Patients were divided into small- and large-value groups according to the median value of each anatomical

characteristic. Differences in the median setup errors, inter- and intra-fraction prostate movements between the two groups, and trends in anatomical characteristics, were analyzed using radar charts. Because the data were not normally distributed and the sample size was limited, continuous variables were divided into two groups according to their median values. The differences in the median setup errors and inter- and intra-fraction prostate movements were calculated by subtracting the median values of the large-value group from those of the small-value group.

Evaluation of trends in setup errors and inter- and intra-fraction prostate movements between groups according to anatomical characteristics

The relationship between setup errors determined by bony matching and anatomical characteristics was evaluated by combining two patient characteristics to define two groups: patients with a low BMI and small lesser pelvic cavity volume and those with a high BMI and large lesser pelvic cavity volume. Similarly, the relationship between inter- and intra-fraction prostate movements and anatomical characteristics was evaluated by combining prostate and rectal volumes to define two groups: patients with large prostate and rectal volumes and those with small prostate and rectal volumes.

Evaluation of the relationship between prostate movement angle and organs surrounding the prostate

The correlations between inter- and intra-fraction prostate movements in the AP and SI directions were analyzed separately in the small- and large-volume groups for the rectum and bladder. The prostate movement angle (θ) was calculated from the slope of the linear approximation (a), which describes the relationship between movement in the AP and SI directions, using the following equation:

$$\theta = tan^{-1}(a) \quad (2)$$

The differences in prostate movement angles between the small- and large-volume groups for rectal and bladder volume were calculated separately for inter- and intra-fraction prostate movements.

Statistical analysis

Statistical significance was assessed using the nonparametric Mann–Whitney *U* test, and Pearson's correlation coefficients (r) were calculated using SPSS Statistics (version 29.0.2.0; IBM SPSS Statistics, Armonk, NY, USA). Results were considered statistically significant at $p < 0.05$.

Results

Fig. 1 shows radar charts depicting the differences in average setup errors and inter- and intra-fraction prostate movements between the small- and large-value groups for each anatomical characteristic. The setup errors determined by bony matching in the LR direction showed relatively large differences between the groups divided according to body-type-related factors, including BMI and pelvic cavity volume (Fig. 1c). Inter-fraction prostate movements in the AP and SI directions showed relatively large differences between groups divided according to pelvic organ-related factors, including rectal, bladder, and prostate volumes (Fig. 1d and e).

Table 1 summarizes the relationships between setup errors and inter- and intra-fraction prostate movements and anatomical characteristics in the two-factor groups (bone setup error: BMI and lesser pelvic cavity volume; intra- and inter-fraction prostate movement: prostate and rectum volumes). For setup errors in the LR direction, lesser pelvic cavity volume was moderately positively correlated ($r = 0.43$; 95% CI, 0.07–0.69; $p = 0.023$) in the small-value group and moderately negatively correlated ($r = -0.45$; 95% CI, −0.70 to −0.10; $p = 0.014$) in the large-value group (based on BMI and lesser pelvic cavity volume) (Fig. 2a and b and Table 1). Thus, the correlation between setup errors in the LR direction and the lesser pelvic cavity volume differed between the small- and large-value groups (BMI and lesser pelvic cavity volume). The average 3D inter- and intra-fraction prostate movements were correlated with BMI in the large-volume group, defined by the prostate and rectal volumes. Inter-fraction prostate movement showed a moderate positive correlation with BMI ($r = 0.43$; 95% CI, 0.10–0.68; $p = 0.012$), whereas intra-fraction prostate movement showed a strong positive correlation with BMI ($r = 0.57$; 95% CI, 0.28–0.76; $p < 0.001$) (Table 1).

Fig. 2 shows the relationship between the large- and small-volume groups for both prostate and rectal volumes, and inter- and intra-fraction prostate movements. Significant differences in the SD of inter-fraction prostate movement were observed between the two groups in the LR direction ($p = 0.0498$) and for 3D distance ($p = 0.047$) (Fig. 2d). Significant differences in the SD of intra-fraction prostate movement were observed between the two groups in the AP ($p = 0.036$) and SI ($p = 0.012$) directions and for 3D distance ($p = 0.028$) (Fig. 2f).

Figs. 3 and 4 show the relationships between inter- and intra-fraction prostate movements in the AP and SI directions in the small- and large-volume groups, divided according to rectal and bladder volumes. Inter- and intra-fraction prostate movements showed moderate correlations between the AP and SI directions, and the slope of the linear approximation equation differed between the small- and large-volume groups for rectal and bladder volumes. Table 2 summarizes the relationship between prostate movement angle direction for the small- and large-volume groups according to rectal and bladder volumes. The large rectal volume group had a smaller slope and showed a tendency toward greater prostate movement in the AP direction than the small rectal volume group. In contrast, the large bladder volume group had a larger slope and showed a tendency toward greater prostate movement in the SI direction than the small rectal volume group.

The inter- and intra-fraction prostate movement angles for the small- and large-volume groups divided according to rectal and bladder volumes, calculated from the linear approximation equation in the AP–SI direction during treatment, are shown in Table 2. In the large rectal volume group, the intra-fraction prostate movement angle tended to be more inclined toward the AP direction by approximately 7°, whereas in the large bladder volume group, the angle tended to be more inclined toward the SI direction by approximately 3°.

Discussion

This study evaluated the trends in patient-specific setup errors and prostate movement angles using anatomical data acquired from pretreatment CT radiotherapy planning. Radar charts illustrating the relationships between matching errors and anatomical characteristics showed that bony matching tended to be associated with factors related to body shape, whereas prostate movement tended to be associated with factors related to the surrounding organs. These findings suggest that matching errors are influenced by multiple patient-specific factors.[7,19,20]

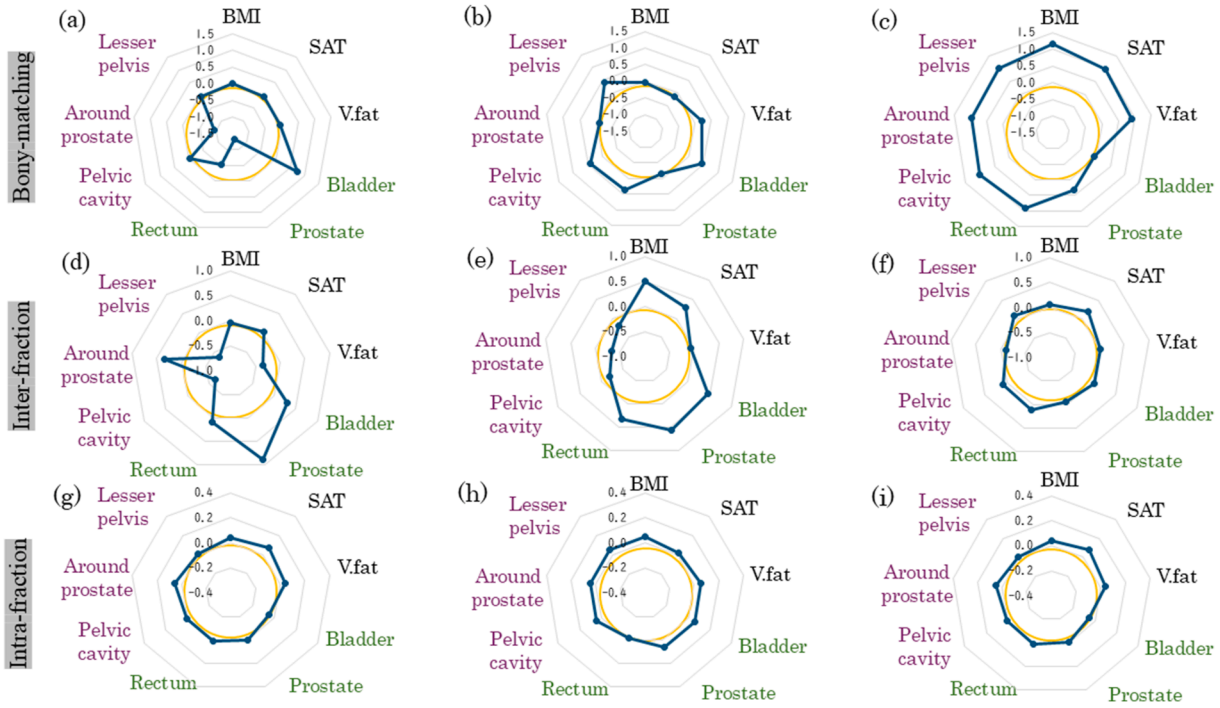


Figure 1. Radar charts showing the differences in the median setup errors and inter- and intra-fraction prostate movements, calculated by subtracting the median values of the large-value groups from those of the small-value groups (Evaluation items: BMI, SAT, V. fat, bladder volume, prostate volume, rectum volume, pelvic cavity volume, pelvic cavity volume around the prostate, and lesser pelvic cavity volume.)
(a–c) Bony matching setup errors: (a) AP (mm), (b) SI (mm), and (c) LR (mm)
(d–f) Inter-fraction prostate movements: (d) AP (mm), (e) SI (mm), and (f) LR (mm)
(g–i) Intra-fraction prostate movements: (g) AP (mm), (h) SI (mm), and (i) LR (mm).
The orange line indicates the zero baseline (no difference).
AP, anterior–posterior; BMI, body mass index; LR, left–right; SAT Subcutaneous adipose tissue; SI, superior–inferior; V. fat, visceral fat volume within the lesser pelvic cavity. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Correlations between setup errors and inter- and intra-fraction prostate movements, and patient-specific anatomical characteristics in small- and large-value two-factor groups.

	Two-factor group	Correlation: r	AP		SI		LR		3D	
			Ave	SD	Ave	SD	Ave	SD	Ave	SD
Bony matching setup error	BMI <23.2 ∩ lesser pelvic cavity <1446.1	Lesser pelvic cavity volume	−0.13	−0.14	0.01	−0.27	0.43	0.1	0.06	−0.03
		BMI	−0.24	0.04	0.07	−0.01	0.26	−0.02	−0.1	0.11
	BMI ≥23.2 ∩ lesser pelvic cavity ≥1446.1	Lesser pelvic cavity volume	0.25	0.13	0.04	0.38	−0.45	−0.06	0.12	0.15
		BMI	0.49	0.26	0.16	0.45	−0.37	0.06	0.3	0.22
Inter-fraction prostate movement	Volume: Prostate <31.7 ∩ rectal <26.5	Prostate volume	0.14	−0.16	−0.01	0.04	0.09	−0.18	0.18	0.11
		Rectal volume	−0.02	−0.05	0.1	0.18	−0.31	0.51	0.18	0.08
	Volume: Prostate ≥31.77 ∩ rectal ≥26.5	Prostate volume	0.38	0.42	0.34	0.44	−0.25	0.39	0.43	0.43
		Rectal volume	−0.13	0.21	−0.15	0.11	0.03	0.21	0.12	0.17
Intra-fraction prostate movement	Volume: Prostate <31.7 ∩ rectal <26.5	Prostate volume	−0.37	−0.13	−0.48	−0.21	−0.22	−0.18	−0.27	−0.03
		Rectal volume	0.06	0.2	0.09	0.45	−0.45	0.25	0.38	0.39
	Volume: Prostate ≥31.77 ∩ rectal ≥26.5	Prostate volume	0.37	0.49	0.33	0.45	0.73	−0.19	0.57	0.33
		Rectal volume	0.26	0.19	0.12	0.17	0.15	−0.08	0.21	0.2

AP, anterior–posterior; BMI, body mass index; LR, left–right; SI, superior–inferior; Ave, average; SD, standard deviation.

The average setup errors in the LR direction exhibited a moderate negative correlation with the lesser pelvic cavity volume in the small-value group, whereas a moderate positive correlation was observed in the large-value group (based on BMI and lesser pelvic cavity volume). We hypothesized that the pelvic bones of thinner patients may be more readily displaced by relatively small forces, whereas in patients with obesity, adjustments may primarily result in skin movement. Variations in fat distribution may affect the mobility of pelvic bones when laser alignment is performed using skin markers placed on the body surface by radiation therapists.[8] Previous studies have examined setup errors associated with weight loss in the head and neck of patients; however, few have quantitatively evaluated this relationship in patients undergoing prostate radiotherapy. The present study is novel in demonstrating the correlation between setup errors and patient-specific factors, including lesser pelvic cavity volume and BMI. These findings may help estimate the magnitude of setup errors and increase pretreatment setup knowledge among staff, thereby facilitating specific precautions during individual patient setup.[21,22]

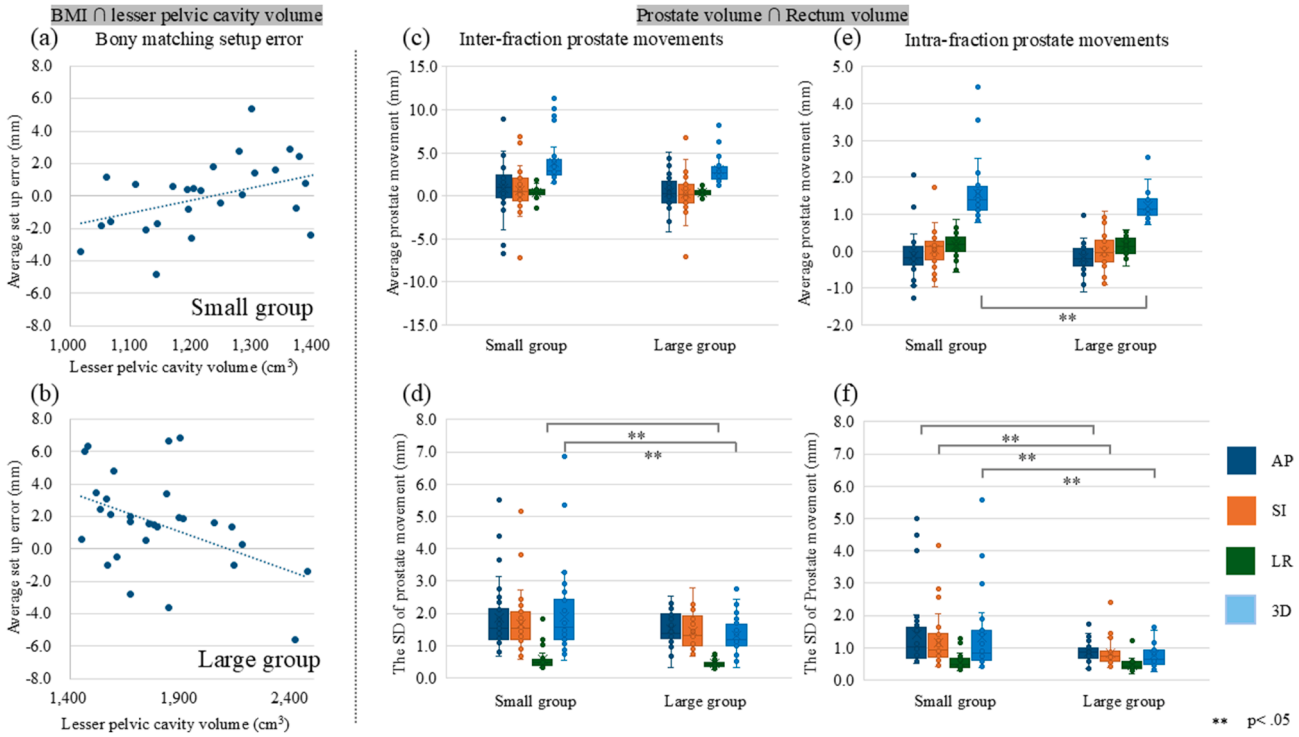


Figure 2. Setup errors determined by bony matching and inter- and intra-fraction prostate movements in the small- and large-value anatomical characteristic groups
(a, b) Relationship between setup error in the LR direction determined by bony matching and lesser pelvic cavity volume: (a) the small-value group (n = 28), comprising patients with low BMI and small lesser pelvic cavity volume, exhibited a moderate correlation (r = 0.43); and (b) the large-value group (n = 29), with a high BMI and large lesser pelvic cavity volume, exhibited a moderate correlation (r = −0.45)
(c–f) Comparisons of mean inter-fraction prostate movements (c), SDs of inter-fraction prostate movement (d), mean intra-fraction prostate movement (e), and SDs of intra-fraction prostate movement (f) between the small- (n = 32) and large- (n = 33) value groups.
Statistical significance was assessed using the nonparametric Mann–Whitney *U* test, with $p < 0.05$ considered significant.
AP, anterior–posterior; BMI, body mass index; LR, left–right; SD, standard deviation; SI, superior–inferior.

Significant differences were observed in the SDs of inter- and intra-fraction prostate movements in terms of 3D distance between the groups categorized by large and small prostate volumes, as well as between the groups with large and small rectal volumes. One possible explanation for the association between prostate movement and rectal volume is that larger prostates have a greater surface area in contact with the rectum, potentially increasing the influence of rectal movement on prostate movement.[15,23] In clinical practice, patients are encouraged to defecate, use laxatives, and release gas to reduce the rectal radiation dose and help control prostate movement.[24,25]

Evaluation of prostate movement in the AP–SI direction according to rectal volume showed that the slope of the approximate line was smaller and movement in the AP direction was greater in patients in the group with large rectal volumes than in those in the small rectal volumes group. The relationship between rectal volume and prostate movement in the AP direction was consistent with the trend reported previously.[23] The difference in intra-fraction prostate movement between the small- and large-rectal-volume groups was approximately 7° in the AP direction. This finding may be explained by the increase in the force exerted on the prostate in the anterior direction as rectal volume increases.[23,24]

In the evaluation of bladder volume, the slope of the approximate line was larger, and movement in the SI direction tended to be greater in patients with large bladder volumes than in those with small bladder volumes. The relationship between bladder volume and prostate movement in the SI direction was consistent with the trend reported previously.[23] During radiotherapy, patients are encouraged to maintain a full bladder to increase bladder volume, suppress prostate movement, and reduce the radiation dose to the bladder wall.[25] Prostate movement in patients with large bladder volumes occurred predominantly in the SI direction, possibly because of contraction of the anal sphincter associated with urine retention.[26,27]

Because prostate movement associated with bladder filling may be variable and can alter the positional relationship between the pelvic bones and prostate, we believe that individualized management of bladder volume is important to prevent bladder distension beyond the patient's physiological tolerance. Additionally, estimating patient-specific prostate movement angles may enable the establishment of anisotropic margins, thereby reducing the risk of underdosage at the target periphery and unintended overdosage to the rectal and bladder walls.

This study has some limitations. First, we did not evaluate changes in the prostate shape or volume during treatment.[19,28] Nevertheless, because prostate deformation is considered minimal during the brief treatment delivery period, our findings provide a useful assessment for robust treatment planning to account for intra-fraction prostate movement.[29,30]

Second, the sample size was relatively small, consisting of 103 patients and approximately 3900 image-matching data points. Additionally, dividing the cohort based on the median value resulted in an imbalance in patient distribution between the two groups. These factors may have limited the statistical power.

Third, the evaluation of inter- and intra-fraction prostate movement was based on three-axis translation and therefore did not

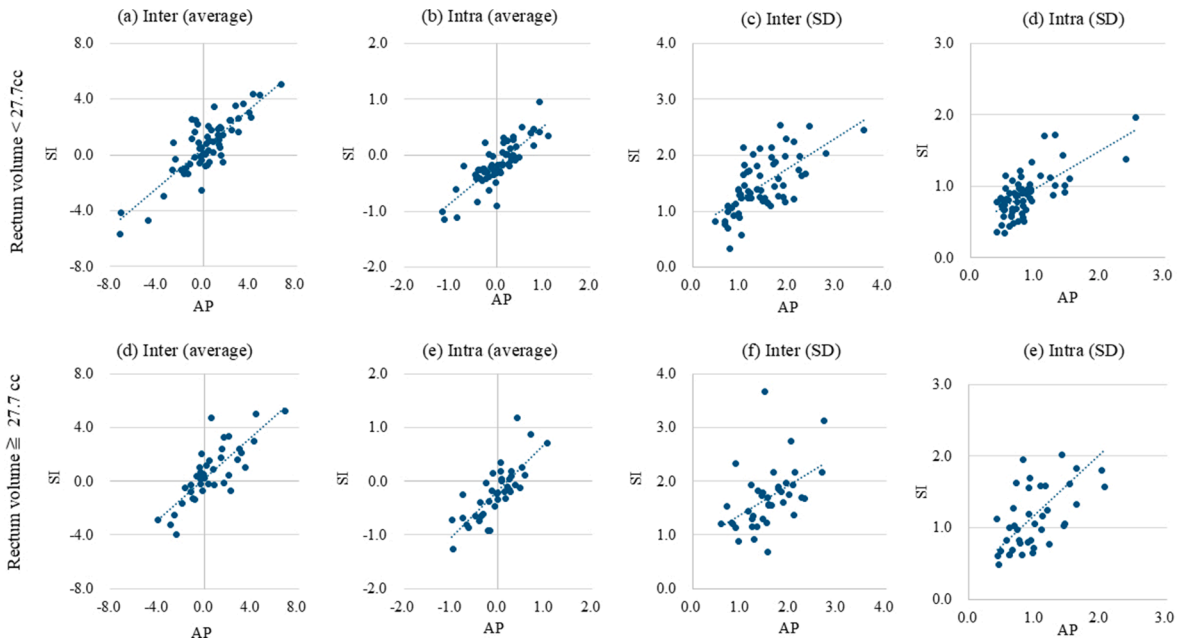


Figure 3. Relationship between inter- and intra-fraction prostate movements in the AP and SI directions in the small- (n = 63) and large- (n = 40) rectal volume groups
(a–d) Rectal volume <27.7 cc: (a) average inter-fraction prostate movement, (b) mean intra-fraction prostate movement, (c) SD of inter-fraction prostate movement, and (d) SD of intra-fraction prostate movement
(e–h) Rectal volume ≥27.7 cc: (e) mean inter-fraction prostate movement, (f) mean intra-fraction prostate movement, (g) SD of inter-fraction prostate movement, and (h) SD of intra-fraction prostate movement.
AP, anterior–posterior; SD, standard deviation; SI, superior–inferior.

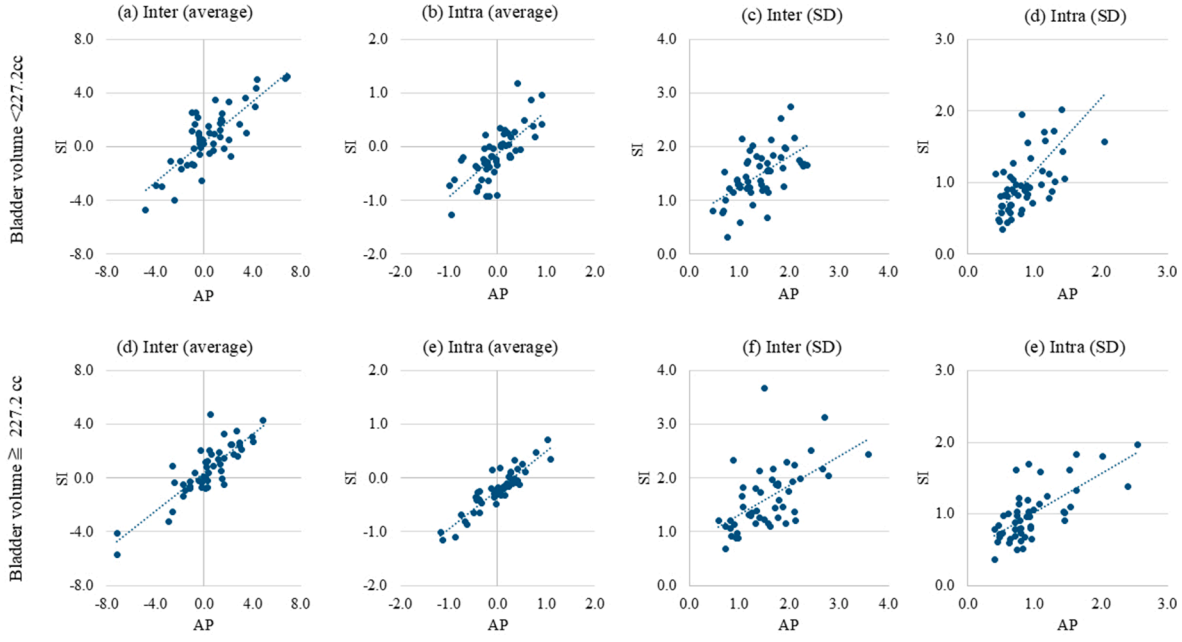


Figure 4. Relationship between inter- and intra-fraction prostate movements in the AP and SI directions in the small- (n = 54) and large- (n = 49) bladder volume groups
(a–d) Bladder volume <227.2 cc: (a) average inter-fraction prostate movement, (b) average intra-fraction prostate movement, (c) SD of inter-fraction prostate movement, and (d) SD of intra-fraction prostate movement
(e–h) Bladder volume ≥227.2 cc: (e) mean inter-fraction prostate movement, (f) mean intra-fraction prostate movement, (g) SD of inter-fraction prostate movement, and (h) SD of intra-fraction prostate movement.
AP, anterior–posterior; SI, superior–inferior; SD, standard deviation.

Table 2
Inter- and intra-fraction prostate movement angles in the small- and large-rectal and bladder volume groups.

Prostate movement angle (°)		Inter-fraction		Intra-fraction	
		Average	SD	Average	SD
Rectal volume	<27.7 cc	54.5	61.1	55.5	62.0
	≥27.7 cc	52.1	61.4	48.8	49.5
	Difference	2.4	−0.3	6.7	12.5
Bladder volume	<227.2 cc	53.2	60.5	51.2	44.3
	≥227.2 cc	54.4	61.6	54.3	61.5
	Difference	−1.2	−1.1	−3.1	−17.2

SD, standard deviation.

account for residual rotational errors. Future studies evaluating the relationship between prostate rotation and patient-specific anatomical structures may provide a better understanding of setup errors and the factors influencing prostate orientation.

Fourth, we did not evaluate the potential dosimetric benefits of incorporating intra-fraction prostate movement angles into robust treatment planning. In future studies, prostate movement angles could be used to determine the angle of incidence for gimbal-based radiotherapy or guide positional adjustments using a six-degree-of-freedom treatment couch, potentially improving treatment robustness and geometric accuracy.[31,32]

Conclusion

Bony matching was associated with BMI and pelvis size, which are related to body shape, whereas prostate matching was associated with pelvic organ volumes, particularly the rectal and bladder volumes. The angle of prostate movement varied with changes in the bladder and rectal volumes. During treatment, the prostate movement angle tended to tilt by approximately 7° toward the AP direction and approximately 3° toward the SI direction in patients with large rectal and bladder volumes, respectively. Evaluating patient-specific anatomical characteristics before radiotherapy planning may facilitate the development of angle-specific robust optimization treatment methods that are more tailored to individual patient characteristics.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Tokuyama Central Hospital (approval number K456-20230,201).

Availability of data

The data used to support the findings of this study are available from the corresponding authors upon reasonable request.

Author contributions

YT: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing.

HT: Data curation, Formal analysis, Visualization, Writing – original draft.

NI: Data curation, Formal analysis, Visualization, Writing – original draft.

AI: Validation, Writing – review & editing.

CI: Validation, Writing – review & editing.

AK: Validation, Writing – review & editing.

YK: Validation, Writing – review & editing.

KN: Conceptualization, Validation, Writing – review & editing.

ST: Validation, Writing – review & editing.

SK: Validation, Writing – review & editing.

AN: Conceptualization, Methodology, Investigation, Data curation, Validation, Writing – review & editing.

Generative AI use

The authors confirm that no Generative AI tools were used at any stage in the preparation of this manuscript.

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Conflict of interest statement

None.

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