



Title	Are simple verbal instructions sufficient to ensure that bladder volume does not deteriorate prostate position reproducibility during spot scanning proton therapy?
Author(s)	Nishioka, Kentaro; Gotoh, Kento; Hashimoto, Takayuki; Abe, Takashige; Osawa, Takahiro; Matsumoto, Ryuji; Yokota, Isao; Katoh, Norio; Kinoshita, Rumiko; Yasuda, Koichi; Yakabe, Toshiaki; Yoshimura, Takaaki; Takao, Seishin; Shinohara, Nobuo; Aoyama, Hidefumi; Shimizu, Shinichi; Shirato, Hiroki
Citation	BJR Open, 3(1), 20210064 https://doi.org/10.1259/bjro.20210064
Issue Date	2021-11-11
Doc URL	http://hdl.handle.net/2115/83300
Rights(URL)	https://creativecommons.org/licenses/by/4.0/
Type	article
File Information	Nishioka et al. - BJROpen - 2021.pdf



[Instructions for use](#)

Received:
14 October 2021

Accepted:
26 October 2021

Cite this article as:

Nishioka K, Gotoh K, Hashimoto T, Abe T, Osawa T, Matsumoto R, et al. Are simple verbal instructions sufficient to ensure that bladder volume does not deteriorate prostate position reproducibility during spot scanning proton therapy?. *BJR Open* 2021; **3**: 20210064.

ORIGINAL RESEARCH

Are simple verbal instructions sufficient to ensure that bladder volume does not deteriorate prostate position reproducibility during spot scanning proton therapy?

¹KENTARO NISHIOKA, MD, PhD, ²KENTO GOTOH, MSc, ¹TAKAYUKI HASHIMOTO, MD, PhD, ³TAKASHIGE ABE, MD, PhD, ³TAKAHIRO OSAWA, MD, PhD, ³RYUJI MATSUMOTO, MD, PhD, ⁴ISAO YOKOTA, PhD, ⁵NORIO KATOH, MD, PhD, ⁶RUMIKO KINOSHITA, MD, PhD, ⁶KOICHI YASUDA, MD, PhD, ⁶TOSHIAKI YAKABE, MD, PhD, ⁷TAKAAKI YOSHIMURA, PhD, ²SEISHIN TAKAO, PhD, ³NOBUO SHINOHARA, MD, PhD, ⁵HIDEFUMI AOYAMA, MD, PhD, ¹SHINICHI SHIMIZU, MD, PhD and ⁸HIROKI SHIRATO, MD, PhD

¹Department of Radiation Medical Science and Engineering, Faculty of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

²Department of Radiation Medical Science and Engineering, Radiation Medical physics, Hokkaido University, Sapporo, Hokkaido, Japan

³Department of Renal and Genitourinary Surgery, Hokkaido University Graduate School of Medicine / School of Medicine, Sapporo, Hokkaido, Japan

⁴Department of Biostatistics, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

⁵Department of Radiation Oncology, Faculty of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

⁶Department of Radiation Oncology, Hokkaido University Hospital, Sapporo, Hokkaido, Japan

⁷Department of Health Sciences and Technology, Faculty of Health Sciences, Hokkaido University, Sapporo, Hokkaido, Japan

⁸Global Center for Biomedical Science and Engineering, Faculty of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

Address correspondence to: Dr Takayuki Hashimoto
E-mail: thashimoto@med.hokudai.ac.jp

Objectives: The purpose of this study is to investigate whether verbal instructions are sufficient for bladder volume (BV) control not to deteriorate prostate position reproducibility in image-guided spot scanning proton therapy (SSPT) for localized prostate cancer.

Methods: A total of 268 treatment sessions in 12 consecutive prostate cancer patients who were treated with image-guided SSPT with fiducial markers were retrospectively analyzed. In addition to strict rectal volume control procedures, simple verbal instructions to void urine one hour before the treatment were used here. The BV was measured by a Bladder Scan just before the treatment, and the prostate motion was measured by intraprostatic fiducial markers and two sets of X-ray fluoroscopy images. The correlation between the BV change and prostate motion was assessed by linear mixed-effects models and systematic and random errors according to the reproducibility of the BV.

Results: The mean absolute BV change during treatment was from -98.7 to 86.3 ml (median 7.1 ml). The

mean absolute prostate motion of the patients in the left-right direction was -1.46 to 1.85 mm; in the cranial-caudal direction it was -6.10 to 3.65 mm, and in the anteroposterior direction -1.90 to 5.23 mm. There was no significant relationship between the BV change and prostate motion during SSPT. The early and late genitourinary and gastrointestinal toxicity was minimal with a minimum follow up of 4.57 years.

Conclusions: Simple verbal instructions about urination was suggested to be sufficient to control the BV not to impact on the prostate motion and clinical outcomes in image-guided SSPT. Careful attention to BV change is still needed when the seminal vesicle is to be treated.

Advances in knowledge: Our data demonstrated that there was no apparent relationship between BV changes and prostate position reproducibility and simple verbal instruction about urination could be sufficient for image-guided SSPT.

INTRODUCTION

External-beam radiotherapy is an established treatment for localized prostate cancer.¹ Proton beam therapy (PBT) is an evolving external-beam radiotherapy with superior dose conformation at the Bragg peak followed by the steep gradient at the end of its range.² This allows reductions in the total dose reaching non-target structures without

compromising tumor dose coverage.³ Spot-scanning proton therapy (SSPT) has become a cutting-edge treatment for prostate cancer improving the dose distribution of PBT further with or without intensity modulation.⁴

Since the radiotherapy is carried out based on treatment planning computed tomography (TPCT) acquired before

the treatment, there is a need to ensure that differences in the prostate position between the treatment plan and the actual position are minimal. Recent advances in image guidance techniques have improved treatment accuracy and clinical outcomes.^{5–8} However, in image-guided SSPT, the water equivalent length of the proton beam pathway from the skin surface to the target may change with volume changes of organs near the prostate and consequently larger margins may be required for robustness.^{9–13} Improvement of prostate position reproducibility in the SSPT is more important than in intensity modulated X-ray therapy (IMXT).

Rectal volume changes affect the position of the prostate.^{14–16} However, the importance of considering bladder volume (BV) changes on prostate position is not commonly agreed on. Previous studies that evaluated the effect of bladder filling on dose-volume statistics in prostate X-ray therapy reported that an increase in the doses to the bladder and bowel loops occurred as a result of treatment plans with small BV.^{17,18} In the real world, considerations to keep a full bladder and the BV constant during fractionated radiotherapy are widely recommended and verbal or written instructions for the patients about the timing of urination and water intake are commonly used without further intervention.^{19–23} However, the compliance to the instructions is not certain, the amount of urine accumulated within a certain period of time can vary among individuals, and daily BV changes can be large even in the same patient.²⁴ From the aspect of value-based health care, strict instruction to the patient about BV control may or may not be recommendable depending on the clinical outcomes after the radiotherapy. In clinical practice, it is important to know whether simple verbal instructions to the patient are sufficient to keep BV changes below the threshold, if one has been set, impacting on the prostate motion also with the precise image-guided radiotherapy. The clinical outcomes and the relationship between BV changes and prostate movements have been reported in the setting of the X-ray therapy; however, these data and the effectiveness of instructions to control BV in the proton setting have not been reported previously.

This study investigated whether simple verbal instructions before radiotherapy are sufficient to maintain a modestly full bladder and keep the variation of BV within limits not to deteriorate prostate position reproducibility and clinical outcomes in image-guided SSPT. Then, correlations between BV and prostate motion and the threshold of BV variations which could improve prostate position reproducibility were investigated.

METHODS

Patients

A total of 268 treatment sessions in 12 consecutive prostate cancer patients treated with image-guided SSPT in our hospital between April and August 2016 were retrospectively analyzed. No patients had received surgical intervention or radiotherapy before the SSPT. Genitourinary (GU) and gastrointestinal (GI) toxicities were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4.0. Acute and late toxicities were defined as side effects occurring within 90 days and after 90 days from the start of

the proton therapy. This study was approved by the Institutional Review Board of our facility for clinical research (016–0210).

Treatment preparation protocol and equipment

Three or four spherical 1.5-mm-diameter fiducial markers were implanted percutaneously in the prostatic gland about one week prior to the TPCT. The TPCT images were acquired with a slice thickness of 1.25 mm from the supine position for all patients using Optima CT580W (GE Healthcare, Waukesha, WI). A vacuum cushion was used to set the patient body and maintain the location of the legs. The patients were verbally instructed to void urine and stool as far as possible and to refrain from urination for one hour before the TPCT. There were neither restrictions nor recommendations for diet or drinking of water before the TPCT. We prescribed laxatives and/or probiotics to patients with constipation. When residual stool or gas was observed in the rectum on the CT images, we evacuated this by catheter or asked patients to void and then acquired images again.

Similarly, instructions for urination and defecation one hour before the treatment were given verbally before each treatment. If residual gas was observed in the patient rectum on the X-ray fluoroscopy on the patient couch at the PBT, the treatment was carried out after evacuation. If the prostate displacement relative to the bone structure determined by two orthogonal X-ray images was more than 5 mm in any direction and 4 mm in the posterior direction, a cone-beam CT (CBCT) was acquired to clarify the cause of the prostate motion. To evaluate the volume change of the rectum, we compared the average rectal cross-sectional area (CSA) on TPCT and CBCT. The average CSA was defined as the average of the rectal area contoured at the level of the prostate.

An image-guided SSPT system (PROBEAT-RT, Hitachi, Ltd., Tokyo) was used for the treatment. Two sets for X-ray fluoroscopy and a six-degree robotic patient couch are used for the precise set-up using bone structures, fiducial markers, and CBCT as described above.

Treatment

The risk of recurrence was classified using the National Comprehensive Cancer Network (NCCN) risk classification.²⁵ In cases where the risk of recurrence was lower than the favorable intermediate risk, only the prostate was defined as the clinical target volume (CTV), whereas in cases where the risk of recurrence was higher than the unfavorable intermediate risk, the seminal vesicle (SV) was also included as CTV in addition to the prostate.

The dose constraints for each target and organ at risk (OAR) are shown in Table 1. Patients whose OAR dose constraints were difficult to achieve with a single field uniform dose (SFUD) were treated with intensity-modulated proton therapy (IMPT). For SFUD, a 3 mm margin that encompassed the internal and setup margins was added laterally to the beam direction. Distal and proximal margins, which were calculated as 3.5% of the distal or proximal range plus 1 mm, respectively, were assigned to account for range uncertainties. For the IMPT planning, robust optimization assuming a setup error of 3 mm and a range uncertainty of

Table 1. Dose constraints for target and organs at risk

Volume	Parameter	Criteria	Acceptable criteria
PTV	D95 (Gy(RBE))	70 Gy(RBE)	-
CTV	D99 (Gy(RBE))	>70 Gy(RBE)	-
	Dmax (Gy(RBE))	<77 Gy(RBE)	<80.5 Gy(RBE)
Rectum	V60 Gy(RBE)	<20%	<30%
	V37.5 Gy(RBE)	<50%	-
Bladder	V37.5 Gy(RBE)	<30%	<50%

CTV: clinical target volume, D95(99): the dose covering 95(99) % of the target, Dmax: max dose, V60(37.5) Gy(RBE): the volume receiving more than 60 (37.5) Gy(RBE)PTV: planning target volume,RBE, relative biological effectiveness.

3.5% was used. In addition, the CTV was geometrically expanded by 4 mm to generate the planning target volume (PTV) for the purpose of the plan evaluation. The relative biological effectiveness (RBE) value was determined to be 1.1 by a previous study and used in the treatment planning.²⁶ Seventy Gy (RBE) was prescribed to 99% of the CTV as well as 95% of the PTV in 30 fractions over 7.5 weeks for all patients. Fiducial markers placed in the prostate may cause dose distortions in proton therapy with a limited number of fields²⁷ and therefore the treatment was performed with three fields from the left and right and the back, or four fields from either side of the slightly anterior and posterior oblique fields. The representative dose distributions for the 3 and 4 field beam arrangements are shown in Figure 1. The beam directions are determined, as far as possible, not to pass through the intestine and bladder, which may change volume daily.

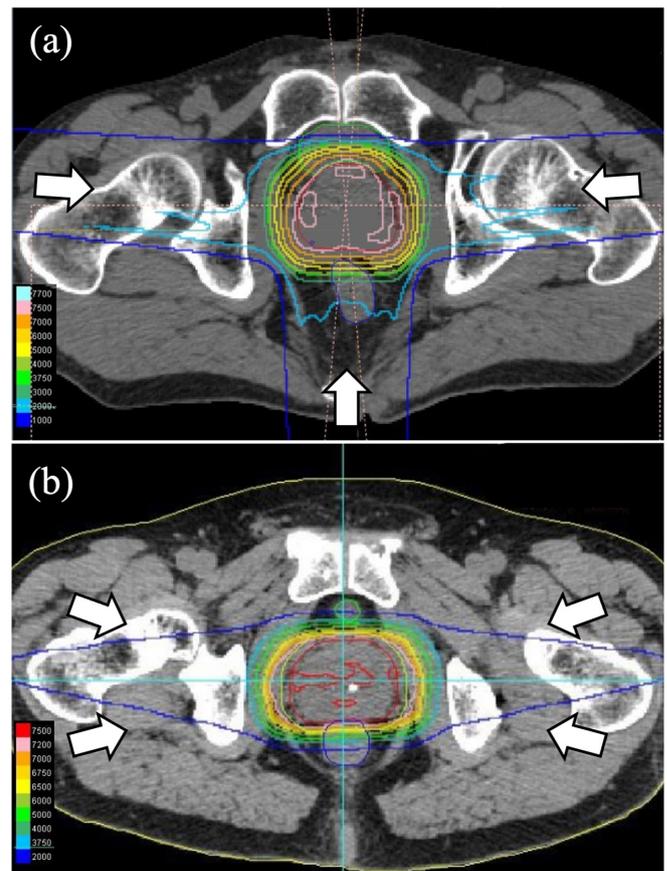
Bladder volume (BV) measurements

The baseline BV was defined as obtained from TPCT images (BV_{TPCT}), calculated by contouring the water dense area in the bladder. Just before the initiation of the treatment, the BV was measured three times with an ultrasound device (Bladder scan BVI9400, Verathon) on the patient couch of the SSPT system. The mean of these three measurements was defined as the BV at the time of treatment ($BV_{Treatment}$). The vendor specifications for the nominal accuracy of the BV measurement is $\pm 15\%$. Previous studies suggested strong correlations between the volumes measured by bladder scan and the CT contoured volume in prostate radiotherapy patients.^{24,28} Since the bladder scan findings are reported to be influenced by the presence of ascites²⁹ and possibly in highly obese patients.³⁰ Therefore, we evaluated ascites by TPCT and obesity by the body mass index (BMI). All BV measurements were performed by the same person.

Prostate position measurements

Initially, registration between the treatment plan and daily set-up of the patient was performed with reference to the bone structure using two simultaneously obtained, orthogonal sets of diagnostic X-ray fluoroscopy images along the anteroposterior and lateral axes. Then, the distance from the planned to the actual position of the fiducial markers was measured in the Left-Right (LR), Cranial-Caudal (CC), and Anteroposterior (AP) directions using the two sets of X-ray fluoroscopy. The distance represents

Figure 1. The representative dose distribution for the 3 (a) and 4 (b) field beam arrangements. The white arrows indicate the direction of proton beams.



the prostate motion relative to the bone structure and includes some degree of uncertainty in bone matching, this distance was termed the prostate motion. The details of this method were reported in a previous study.³¹

Analysis of the correlation between BV changes and prostate motion

The amount of BV changes was defined as the $BV_{Treatment}$ minus BV_{TPCT} . The linear correlation between the BV change and prostate motion was assessed by a linear mixed-effects model. The significance level was set at $p < 0.05$. The statistical analysis was performed using JMP Pro (v. 16, SAS institute, Cary, NC, USA).

If there is a non-linear correlation with a threshold between the BV change and prostate motion, the linear model may not show significance, and we also calculated the systematic error (Σ) and random error (σ) of the prostate position according to the reproducibility of BV and examined whether there was a threshold value for improving the reproducibility of the prostate motion. For a patient i , the mean value (m_i) and standard deviation (σ_i) of the prostate motion were calculated from all of the measurements. The Σ and σ were calculated as the standard deviation of m_i and the root mean square of σ_i among all patients in our cohort. As a provisional threshold of BV change from the BV_{TPCT} , both absolute BV changes (less than 50 ml, 100 ml, 150

Table 2. Patient characteristics and dose volume histogram parameters

Median age (years) (range)	63 (46–75)	
Median number of BV measurements (range)	27 (8–30)	
Mean BMI (range)	23.9 (17.7–35.1)	
Mean BV at TPCT (ml) (range) (1 SD)	78.9 (29.4–196.1) (58.8)	
Median of mean BV at the time of treatment (ml) (range)	79.5 (24.9–142.9)	
Median of mean BV changes (ml) (range)	7.1 (–98.7– + 86.3)	
Tumor stage – No. (%)	T1c	6 (50%)
	T2a	3 (25%)
	T2b	0 (0%)
	T2c	1 (8%)
	T3a	2 (17%)
Hormone therapy – No. (%)	–	6 (50%)
	+	6 (50%)
NCCN risk classification	Low	3
	Favorable intermediate	3
	Unfavorable intermediate	0
	High	6
PTV	Mean D95Gy(RBE) (range)	70.3 (70.0–71.0)
	Mean D99Gy(RBE) (range)	73.1 (71.2–74.3)
CTV	Mean Dmax Gy(RBE) (range)	76.2 (74.7–77.9)
	Mean V60 Gy(RBE) (%) (range)	17.6 (11.2–20.0)
Rectum	Mean V37.5Gy(RBE) (%) (range)	37.2 (28.7–43.2)
	Mean V37.5Gy(RBE) (%) (range)	23.1 (12.5–36.3)
Bladder	Mean V37.5Gy(RBE) (%) (range)	23.1 (12.5–36.3)

BMI: body mass index, BV: bladder volume, CTV: clinical target volume, D95(99): the dose covering 95(99) % of the target, Dmax: max dose, NCCN: National Comprehensive Cancer Network, PTV: planning target volume, RBE, relative biological effectiveness; SD: standard deviation, TPCT: treatment planning computed tomography, V60(37.5)Gy(RBE): the volume receiving more than 60 (37.5) Gy(RBE)

ml, and 200 ml) and relative BV changes (less than 50%, 100%, 150 and 200%) were evaluated.

RESULTS

Patient characteristics and data sets

Details of patient characteristics and dose volume statistics are shown in Table 2. There were two obese patients (BMI 27.7 and 35.1) and none of the other patients exceeded BMI 25. None of the patients had significant ascites on the TPCT images. All treatment plans met dose constraints for both target and organs at risk within acceptable criteria. Ten patients were treated with SFUD and the remaining two were treated with IMPT. The follow-up period for patients from the start of radiotherapy was from 4.57 to 5.15 years (median 4.86 years).

Table 3. Acute and late genitourinary and gastrointestinal toxicities

Acute (within 90 days)– No. (%)	Grade0	Grade 1	Grade 2
Genitourinary toxicities			
Urinary frequency	4 (33.3)	8 (66.7)	0
Urinary incontinence	12 (100)	0	0
Urinary retention	11 (91.7)	1 (8.3)	0
Urinary tract pain	9 (75.0)	3 (25.0)	0
Urinary urgency	9 (75.0)	3 (25.0)	0
Hematuria	12 (100)	0	0
Gastrointestinal toxicity			
Proctitis	8 (66.7)	4 (33.3)	0
Genitourinary toxicities			
Hematuria	11 (83.3)	1 (8.3)	0
Urinary urgency	10 (83.3)	2 (16.7)	0
Gastrointestinal toxicity			
Rectal hemorrhage	4 (33.3)	6 (50.0)	2 (16.7)

Clinical outcomes

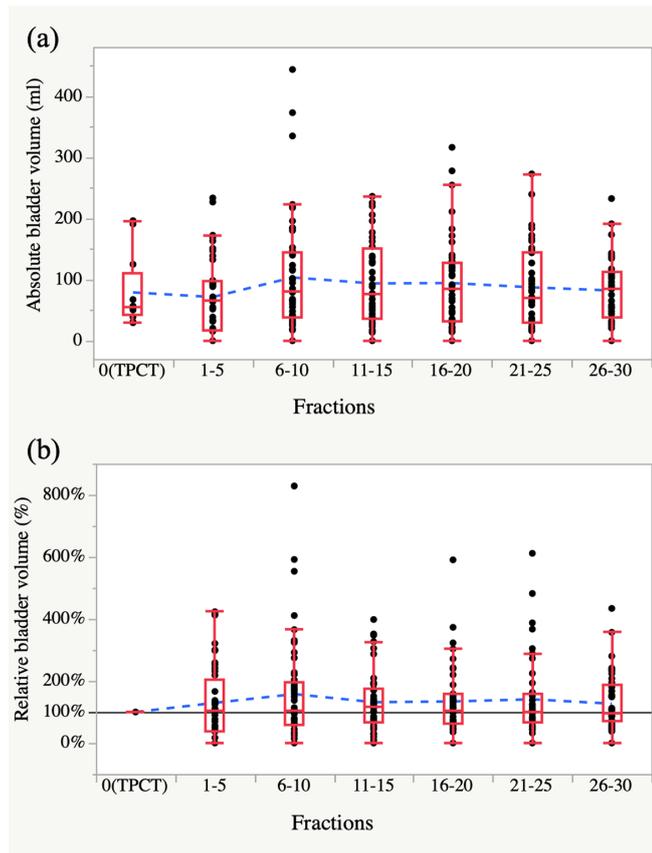
Adverse events, acute and late GU and GI toxicities are shown in Table 3. The BV_{TPCT} and bladder V37.5Gy(RBE) in the two patients who experienced late Grade 1 GU toxicity (urinary urgency) was 196.1 ml and 12.6 %, and 190.7 ml and 12.7%, respectively. Two patients experienced late Grade 2 GI toxicity (rectal bleeding) during the follow-up. The BV_{TPCT}, Bladder V37.5Gy(RBE), Rectum V37.5Gy(RBE) and V60Gy(RBE) of the two patients who experienced Grade 2 GI toxicity were 196.1 ml, 12.6%, 42.7%, and 20.0%; and 56.6 ml, 27.7 %, 36.0%, and 18.4%, respectively. Overall, there was no relationship between the GU/ GI toxicity and BV_{TPCT} or BV change.

One high-risk patient showed prostate-specific antigen (PSA) elevation during adjuvant hormone therapy (luteinizing-hormone releasing hormone agonist) after the SSPT and salvage hormone therapy (complete androgen blockade) was initiated before the PSA value elevated above the nadir +2 ng ml⁻¹. One patient died of another disease (pneumonia) at 4.72 years after SSPT. All other patients survived without recurrence until the final observation period. No relationship was observed between tumor control and BV_{TPCT} or BV changes.

Correlation between bladder volume and prostate motion

The details of the BV_{TPCT}, BV_{Treatment} and BV changes are shown in Table 2. The distribution of absolute BV_{Treatment} of all patients

Figure 2. Absolute (a) and relative values of BV (b) from the treatment planning CT (TPCT) till the end of the treatment (30 fractions). In the box plots, the center line in the box indicates the median, and the upper and lower limits of the box indicate the third and first quartiles, respectively. The maximum and minimum of the whiskers indicate the “third quartile +1.5×IQR” and the “first quartile +1.5×IQR”. The horizontal dashed line is drawn to connect the mean BV values at the respective TPCT fractions. BV: bladder volume, IQR: interquartile range



did not show any significant trend during the treatment course (Figure 2a). The mean relative BV change for the patients was from 48.3 to 252.6% (median 118.0 %). The distribution of relative BV in % also did not show any significant trend throughout the treatment (Figure 2b).

The mean absolute prostate motion from the TPCT position (range of SD in the 12 patients) was from -1.46 to 1.85 mm (0.21 to 0.60 mm), -6.10 to 3.65 mm (0.77 to 2.52 mm), and -1.90 to 5.23 mm (0.58 to 2.19 mm) in the LR, CC, and AP directions, respectively. The positive values indicate that the prostate moved to the left, cranial, and anterior directions in a patient.

The linear mixed effects model showed no significant relationship between the BV change and prostate motion in any direction (Figure 3). The detailed results are shown in Table 4. The largest estimated coefficient of regression (β) was found in the AP direction as -0.140 mm/100 ml (95% confidence interval (CI) was from -0.414 to 0.134 mm/100 ml), and still it showed almost no clinical relationship.

The Σ and σ according to the BV change reproducibility are shown in Table 5. Both Σ and δ of the prostate motion were very little changed regardless of the amount of BV change. The results were the same whether the threshold value was the absolute amount or the relative amount of BV change. These data suggest that there was no apparent non-linear correlation within the range of the BV change and prostate motion.

The CBCT was acquired in six sessions for five patients when a large prostate motion was observed. The relative value of the average rectal CSA and BV based on the area of the TPCT was from 76.4 to 111.8% (median 104.7%) and 21.4 to 371.6% (median 133.4%), respectively. No obvious CSA change was observed in the rectum. In four sessions for three patients with no change in volume observed in either rectum or bladder, it may be speculated that the cause of the prostate motion could be changes in muscle tone in the pelvic floor.

DISCUSSION

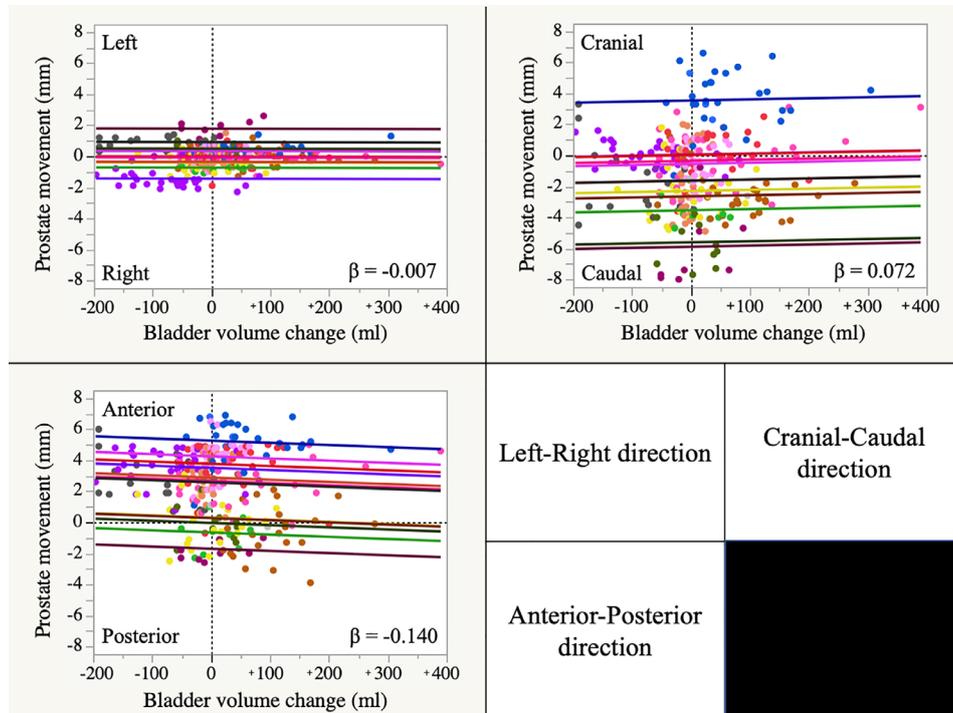
Recently, the effect of BV and BV changes on the prostate position is one of the active debates in the field of X-ray radiotherapy for prostate cancer.^{15,17,18,24,32–37} Theoretically, if BV or BV changes impact on the internal displacement of the prostate, it will obscure the potential benefits of cutting-edge external-beam radiotherapy, such as image-guided SSPT in relation to the conventional treatment.^{9–13}

In the present study, neither Grade 3 or more early and late GU and GI toxicity nor PSA recurrence except for one clinical recurrence was observed in the follow-up period after the image-guided SSPT. We have also seen no impact of BV and BV changes on the early and late clinical outcomes. Regarding the relationship between BV_{TPCT} and BV changes, the amount of the absolute BV change was smaller in our present series compared to previous series.²⁴ This finding, that small BV_{TPCT} resulted in small BV changes, is consistent with many previous studies which reported that the smaller BV_{TPCT} in ml is associated with less BV change in %.^{18,38–40}

Although we have seen small BV in this study compared to the previous reports in X-ray therapy, the early and late GU and GI toxicity was minimal. Recently, Byun et al reported that BV had no impact on early and late GU and GI toxicities in the prostate hypofractionated stereotactic body radiotherapy (SBRT).⁴¹ Chetiyawardana et al also reported findings about the bladder filling for patients with localized prostate cancer after image-guided VMAT administered 60 Gy in 20 fractions with a median follow-up of 48 months (range 36–60 months). They found non-inferiority of an empty bladder filling protocol comparing to a full bladder filling protocol in respect to biological progression-free survival and GU and GI toxicities.⁴² Our clinical findings in image-guided SSPT were consistent with the reports of X-ray therapy from Byun et al and Chetiyawardana et al and, therefore, a bladder-emptying protocol could be preferable by virtue of reducing BV variation. Past studies which found correlations between BV and clinical outcome is for early GU toxicity and needs to be evaluated further for late toxicities but the inclusion of patients who received irradiation or surgery of the pelvis in

Figure 3. Regression plot graphs of the linear mixed effect model. The horizontal axis shows the change in bladder volume from the baseline and the vertical axis shows the movement of the prostate. The color of the data points and fitting lines are different for each patient. The positive values of the vertical axis indicate that the prostate moved to the cranial, left and anterior directions in the patients, respectively.

β : estimated coefficient of regression (mm/100 ml)



their series may be related to the correlation between BV and GU toxicity.^{23,36,40}

In X-ray therapy, Stam et al have published a study which investigated the relationship between BV changes and prostate position using BVI 3000 Bladder scan and fiducial markers in the prostate and found no correlation between BV changes in ml and the prostate motion.²⁴ Stam et al have also shown that simple instructions are sufficient without any further intervention. The results in this study confirm the findings by Stam et al that there was no apparent relationship between BV changes and prostate position during fractionated radiotherapy. However, Pang et al have reported that by using instruction and education, CBCT, and daily transperineal ultrasound BV measurement, BV larger than 200 ml was weakly associated with prostate motion and that there was a reduction in prostate motion in both the CC ($p = 0.008$) and AP ($p = 0.0001$) directions when the daily bladder was filled between 82 and 113% (3rd Quartiles), independent of the BV_{TPCT} .³⁶ It is notable that the Pang et al study included

57.7% of patients who received whole pelvic irradiation before image-guided IMXT or volumetric modulated arc therapy (VMAT) whereas the Stam et al and the present report do not include patients who received pelvic irradiation. Our results cannot refute a relationship between the BV changes and prostate motion for the whole possible range of BV under instruction to the patient but the impact of BV changes on the prostate motion is suggested to be insignificant in the range of BV which we observed and involving just verbal instruction.

As other ways to improve the reproducibility of the prostate position, a rectal balloon would help to immobilize the prostate and reduce intrafractional prostate movements, however, this would not reduce interfractional variations.⁴³ Since the number of sessions of our treatment was large, we did not use a rectal balloon in consideration of the invasiveness for the patients by balloon insertion. However, in the setting of ultrahypofractionated radiotherapy where the number of treatments is small, the dose of one treatment is large, and the treatment time is long, the

Table 4. Estimated coefficient of regression and 95% confidence interval derived from the linear mixed effect model

Left-Right			Cranial-Caudal			Anteroposterior		
β	p	95% CI	β	p	95% CI	β	p	95% CI
-0.007	0.88	-0.099 to 0.086	0.072	0.65	-0.243 to 0.386	-0.140	0.31	-0.414 to 0.134

CI, confidence interval (mm/100ml); β , estimated coefficient of regression (mm/100ml).

Table 5. Systematic (Σ) and random errors (σ) (mm) according to the BV change reproducibility

		Absolute BV changes					Relative BV changes				
		<50 ml	<100 ml	<150 ml	<200 ml	Overall	-50%– +50%	-100%– +100%	-100%– +150%	-100%– +200%	Overall
No. of sessions		162	217	245	262	268	126	211	228	239	268
LR	Σ	0.800	0.862	0.848	0.839	0.841	0.810	0.806	0.817	0.840	0.841
	σ	0.471	0.487	0.469	0.464	0.464	0.430	0.464	0.478	0.479	0.464
CC	Σ	2.526	2.637	2.678	2.668	2.674	2.395	2.628	2.666	2.643	2.674
	σ	1.761	1.626	1.604	1.692	1.694	1.799	1.774	1.733	1.694	1.694
AP	Σ	2.307	2.25	2.264	2.289	2.275	2.174	2.251	2.255	2.243	2.275
	σ	1.447	1.389	1.336	1.362	1.367	1.517	1.437	1.413	1.397	1.367

AP, anterior-posterior; BV, bladder volume; CC, cranial-caudal; LR, left-right.

insertion of a rectal balloon is a preferable method to suppress intrafractional movement of the prostate. In addition, the spacer gel that could not be used at the time of this study is nowadays available. This may also be useful for improving the reproducibility of the prostate position, however, previous studies showed no significant improvement in prostate immobilization by spacer gel implantation.^{44,45}

The primary limitations of this study are the small number of patients and the retrospective nature. Another limitation is that we have no information about rectal volume, the deformation and rotation of the prostate, SV, and other adjacent OAR during fractionated SSPT. An evaluation using CBCT or CT imaging would be needed to accurately assess the motion of SV and whether the entire target is still covered sufficiently if the BV is changed. In the study we used a strict protocol for rectal volume control, however factors that change the position of the prostate other than the changes in rectal and bladder volume need to be investigated further.

CONCLUSIONS

The present study suggests that limited simple verbal instructions about urination is sufficient to control the BV and BV change not to impact on the prostate motion and clinical outcome in image-guided SSPT. However, careful attention to BV change is still needed when the SV is to be treated as CTV. The small variations in BV recorded in this study provide support to reduce uncertainties in determining the length of passage of the proton

beam from the viewpoint of dose distribution in SSPT. Further research will be needed to identify other factors that could affect the daily prostate position and ways to reduce uncertainties in the dose distribution.

AUTHOR CONTRIBUTION STATEMENT

KN, KG, TH and SS carried out the treatment planning, participated in the data collection and interpretation, performed the analysis, and participated in the drafting and final revision of the manuscript. TA, TO, RM, NK, RK, KY, and ST participated in the patient care, data collection, and interpretation and in the drafting and final revising of the manuscript. IY participated in the statistical analysis. TY and TY participated in the data analysis and in drafting the manuscript. NS, HA and HS conceived of the study and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

Isao Yokota reports grants from KAKENHI, AMED, and Health, Labour and Welfare Policy Research Grants, research fund by Nihon Medi-Physics, and speaker fees from Chugai Pharmaceutical Co, AstraZeneca plc, Japan Tobacco Pharmaceutical Division, and Nippon Shinyaku Co, outside the submitted work.

FUNDING

This work was supported by JSPS KAKENHI Grant Numbers 18K15577 and 21K15818.

REFERENCES

- National Comprehensive Cancer Network Prostate cancer. 2020;.
- Brown A, Suit H. The centenary of the discovery of the Bragg peak. *Radiother Oncol* 2004; 73: 265–8. doi: <https://doi.org/10.1016/j.radonc.2004.09.008>
- Royce TJ, Efstathiou JA. Proton therapy for prostate cancer: a review of the rationale, evidence, and current state. *Urol Oncol* 2019; 37: 628–36. doi: <https://doi.org/10.1016/j.urolonc.2018.11.012>
- Shimizu S, Miyamoto N, Matsuura T, Fujii Y, Umezawa M, Umegaki K, et al. A proton beam therapy system dedicated to spot-scanning increases accuracy with moving tumors by real-time imaging and gating and reduces equipment size. *PLoS One* 2014; 9: e94971–10. doi: <https://doi.org/10.1371/journal.pone.0094971>
- Gill S, Thomas J, Fox C, Kron T, Rolfo A, Leahy M, et al. Acute toxicity in prostate cancer patients treated with and without image-guided radiotherapy. *Radiat Oncol* 2011; 6: 1–7. doi: <https://doi.org/10.1186/1748-717X-6-145>

6. Sveistrup J, af Rosenschöld PM, Deasy JO, Oh JH, Pommer T, Petersen PM, et al. Improvement in toxicity in high risk prostate cancer patients treated with image-guided intensity-modulated radiotherapy compared to 3D conformal radiotherapy without daily image guidance. *Radiat Oncol* 2014; **9**: 1–8. doi: <https://doi.org/10.1186/1748-717X-9-44>
7. Ariyaratne H, Chesham H, Pettingell J, Alonzi R. Image-Guided radiotherapy for prostate cancer with cone beam CT: dosimetric effects of imaging frequency and PTV margin. *Radiother Oncol* 2016; **121**: 103–8. doi: <https://doi.org/10.1016/j.radonc.2016.07.018>
8. Zelefsky MJ, Kollmeier M, Cox B, Fidaleo A, Sperling D, Pei X, et al. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; **84**: 125–9. doi: <https://doi.org/10.1016/j.ijrobp.2011.11.047>
9. Soukup M, Söhn M, Yan D, Liang J, Alber M. Study of robustness of IMPT and IMRT for prostate cancer against organ movement. *Int J Radiat Oncol Biol Phys* 2009; **75**: 941–9. doi: <https://doi.org/10.1016/j.ijrobp.2009.04.032>
10. Vargas C, Wagner M, Indelicato D, Fryer A, Horne D, Chellini A, et al. Image guidance based on prostate position for prostate cancer proton therapy. *Int J Radiat Oncol Biol Phys* 2008; **71**: 1322–8. doi: <https://doi.org/10.1016/j.ijrobp.2007.12.016>
11. Lomax AJ. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 2: the potential effects of inter-fraction and inter-field motions. *Phys Med Biol* 2008; **53**: 1043–56. doi: <https://doi.org/10.1088/0031-9155/53/4/015>
12. Maeda Y, Sato Y, Shibata S, Bou S, Yamamoto K, Tamamura H, et al. Effects of organ motion on proton prostate treatments, as determined from analysis of daily CT imaging for patient positioning. *Med Phys* 2018; **45**: 1844–56. doi: <https://doi.org/10.1002/mp.12869>
13. Jagt T, Breedveld S, van de Water S, Heijmen B, Hoogeman M. Near real-time automated dose restoration in IMPT to compensate for daily tissue density variations in prostate cancer. *Phys Med Biol* 2017; **62**: 4254–72. doi: <https://doi.org/10.1088/1361-6560/aa5c12>
14. van Herk M, Bruce A, Kroes AP, Shouman T, Touw A, Lebesque JV, MVAN H, Ph D. Quantification of organ motion during conformal radiotherapy of the prostate by three dimensional image registration. *Int J Radiat Oncol Biol Phys* 1995; **33**: 1311–20. doi: [https://doi.org/10.1016/0360-3016\(95\)00116-6](https://doi.org/10.1016/0360-3016(95)00116-6)
15. Roeske JC, Forman JD, Mesina CF, He T, Pelizzari CA, Fontenla E, et al. Evaluation of changes in the size and location of the prostate, seminal vesicles, bladder, and rectum during a course of external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 1995; **33**: 1321–9. doi: [https://doi.org/10.1016/0360-3016\(95\)00225-1](https://doi.org/10.1016/0360-3016(95)00225-1)
16. Beard CJ, Kijewski P, Bussi ere M, Gelman R, Gladstone D, Shaffer K, et al. Analysis of prostate and seminal vesicle motion: implications for treatment planning. *Int J Radiat Oncol Biol Phys* 1996; **34**: 451–8. doi: [https://doi.org/10.1016/0360-3016\(95\)02081-0](https://doi.org/10.1016/0360-3016(95)02081-0)
17. Moiseenko V, Liu M, Kristensen S, Gelowitz G, Berthelet E. Effect of bladder filling on doses to prostate and organs at risk: a treatment planning study. *Journal of Applied Clinical Medical Physics* 2007; **8**: 55–68. doi: <https://doi.org/10.1120/jacmp.v8i1.2286>
18. Pinkawa M, Asadpour B, Gagel B, Piroth MD, Holy R, Eble MJ. Prostate position variability and dose-volume histograms in radiotherapy for prostate cancer with full and empty bladder. *Int J Radiat Oncol Biol Phys* 2006; **64**: 856–61. doi: <https://doi.org/10.1016/j.ijrobp.2005.08.016>
19. Nightingale H, Conroy R, Elliott T, Coyle C, Wylie JP, Choudhury A. A national survey of current practices of preparation and management of radical prostate radiotherapy patients during treatment. *Radiography* 2017; **23**: 87–93. doi: <https://doi.org/10.1016/j.radi.2017.01.003>
20. Heng SP, Low SH, Sivamany K. The influence of the bowel and bladder preparation protocol for radiotherapy of prostate cancer using kilo-voltage cone beam CT: our experience. *Indian J Cancer* 2015; **52**: 639–44. doi: <https://doi.org/10.4103/0019-509X.178386>
21. McNair HA, Wedlake L, Lips IM, Andreyev J, Van Vulpen M, Dearnaley D. A systematic review: effectiveness of rectal emptying preparation in prostate cancer patients. *Pract Radiat Oncol* 2014; **4**: 437–47. doi: <https://doi.org/10.1016/j.prro.2014.06.005>
22. Fujioka C, Ishii K, Yamanaga T, Ogino R, Kishimoto S, Kawamorita R, et al. Optimal bladder volume at treatment planning for prostate cancer patients receiving volumetric modulated Arc therapy. *Pract Radiat Oncol* 2016; **6**: 395–401. doi: <https://doi.org/10.1016/j.prro.2016.05.007>
23. Gr un A, Kawgan-Kagan M, Kaul D, Badakhshi H, Stromberger C, Budach V, et al. Impact of bladder volume on acute genitourinary toxicity in intensity modulated radiotherapy for localized and locally advanced prostate cancer. *Strahlenther Onkol* 2019; **195**: 517–25. doi: <https://doi.org/10.1007/s00066-018-1398-8>
24. Stam MR, van Lin ENJT, van der Vight LP, Kaanders JHAM, Visser AG, ENJT van L, . Bladder filling variation during radiation treatment of prostate cancer: can the use of a bladder ultrasound scanner and biofeedback optimize bladder filling? *Int J Radiat Oncol Biol Phys* 2006; **65**: 371–7. doi: <https://doi.org/10.1016/j.ijrobp.2005.12.039>
25. National Comprehensive Cancer NetworkNCCN Clinical Practice Guidelines in Oncology for Prostate cancer, Version 2. 2021. Available from: Available from <https://www.nccn.org/home> [Accessed July 14, 2021].
26. Maeda K, Yasui H, Matsuura T, Yamamori T, Suzuki M, Nagane M, et al. Evaluation of the relative biological effectiveness of spot-scanning proton irradiation in vitro. *J Radiat Res* 2016; **57**: 307–11. doi: <https://doi.org/10.1093/jrr/rrv101>
27. Matsuura T, Maeda K, Sutherland K, Takayanagi T, Shimizu S, Takao S, et al. Biological effect of dose distortion by fiducial markers in spot-scanning proton therapy with a limited number of fields: a simulation study. *Med Phys* 2012; **39**: 5584–91. doi: <https://doi.org/10.1118/1.4745558>
28. Gawthrop J, Oates R. Measured bladder volume for radiotherapy of the prostate using the hand-held BladderScan® BVI 3000. *J Med Radiat Sci* 2012; **59**.
29. Janardanan S, Moussa AEM, James P. False positive bladder scan in ascites with anuria. *Clin Case Rep* 2019; **7**: 1549–50. doi: <https://doi.org/10.1002/ccr3.2281>
30. Ahmad R, Hoogeman MS, Quint S, Mens JW, de Pree I, Heijmen BJM. Inter-fraction bladder filling variations and time trends for cervical cancer patients assessed with a portable 3-dimensional ultrasound bladder scanner. *Radiother Oncol* 2008; **89**: 172–9. doi: <https://doi.org/10.1016/j.radonc.2008.07.005>
31. Shimizu S, Osaka Y, Shinohara N, Sazawa A, Nishioka K, Suzuki R, et al. Use of implanted markers and interportal adjustment with real-time tracking radiotherapy system to reduce intrafraction prostate motion. *Int J Radiat Oncol Biol Phys* 2011; **81**: e393–9. doi: <https://doi.org/10.1016/j.ijrobp.2011.04.043>
32. Schild SE, Casale HE, Bellefontaine LP. Movements of the prostate due to rectal and bladder distension: implications for radiotherapy. *Med Dosim* 1993; **18**: 13–15. doi: [https://doi.org/10.1016/0958-3947\(93\)90021-K](https://doi.org/10.1016/0958-3947(93)90021-K)
33. Melian E, Mageras GS, Fuks Z, Leibel SA, Niehaus A, Lorant H, et al. Variation in prostate position quantitation and

- implications for three-dimensional conformal treatment planning. *Int J Radiat Oncol Biol Phys* 1997; **38**: 73–81. doi: [https://doi.org/10.1016/S0360-3016\(97\)00221-6](https://doi.org/10.1016/S0360-3016(97)00221-6)
34. Zellars RC, Roberson PL, Strawderman M, Zhang D, Sandler HM, Ten Haken RK, et al. Prostate position late in the course of external beam therapy: patterns and predictors. *Int J Radiat Oncol Biol Phys* 2000; **47**: 655–60. doi: [https://doi.org/10.1016/S0360-3016\(00\)00469-7](https://doi.org/10.1016/S0360-3016(00)00469-7)
35. Langen KM, Jones DT. Organ motion and its management. *Int J Radiat Oncol Biol Phys* 2001; **50**: 265–78. doi: [https://doi.org/10.1016/S0360-3016\(01\)01453-5](https://doi.org/10.1016/S0360-3016(01)01453-5)
36. Pang EPP, Knight K, Hussain A, Fan Q, Baird M, Tan SXF, et al. Reduction of intra-fraction prostate motion - Determining optimal bladder volume and filling for prostate radiotherapy using daily 4D TPUS and CBCT. *Tech Innov Patient Support Radiat Oncol* 2018; **5**: 9–15. doi: <https://doi.org/10.1016/j.tipsro.2018.01.003>
37. Tsai C-L, Wu J-K, Wang C-W, Hsu F-M, Lai M-K, Cheng J-C-H, JK W, Chia-Hsien Cheng J. Using cone-beam computed tomography to evaluate the impact of bladder filling status on target position in prostate radiotherapy. *Strahlenther Onkol* 2009; **185**: 588–95. doi: <https://doi.org/10.1007/s00066-009-1987-7>
38. Nakamura N, Shikama N, Takahashi O, Ito M, Hashimoto M, Uematsu M, et al. Variability in bladder volumes of full bladders in definitive radiotherapy for cases of localized prostate cancer. *Strahlenther Onkol* 2010; **186**: 637–42. doi: <https://doi.org/10.1007/s00066-010-2105-6>
39. Lebesque JV, Bruce AM, Kroes AP, Touw A, Shouman RT, van Herk M. Variation in volumes, dose-volume histograms, and estimated normal tissue complication probabilities of rectum and bladder during conformal radiotherapy of T3 prostate cancer. *Int J Radiat Oncol Biol Phys* 1995; **33**: 1109–19. doi: [https://doi.org/10.1016/0360-3016\(95\)00253-7](https://doi.org/10.1016/0360-3016(95)00253-7)
40. Jain S, Loblaw DA, Morton GC, Danjoux C, Szumacher E, Chu W, et al. The effect of radiation technique and bladder filling on the acute toxicity of pelvic radiotherapy for localized high risk prostate cancer. *Radiation Oncol* 2012; **105**: 193–7. doi: <https://doi.org/10.1016/j.radonc.2012.09.020>
41. Byun DJ, Gorovets DJ, Jacobs LM, Happersett L, Zhang P, Pei X, et al. Strict bladder filling and rectal emptying during prostate SBRT: does it make a dosimetric or clinical difference? *Radiat Oncol* 2020; **15**: 1–9. doi: <https://doi.org/10.1186/s13014-020-01681-6>
42. Chetiyawardana G, Hoskin PJ, Tsang YM. The implementation of an empty bladder filling protocol for localised prostate volumetric modulated arctherapy (VMAT): early results of a single institution service evaluation. *Br J Radiol* 2020; **93**: 20200548. doi: <https://doi.org/10.1259/bjr.20200548>
43. Smeenk RJ, Louwe RJW, Langen KM, Shah AP, Kupelian PA, van Lin ENJT, et al. An endorectal balloon reduces intrafraction prostate motion during radiotherapy. *Int J Radiat Oncol Biol Phys* 2012; **83**: 661–9. doi: <https://doi.org/10.1016/j.ijrobp.2011.07.028>
44. Picardi C, Rouzaud M, Kountouri M, Lestrade L, Vallée JP, Caparrotti F, et al. Impact of hydrogel spacer injections on interfraction prostate motion during prostate cancer radiotherapy. *Acta Oncol* 2016; **55**: 834–8. doi: <https://doi.org/10.3109/0284186X.2015.1128118>
45. Juneja P, Kneebone A, Booth JT, Thwaites DI, Kaur R, Colvill E, et al. Prostate motion during radiotherapy of prostate cancer patients with and without application of a hydrogel spacer: a comparative study. *Radiat Oncol* 2015; **10**: 1–7. doi: <https://doi.org/10.1186/s13014-015-0526-1>