Relationship between seminal vesicle displacement and distribution of hydrogel spacer within the perirectal space in prostate radiotherapy

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Abstract. The influence of a hydrogel spacer (HS) on seminal vesicle (SV) displacement in prostate radiotherapy was examined in the present study. A total of 20 patients with prostate cancer, who received intensity-modulated radiation therapy (IMRT), were enrolled. Computed tomography and magnetic resonance imaging were performed before and after HS insertion within the peripheral space for IMRT planning. Before and after HS insertion, The SV was delineated, and the amount of SV displacement was evaluated. Large SV cranial displacements (≥0.50 cm) were observed in 25% of patients. A HS lateral distribution of ≥1.00 cm in the upper two slices (midgland + superior) influenced the SV cranial displacements (P<0.01) and was associated with large SV cranial displacements (≥0.5 cm) (P<0.01). The HS cranial distribution in the upper slices did not influence SV cranial displacements (P=0.16). In addition, any HS lateral distribution of ≥1.00 cm in all slices did not induce the SV lateral and anterior-posterior displacements (P=0.50 and 0.70, respectively). In conclusion, SV cranial displacement was influenced by HS lateral distribution of ≥1.00 cm in the upper two slices. Therefore, when the sigmoid colon or small bowel is depressed in rectovesical excavation and SV needs to be included in the target volume, HS insertion should be performed carefully.

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Abbreviations: PCa, prostate cancer; EBRT, external beam radiotherapy; IMRT, intensity-modulated radiation therapy; IGRT, image guided radiotherapy; HS, hydrogel spacer; SV, seminal vesicle; CT, computed tomography; MR, magnetic resonance; TPS, treatment planning system; RWI, rectal wall infiltration

Key words: PCa, radiotherapy, HS, SV, IMRT

Introduction

Prostate cancer (PCa) is the most common type of cancer in men and external beam radiation therapy (EBRT) is one of the useful treatment modalities for PCa (1,2). In the last two decades, radiation technologies such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) have advanced in the field of EBRT. They have achieved dose escalation to target volumes and dose reduction in normal organs. Furthermore, precise radiation technologies, such as ultra-hypofractionated IMRT, are emerging (3,4). Therefore, a subtle attentiveness is required.

In previous studies, a hydrogel spacer (HS; SpaceOAR System, Augmenix, Inc., Waltham, MA, USA) was inserted between the prostate and rectum to reduce rectal toxicity (5,6). Though the safety and efficacy of HS in EBRT for PCa have been reported in several studies (6,7), the effectiveness presented in these studies reduced rectal toxicity. Therefore, HS assumes importance as an IMRT tool for PCa, especially in ultra-hypofractionated IMRT.

Additionally, the seminal vesicle (SV), one of the targeted structures in EBRT for PCa, is an organ whose anatomical position fluctuates with HS insertion. Nevertheless, to best our knowledge, no studies have examined SV displacement in relation to HS insertion. Therefore, in our present study, we aimed to examine the SV displacement associated with HS insertion.

Materials and methods

Study population. Between March 2019 and March 2022, 95 patients were treated with definitive IMRT for PCa at our institution. Of these, patients with the following characteristics were excluded from the study: i) No use of HS (n=56); ii) absence of computed tomography (CT) and magnetic resonance (MR) imaging data before HS insertion (n=6); and iii) large changes in bladder volume (>50 cm^3) and rectal

volume (>15 cm^3) between simulation CT images for planning after HS insertion and CT images before HS insertion (n=10). Finally, twenty consecutive PCa patients [median age (range): 71 years (61-84 years), median pretreatment body mass index (range): 23.7 (18.1-30.3)] from the twenty-three remaining patients were included in the analysis. When SV invasion and tumor infiltration around SV, HS insertion is prohibited because of the possibility of scattering the tumor cells. All patients had bladder volumes of >50 cm^3 on simulation CT. None of the patients had received hormone therapy because EBRT doses for intermediate-risk PCa in our institution are sufficiently dose-escalated (8). The baseline characteristics of the patients are shown in Table I. The Ethics Committee of the National Hospital Organization Shikoku Cancer Center (Matsuyama, Japan) approved the study protocol (approval no. Rin 202105). The need for informed consent was waived due to the study's retrospective nature.

HS insertion. Under general anesthesia and *transrectal ultrasound* guidance, all patients underwent transperineal insertion of two intra-prostatic gold seed markers (9) and HS at our institution. Approximately 8-10 ml of HS was inserted into the anterior perirectal space between the Denonvilliers' fascia and the anterior rectal wall. A urologist performed the insertion of the gold seed markers and HS.

Evaluation. CT images of the region, including the prostate and SV, were collected at 2.5 mm between two slices (thickness of 2.5 mm). The images were loaded onto our Eclipse 3D treatment planning system (TPS; Varian Medical Systems, Palo Alto, CA, USA), and a radiation oncologist created each SV delineation. To obtain SV delineation from the CT images, the radiation oncologist adhered to the European Society for Therapeutic Radiology and Oncology (ESTRO) Advisory Committee for Radiation Oncology Practice (ACROP) consensus guideline and actual anatomy (10). Registration of the CT images before and after HS insertion depended on the base of the prostate. The amount of SV displacement owing to HS insertion was measured. Displacement in the cranial, lateral, and anterior translation directions was given positive values. In contrast, displacement was given as negative values in the caudal, medial, and posterior directions.

Statistical analysis. Statistical analyses were performed using the JMP software (JMP version 14.3.0; SAS Institute, Cary, NC, USA). An unpaired Student's t-test and Fisher's exact test were used to assess the significance of group differences in the variables.

Results

Amount of SV displacement. The maximum cranial displacements mean was 0.16 cm (range, -0.25-1.00 cm), the maximum anterior displacements mean it was 0.00 cm (range, -0.45-1.14 cm), and the maximum lateral displacements mean was 0.00 cm (range, -0.24-0.58 cm). Rectal wall infiltration (RWI) score (10) was 1 (range, 0-3). Large displacements (≥0.5 cm) were observed in six patients (cranial, 4; anterior, 1; cranial + anterior + lateral, 1).

SV cranial displacement. SV cranial displacements of 1.00 cm were observed in 5% (1/20) and 0.50-1.00 cm in 20% (4/20) of all patients. An example of HS insertion is shown in Fig. 1.

An HS lateral distribution of ≥1.00 cm in the upper two slices (midgland + superior) influenced the SV cranial displacements ($P<0.01$) and influenced the large (≥0.5 cm) SV cranial displacements ($P<0.01$, Table II). The HS cranial distribution, where the evaluation point was the middle of the HS in the upper slices, did not influence the SV cranial displacements ($P=0.16$). In addition, HS thickness, as an indicator of anterior distribution, did not influence SV cranial displacements ($P=0.51$).

SV lateral displacement. SV lateral displacements of 0.50-1.00 cm were observed in only 5% (1/20) of the patients.

An HS lateral distribution of ≥1.00 cm in the upper two slices (midgland + superior) did not influence the SV lateral displacements ($P=0.50$, Table II). The HS cranial distribution in the upper slices did not induce SV lateral displacements ($P=0.95$). In addition, the HS thickness did not affect the SV lateral displacements ($P=0.99$).

SV anterior displacement. SV anterior displacements of 1.00 cm were observed in 5% (1/20) and 0.50-1.00 cm in 10% (2/20) of all patients.

An HS lateral distribution of ≥1.00 cm in the upper two slices (midgland + superior) did not influence the SV lateral displacements ($P=0.70$, Table II). The cranial distribution of HS in the upper slices did not induce SV lateral displacements ($P=0.36$). In addition, the HS thickness did not affect the SV lateral displacements ($P=0.75$).

Discussion

This study investigated the influence of HS distribution on SV position for patients with PCa treated with IMRT. Our results indicated that HS distribution caused rare clinically significant changes in SV position. We observed large SV cranial displacements according to asymmetrical HS insertion [HS lateral distribution of ≥1.00 cm in the upper two slices (midgland + superior)].

In radiotherapy for PCa, the rectum and bladder are considered important organs at risk. Therefore, the use of HS in IMRT planning for PCa significantly reduces the rectal dose, toxicity, and quality of life (6). However, in radiotherapy for PCa, the sigmoid colon and small bowel often limit the dose distribution of the planning target volume (11). This is attributed to these organs receiving higher doses, which is also related to intestinal toxicity (12). Although Fischer-Valuck *et al* (13) suggested that asymmetric HS insertion also leads to an adequate reduction of rectal dose as symmetric HS insertion, they did not evaluate the association between the sigmoid colon and the small bowel. In our study, the incidence of SV cranial displacement was associated with long-distance asymmetric HS insertion from the superior to the midgland space. Symmetric HS insertion assumed importance regarding a few SV cranial displacements.

Furthermore, in our study, SV cranial displacement was associated with two factors (HS insertion in the upper two slices + HS insertion in a lateral distribution of ≥1.00 cm).

Table I. Baseline characteristics.

Characteristic	No. of patients
Prostate size, cm^3	
<38	10
≥38	10
Rectum size, cm^3	
Before HS insertion	
<45	9
≥45	11
After HS insertion	
<45	10
≥45	10
Bladder size, cm^3	
Before HS insertion	
<120	12
≥120	8
After HS insertion	
<120	13
≥120	7
BMI	
<23	7
≥23	13
PSA at diagnosis	
<8	10
≥8	10
Biopsy Gleason score	
3 + 3	2
3 + 4	10
4 + 3	8
Clinical T-stage	
1	11
2	9
Radiation dose	
74-78 Gy/37-39 fractions	11
70 Gy/28 fractions	4
60 Gy/20 fractions	5

HS, hydrogel spacer; BMI, body mass index; PSA, prostate-specific antigen.

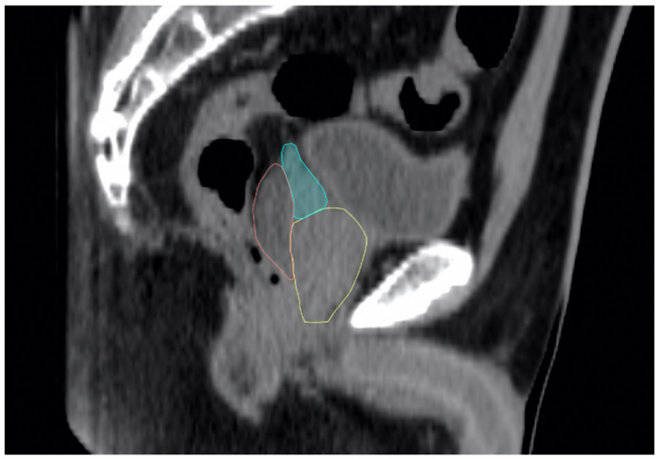

Figure 1. HS insertion of the lateral distribution of ≥1.00 cm in upper two slices (midgland + superior). Yellow line, prostate; blue line, SV; pink line, HS. The HS insertion of the lateral distribution of ≥1.00 cm in the upper two slices led to the large cranial displacement of the SV position. HS, hydrogel spacer; SV, seminal vesicle.

HS insertion in the inferior perirectal space did not lead to SV cranial displacement. Pinkawa *et al* (14) demonstrated that there was a learning curve for symmetrical HS insertion (i.e., modifying the HS lateral displacement), improved treatment planning, and less treatment-related acute toxicity. Fukumitsu *et al* (15) proposed a new technique to enhance HS craniocaudal displacement. Though this novel technique requires further proficiency, it may prove useful in reducing the risk of SV cranial displacement. Although multiple studies have investigated the usefulness of hypofractionated radiation therapy for PCa (16,17), a recent meta-analysis showed that hypofractionated radiation therapy induced a significant risk of acute gastrointestinal toxicity (18). Hence, appropriate HS insertion is extremely important when a patient with PCa is treated with hypofractionated radiation therapy. The sigmoid colon or small bowel is depressed in rectovesical excavation; even so, the SV needs to be included in the target volume. An expert physician with proficiency in HS insertion is thus required for HS insertion.

This study had limitations associated with a small sample size. We selected only twenty cases with acceptable differences in bladder and rectum volume variations before and after HS insertion. This is because many clinical cases did not have an equivalent volume of bladder and rectum before and after HS insertion. In our study, SV displacement was unaffected by volume variation of the rectum or bladder (data not shown). In addition, the inter- and intra-fractional motion of the SV was approximately 8 mm (19). Most of the results were within the range of intra- and inter-fraction motion of the SV; however, only SV cranial displacement correlated with the position of HS insertion. Therefore, HS insertion has an impact on the cranial displacement of the SV. Although our present study was inadequate in concluding the influence of HS insertion and further studies are needed, we suggest that HS insertion in the upper two slices and the lateral distribution of ≥1.00 cm had increased the dose constraint of the target volume when the sigmoid colon or small bowel is depressed in the rectovesical excavation. SV needs to be included in the target volume.

In conclusion, SV displacements were influenced by the position of the inserted HS. HS insertion in the upper two slices and lateral distribution of ≥1.00 cm had impacted the SV cranial displacement. HS insertion must be carefully performed when the sigmoid colon or small bowel is depressed during rectovesical excavation.

Acknowledgments

Not applicable.

Table II. Seminal vesicle displacements according to hydrogel spacer insertion.

A, SV cranial displacement

Factors	Mean displacement (SE)	P-value	>0.5 cm displacement (%)	P-value
HS lateral distribution		<0.01		<0.01
Upper 2 slices	0.41 (0.10)		5/8 (62.5)	
Lower 1 slice	0 (0.08)		0/12 (0)	
HS cranio-caudal distribution		0.16		0.13
Midgland-surperior	0.23 (0.09)		5/14 (35.7)	
Inferior	0 (0.13)		0/6 (0)	
HS thickness		0.51		0.52
≥1.5 cm	0.19 (0.09)		4/14 (28.6)	
<1.5 cm	0.08 (0.14)		1/6 (16.7)	

B, SV lateral displacement

Factors	Mean displacement (SE)	P-value	>0.5 cm displacement (%)	P-value
HS lateral distribution		0.50		0.40
Upper 2 slices	0.13 (0.06)		1/8 (12.5)	
Lower 1 slice	0.07 (0.05)		0/0 (0)	
HS cranio-caudal distribution		0.95		0.70
Midgland-surperior	0.09 (0.05)		1/14 (7.1)	
Inferior	0.09 (0.07)		0/0 (0)	
HS thickness		>0.99		0.70
≥1.5 cm	0.09 (0.07)		1/14 (7.1)	
<1.5 cm	0.09 (0.05)		0/0 (0)	

C, SV anterior displacement

Factors	Mean displacement (SE)	P-value	>0.5 cm displacement (%)	P-value
HS lateral distribution		0.70		0.66
Upper 2 slices	0.19 (0.12)		2/12 (16.7)	
Lower 1 slice	0.25 (0.10)		1/8 (12.5)	
HS cranio-caudal distribution		0.36		0.80
Midgland-surperior	0.28 (0.09)		2/14 (14.3)	
Inferior	0.12 (0.14)		1/6 (16.7)	
HS thickness		0.75		0.80
≥1.5 cm	0.25 (0.09)		2/14 (14.3)	
<1.5 cm	0.19 (0.14)		1/6 (16.7)	

SV, seminal vesicle; SE, standard error; HS, hydrogel spacer.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KM, YH, HK and KN were involved in the conception and design of the study. KM, YH, HK, KN and KH collected patient data and drafted the manuscript. KM, YH, HK, KN and KH interpreted the data. KM and YH prepared the manuscript, and HK, KN and KH edited the manuscript. All authors confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were conducted according to the ethical standards of the institutional research committee and The 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This retrospective study was approved by the institutional review board of National Hospital Organization Shikoku Cancer Center (Matsuyama, Japan; approval no. Rin 202105). The need for informed consent was waived due to the study's retrospective nature.

Patient consent for publication

The need for informed consent was waived due to the study's retrospective nature.

Competing interests

The authors declare that they have no competing interests.

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