Preliminary analysis of prostate positional displacement using hydrogel spacer during the course of proton therapy for prostate cancer

Hiroki Sato[1], Takahiro Kato[1,2,*], Tomoaki Motoyanagi[1], Kimihiro Takemasa[1], Yuki Narita[1], Masato Kato[1], Takuya Matsumoto[1], Sho Oyama[1], Hisashi Yamaguchi[3], Hitoshi Wada[3] and Masao Murakami[3]

[1]Department of Radiation Physics and Technology, Southern Tohoku Proton Therapy Center, Fukushima, Japan
[2]Preparing Section for New Faculty of Medical Science, Fukushima Medical University, Fukushima, Japan
[3]Department of Radiation Oncology, Southern Tohoku Proton Therapy Center, Fukushima, Japan
*Corresponding author. Department of Radiation Physics and Technology, Southern Tohoku Proton Therapy Center, 172 Yatsuyamada 7 Chome, Koriyama City, Fukushima, 963-8563, Japan. Tel: +81-24-934-3888; Fax: +81-24-934-5393; Email: kato.newjapan@gmail.com
(Received 14 July 2020; revised 29 September 2020; editorial decision 31 October 2020)

ABSTRACT

In recent years, a novel technique has been employed to maintain a distance between the prostate and the rectum by transperineally injecting a hydrogel spacer (HS). However, the effect of HS on the prostate positional displacement is poorly understood, despite its stability with HS in place. In this study, we investigated the effect of HS insertion on the interfraction prostate motion during the course of proton therapy (PT) for Japanese prostate cancer patients. The study population consisted of 22 cases of intermediate-risk prostate cancer with 11 cases with HS insertion and 11 cases without HS insertion. The irradiation position and preparation were similar for both groups. To test for reproducibility, regular confirmation computed tomography (RCCT) was done four times during the treatment period, and five times overall [including treatment planning CT (TPCT)] in each patient. Considering the prostate position of the TPCT as the reference, the change in the center of gravity of the prostate relative to the bony anatomy in the RCCTs of each patient was determined in the left–right (LR), superior–inferior (SI) and anterior–posterior (AP) directions. As a result, no significant difference was observed across the groups in the LR and SI directions. Conversely, a significant difference was observed in the AP direction ($P < 0.05$). The proportion of the 3D vector length ≤5 mm was 95% in the inserted group, but 55% in the non-inserted group. Therefore, HS is not only effective in reducing rectal dose, but may also contribute to the positional reproducibility of the prostate.

Keywords: hydrogel spacer; interfraction motion; prostate cancer; proton therapy

INTRODUCTION

External radiation therapy for prostate cancer is becoming more sophisticated, with methods such as intensity-modulated radiation therapy (IMRT), CyberKnife and particle therapy [proton therapy (PT) and carbon ion therapy] [1, 2]. As the prostate is adjacent to the bladder and the rectum, it is imperative to minimize the dosage administered through these organize to avoid genitourinary and gastrointestinal toxicity. Particularly, it is imperative to avoid rectal bleeding, and image-guided radiation therapy (IGRT) should be maximized, as it improves the positional accuracy of the target.

However, in order to prescribe a sufficient dose to the clinical target volume (CTV), it is unavoidable that the same dose is delivered to the anterior rectal wall that is adjacent to the CTV. This shortcoming is unavoidable, even with IMRT and particle therapy, and this causes moderate to severe rectal bleeding (grade 2 or higher) in rare conditions.

There is no doubt that the most reliable way to reduce the incidence of rectal bleeding without compromising tumor control is to increase the distance between the prostate and the rectum. Recent reports have shown several methods to achieve this. For example,

adjusting the irradiation position (irradiation in the prone position) is a non-invasive method widely in use [3, 4]. The prone position is known to increase the prostate–rectum distance in prostate cancer external radiation therapy, but possibly not in all cases [5]. In other words, it is considered to be a method with large uncertainty. On the other hand, a technique for securing a suitable distance between the prostate and the rectum by transperineally injecting a hydrogel spacer (HS) has been reported and has become widespread in recent times [6–17]. Though invasive, a proper infusion maintains the prostate–rectum distance throughout the treatment course. Recently, it is used in the hypofractionated PT for prostate cancer, especially in Japan.

Interfraction prostate motion has always been a concern in modern radiation therapy, regardless of the treatment modality. In particular, current knowledge reveals that changes in rectal volume have an effect on the treatment techniques employed [18]. Thus, various methods have been devised to make the rectal volume constant (ranging from active methods using balloons to mild methods such as direct defecation and exhaust gas infusion) immediately before treatment [10, 19]. There have been numerous reports regarding interfraction prostate motion without HS during the treatment period, and it is not clear whether these findings apply when HS placement is involved. With this in mind, Pinkawa *et al.* reported that posterior prostate displacement could be decreased in groups with HS [6]. However, studies reporting this same fact are scarce, making the standardization of these findings impossible. Although the HS volume is constant, the size of the pelvic cavity may differ between Japanese and Westerners. Thus, this also affects the positional changes of the prostate during the treatment period. However, there are very few reports from Japan regarding HS [14–17], and in particular no reports regarding interfraction prostate motion. Therefore, in this study, we investigated the effect of HS insertion on prostate positional displacement during the course of PT for Japanese prostate cancer patients.

MATERIALS AND METHODS
Patient background

We enrolled 22 cases of intermediate-risk prostate cancer with androgen deprivation who underwent PT, with 11 HS-inserted cases and 11 HS non-inserted cases. The patient characteristics are shown in Table 1. SpaceOAR (Augmenix, Inc., MA, USA) was used as a HS. The HS-inserted cases were injected transperineally with HS in the rectoprostatic space. Approximately 10 mL of the HS was injected, creating a 7–10 mm separation between the prostate and the rectum [9]. We started with HS insertion in November 2018 using the hypofractionation protocol of 63 Gy relative biological effectiveness (RBE) in 21 fractions. Here, the RBE correction factor for physical to biologic dose was 1.1. For the HS-inserted group, 11 patients receiving treatment after November 2018 were selected. The indication criteria for HS insertion basically conformed to the Japanese Society for Radiation Oncology guideline [20]. Prior to starting this protocol, the standard fractionation protocol of 74 Gy (RBE) in 37 fractions was used. For the non-inserted group, 11 patients following the standard protocol before November 2018 were selected. The institutional review board of our institution approved this study.
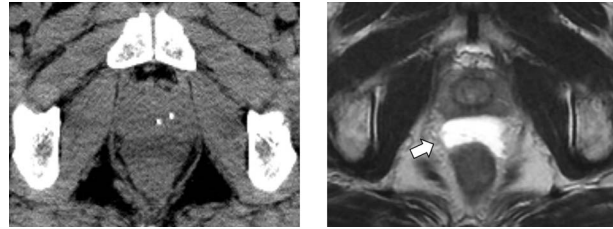

Fig. 1. Examples demonstrating a patient with HS. Axial plane of treatment planning computed tomography (left) and T2-weighted magnetic resonance imaging (MRI) (right). MRI acquired on the same day to visualize the prostate and HS is indicated by white arrow.

Imaging procedure

The irradiation position and preparation were similar for both groups. The irradiation position was supine and the lower legs were fixed with a vacuum cushion to reproduce femoral head. Thirty to sixty minutes prior to the treatment planning computed tomography (TPCT) scan, patients were instructed to drink 200 mL water to ensure that the bladder was comfortably full. In addition, all patients were instructed to defecate and exhaust gas before examination as much as possible. Aquilion LB (Canon Medical Systems, Otawara, Japan) was used for CT scans, and images were taken in 2 mm slices. All patients also underwent magnetic resonance imaging (MRI) scans on the same day to improve target visualization. MRI scans were also useful for visualizing the HS (Fig. 1). Signa HDx (GE Healthcare, IL, USA) was used for MRI, and images were taken in 4 mm slices. The images were imported into the XiO-M treatment planning system (Hitachi, Kashiwa, Japan), and two data sets were automatically fused. The prostate, seminal vesicles, rectum, bladder and HS were contoured on co-registered CT and MRI images. The prostate plus the proximal seminal vesicles were contoured as a CTV. The rectum was contoured 10 mm superiorly and inferiorly beyond the CTV. The bladder was contoured entirely. In order to confirm the reproducibility, regular confirmation CT (RCCT) was done four times during the treatment period, and five times overall (including TPCT) in each patient. Hitachi's proton-type particle therapy system (Hitachi, Kashiwa, Japan) was used as the PT machine. Since this system is not equipped with cone-beam CT or an in-room CT system, the RCCT was done in the treatment position immediately after irradiation in the CT room adjacent to the treatment room.

Dose–volume comparison of rectal dose

The original purpose of HS is to reduce rectal dose by increasing the distance between the prostate and the rectum. Therefore, it is necessary to perform the study to confirm that the original purpose has been achieved in the analysis target samples. In both groups, we carried out a treatment planning simulation of PT for the TPCT under the same conditions and compared the rectal dose to evaluate the validity of the target samples.

The irradiation method is the wobbler method [21], which is one of the passive scattering methods. The PT plans were designed using the standard lateral opposed fields with 210 MeV proton beams. The planning target volume (PTV) included the CTV plus a 7 mm safety

Table 1. Patient and tumor characteristics ($n = 22$). P value is calculated by Welch's *t*-test or Fisher's exact test as appropriate

	HS (+)	HS (−)	P value
Patients	11	11	–
Mean age (95% CI)	72(68/75)	69(65/73)	0.34
T stage (T1/T2)	4/7	1/10	0.31
Prostate volume (cc) [mean ± SD (95% C.I.)]	33.1 ± 11.5 (26.4/39.9)	27.7 ± 0.8 (21.9/33.5)	0.25

SD = standard deviation, CI = confidence interval.

margin, except at the prostate–rectum interface where a 6 mm margin was used to decrease the risk of rectal toxicity. The key parameters for passive scattering PT plans are distal, proximal, lateral and smearing margins. Most of the planning parameters are selected using the methods described by Moyers *et al.* [22]. The compensator was designed for the CTV using a custom distal margin that included a 3.5% depth to account for uncertainty for CT number accuracy and conversion to proton relative linear stopping power, and a 3 mm range uncertainty to take into account uncertainties in the accelerator energy, variable scattering system thickness and compensator density. The radiation field was formed using the multi-leaf collimator built in the snout. The prescribed dose for each plan was set to 74 Gy (RBE)/37 fractions to 95% of the PTV. V_{10}, V_{30}, V_{50}, V_{70} and mean dose of rectum were obtained from a rectal dose–volume histogram and comparatively examined. Here, V_{10}–V_{70} is the mean percentage of volume receiving doses of 10–70 Gy (RBE) of rectum. Welch's *t*-test was used to analyze the difference between the HS-inserted and non-inserted group in each dose parameter. *P*-values < 0.05 were considered statistically significant.

Analysis of interfraction prostate motion

Considering the prostate position of the TPCT as the reference, the change in the center of gravity of the prostate relative to the bony anatomy in the RCCTs of each patient was determined in the left–right (LR), superior–inferior (SI) and anterior–posterior (AP) directions and 3D vector length was calculated. The proportions of the 3D vector length ≤5 mm were compared between the two groups. This length is the index on the safe side at our institution, considering that the changes in beam path density can affect dose distribution, even if it is assumed that marker matching excludes the interfraction errors perpendicular to the beam axis. Welch's *t*-test was used to analyze the difference between the HS-inserted and non-inserted group in each direction. *P*-values < 0.05 were considered statistically significant. In addition, to assess a possible relationship between prostate positional displacements along the three axes and changes in rectal and bladder volumes during the treatment course, we analyzed the Pearson correlation between these variables in both groups.

RESULTS

Table 2 shows the comparison results of rectal dose by treatment planning simulation. It was confirmed that the rectal dose was significantly reduced in the HS-inserted group for all dose parameters compared with the non-inserted group. Interfraction prostate motion analyses per direction are shown in Fig. 2 and Table 3. No significant
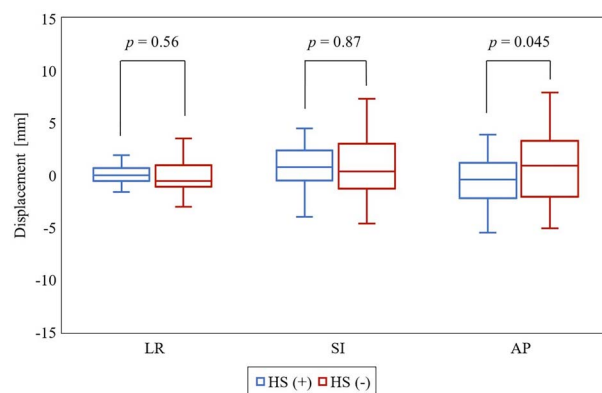

Fig. 2. Box-plot representation of the prostate positional displacement in the LR, SI and AP directions between the HS-inserted group (blue) and non-inserted group (red). The bottom and top edges of the box represent 25th and 75th percentiles, with a line at the median. The bottom and top edges of the vertical lines represent minimum and maximum values.

differences were observed between the groups in the LR and SI directions. On the other hand, a significant difference was observed in the AP direction ($P < 0.05$). The results of the 3D vector length of both groups are illustrated in Fig. 3. The proportion of the 3D vector length ≤5 mm was 95% in the HS-inserted group, but 55% in the non-inserted group. In addition, the maximum displacement in the anterior direction was 7.9 mm in the non-inserted group, but 3.9 mm in the HS-inserted group, with a small variation in the anterior direction. Finally, the results of the correlation between changes in rectal and bladder volumes and interfraction prostate motion are shown in Figs 4 and 5, respectively. In both the HS-inserted group and the non-inserted group, the AP prostate displacement showed a significant correlation with changes in rectal volume ($r = 0.49$; $P < 0.0008$, $r = 0.49$; $P < 0.0007$, respectively). In addition, only in the HS-inserted group, did the LR prostate displacement show a significant correlation with change in rectal volume ($r = −0.41$; $P < 0.006$). Although there was a trend toward significance in the correlation between AP prostate displacement and change in bladder volume in the non-inserted group ($r = −0.29$; $P = 0.053$), there was no significant difference between change in bladder volume and prostate positional displacement among any groups or directions.

Table 2. Dose–volume comparison of rectal dose between HS-inserted and non-inserted groups. Percentage of rectal volume receiving doses between 10 and 70 Gy (RBE) and mean dose [mean ± standard deviation (95% confidence interval)] in the HS-inserted and non-inserted groups

	HS (+)	HS (−)	*P* value
V_{10} (%)	43.9 ± 11.3 (37.3/50.6)	62.1 ± 7.8 (57.5/66.7)	<0.0001
V_{30} (%)	22.5 ± 9.5 (16.9/28.1)	43.0 ± 6.5 (39.2/46.9)	<0.0001
V_{50} (%)	9.4 ± 6.7 (5.5/13.4)	28.8 ± 5.3 (25.7/32.0)	<0.0001
V_{70} (%)	1.4 ± 2.6 (0.0/3.0)	13.9 ± 3.8 (11.7/16.2)	<0.0005
Mean dose [Gy (RBE)]	16.2 ± 5.7 (12.8/19.5)	29.8 ± 4.3 (27.3/32.3)	<0.0001

Table 3. Comparison of prostate positional displacement given as mean ± standard deviation (95% confidence interval) in the LR, SI and AP directions between the HS-inserted and non-inserted groups

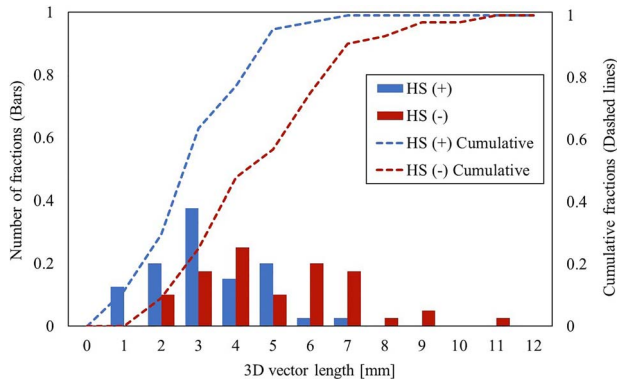|	HS (+)	HS (−)	*P* value
LR (mm)	0.1 ± 0.8 (−0.2/0.3)	-0.1 ± 1.5 (−0.5/0.3)	0.56
SI (mm)	0.8 ± 1.9 (0.2/1.4)	0.7 ± 3.2 (−0.3/1.7)	0.87
AP (mm)	-0.5 ± 2.1 (−1.1/0.1)	0.7 ± 3.4 (−0.3/1.7)	0.045

Fig. 3. Histogram of 3D vector length distribution of the prostate for the HS-inserted group (blue) and non-inserted group (red). Dashed lines indicate cumulative fractions.

DISCUSSION

This study is the first attempt to analyze the interfraction prostate motion for HS-inserted in Japanese prostate cancer patients. In recent years, HS has been widely used to increase the distance between the prostate and the rectum. Although there are many reports on the effect of reducing rectal dose, there is no universal concensus on how the interfraction prostate motion changes with HS-insertion compared with non-HS insertion. Because the prostate displacement depends on the contents of the bladder and rectum, a range of analysis results have been reported to date [18, 19]. However, most of them were non-HS inserted cases, and no evidence implies a similar finding in HS-inserted cases. HS is likely to become popular as a useful tool that makes it possible to avoid rectal bleeding in external irradiation for prostate cancer. It is considered one of the urgent issues for verification studies and standardization in the analysis of prostate positional displacement in prostate cancer radiation therapy. Therefore, in this study, we initially examined whether rectal dose could be reduced by inserting HS as in previous reports [12–16]. Next, we examined how HS insertion affects the interfraction prostate motion.

As a result, we confirmed that rectal dose was significantly reduced in the HS-inserted group compared with the non-inserted group as in a previous report [13]. In addition, both groups showed a significant correlation with changes in rectal volume in the AP prostate displacement, but the absolute amount tended to be smaller in the HS-inserted group. This is possibly because HS exerts slight pressure on the rectum just below the prostate. This makes it difficult for rectal gas to stay at the dorsal level of the prostate, resulting in suppression of changes in rectal volume. An example is seen on TPCT and RCCT images of a patient as shown in Fig. 6. Rectal gas was seen on the RCCT scan, though it appeared to remain at the prostatic head level due to the effect of HS. However, since the proportion of such cases was not high, further examination is considered necessary. Pinkawa *et al.* also reported that the insertion of HS improves the reproducibility of the prostate position, especially in the posterior direction [6]. However, the evaluation was done with TPCT and a single CT taken in the last treatment week, which prove to be unreliable. On the other hand, Picardi *et al.* reported that there was no significant difference in prostate positional change with and without HS [9]. The present study supports the report of Pinkawa *et al.*, however, it is considered that there are various factors that can influence these results, such as differences in the imaging frequency of the RCCT and differences in body shape between races. Therefore, direct comparison needs to be carried out carefully and further examination is still needed. In addition, it should be noted that inserting HS does not always give the same result. Fischer-Valuck *et al.* reported that HS can be inserted asymmetrically with a relatively high frequency [11]. Although there were no visually obvious asymmetric cases in this study, it is important to understand that the effect may differ depending on the insertion state. In addition, in the HS-inserted group, a significant correlation was observed between change in rectal volume and the LR prostate displacement, but the amount
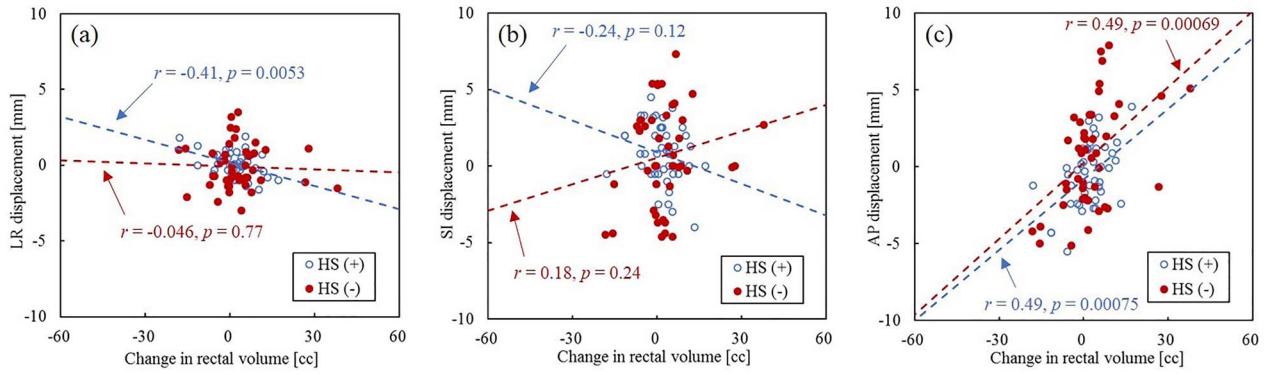
Fig. 4. Scatterplot of the prostate positional displacement from the TPCT vs change in rectal volume for HS-inserted group (blue) and non-inserted group (red). Shown separately for (a) LR, (b) SI and (c) AP prostate positional displacements. Also shown are linear fit to the data, where *r* is the linear-correlation coefficient and *P* is the probability for no correlation.
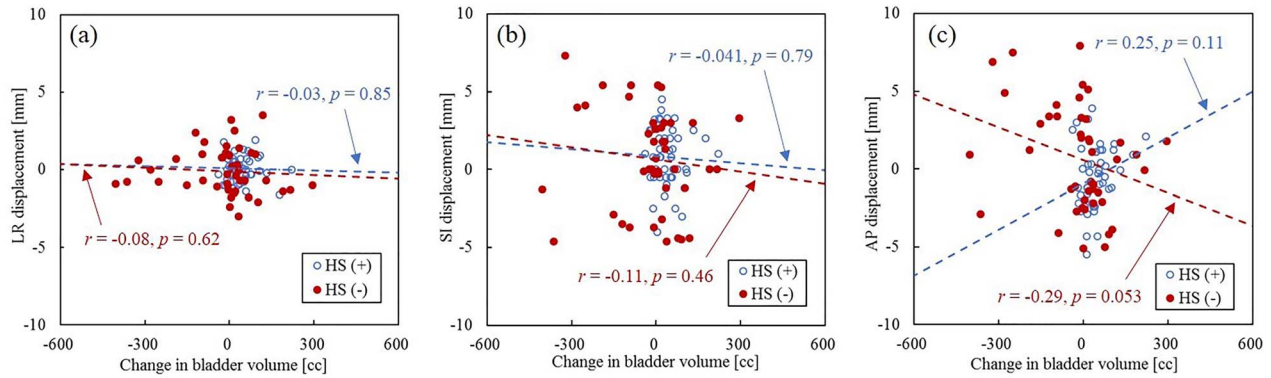

Fig. 5. Scatterplot of the prostate positional displacement from the TPCT vs change in bladder volume for HS-inserted group (blue) and non-inserted group (red). Shown separately for (a) LR, (b) SI and (c) AP prostate positional displacements. Also shown are linear fit to the data, where *r* is the linear-correlation coefficient and *P* is the probability for no correlation.
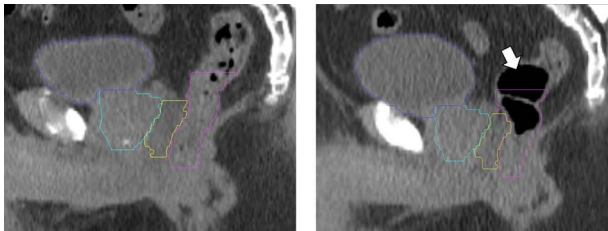

Fig. 6. Examples demonstrating a patient with HS. Mid-sagittal plane of TPCT (left) and RCCT (right) on the same patient, indicating the prostate (light blue), rectum (purple), bladder (blue), and HS (yellow). Although gas filling within the rectum was not observed on the TPCT image, significant gas filling indicated by a white arrow was observed in the proximal side of the rectum on RCCT.

of movement was as small as 1.9 mm at the maximum, which is not considered to be a remarkable result.

Currently, our institution requires HS insertion in the hypofractionation protocol of PT for prostate cancer. We analyzed this initial set of cases because there is insufficient evidence on whether spatial uncertainty is equivalent in HS-inserted cases as in previously non-inserted cases; data collection is ongoing for future research. As a result, a significant difference was found in the AP direction only. In addition, the proportion of the 3D vector length ≤5 mm was 95% in the HS-inserted group, but 55% in the non-inserted group. Although our imaging frequency is higher than reported by Pinkawa *et al.* [6], it is still not as high in the four times evaluation during the treatment period. Thus, it is not necessarily representative of the entire treatment. The fact that RCCTs were obtained off-line and not within treatment delivery, is a possible limitation. In addition, especially when the marker is present, the interfraction error is excluded, so the handling of the intrafraction error becomes more important. Suzuki *et al.* reported that there was no effect of HS on intrafaction prostate motion in three axes during Cyberknife treatment for Japanese prostate cancer patients [17]. However, since intrafraction prostate motion may also be affected by irradiation conditions, such as preparation methods and irradiation time, strictly speaking, it is necessary to study each facility, and we are currently continuing to do that. We have placed metallic markers in the prostate, but the required PTV margin may differ depending on the presence or absence of markers. Although the conditions to set a

suitable PTV margin in HS-inserted groups vary across institutions, it is necessary to use large sample-sized studies to gather substantial evidence. In Japan, the number of facilities that use HS is increasing, and it is expected that evidence will be gathered progressively.

CONCLUSION

We investigated whether there was a difference in the tendency of prostate positional displacement during the treatment period between the HS-inserted and non-inserted group. HS insertion significantly reduced the change in prostate position in the AP direction. It was suggested that HS is not only effective in reducing rectal dose, but may also contribute to the positional reproducibility of the prostate.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Podder TK, Fredman ET, Ellis RJ. Advances in radiotherapy for prostate cancer treatment. *Adv Exp Med Biol.* 2018;1096: 31–47.

2. Ishikawa H, Tsuji H, Murayama S et al. Particle therapy for prostate cancer: The past, present and future. *Int J Urol.* 2019;26(10):971–979.

3. Zelefsky MJ, Happersett L, Leibel SA et al. The effect of treatment positioning on normal tissue dose in patients with prostate cancer treated with three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys.* 1997;37(1):13–19.

4. McLaughlin PW, Wygoda A, Sahijdak W et al. The effect of patient position and treatment technique in conformal treatment of prostate cancer. *Int J Radiat Oncol Biol Phys.* 1999;45(2):407–413.

5. Kato T, Obata Y, Kadoya N et al. A comparison of prone three-dimensional conformal radiotherapy with supine intensity-modulated radiotherapy for prostate cancer: Which technique is more effective for rectal sparing? *Br J Radiol.* 2009;82(980):654–661.

6. Pinkawa M, Piroth MD, Holy R et al. Spacer stability and prostate position variability during radiotherapy for prostate cancer applying a hydrogel to protect the rectal wall. *Radiother Oncol.* 2013;106(2):220–224.

7. Mariados N, Sylvester J, Shah D et al. Hydrogel spacer prospective Multicenter randomized controlled pivotal trial: Dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys.* 2015;92(5):971–977.

8. Juneja P, Kneebone A, Booth JT et al. Prostate motion during radiotherapy of prostate cancer patients with and without application of a hydrogel spacer: A comparative study. *Radiat Oncol.* 2015;10:215.

9. Picardi C, Rouzaud M, Kountouri M et al. Impact of hydrogel spacer injections on interfraction prostate motion during prostate cancer radiotherapy. *Acta Oncol.* 2016;55(7):834–838.

10. Hedrick SG, Fagundes M, Robison B et al. A comparison between hydrogel spacer and endorectal balloon: An analysis of intrafraction prostate motion during proton therapy. *J Appl Clin Med Phys.* 2017;18(2):106–112.

11. Fischer-Valuck BW, Chundury A, Gay H et al. Hydrogel spacer distribution within the perirectal space in patients undergoing radiotherapy for prostate cancer: Impact of spacer symmetry on rectal dose reduction and the clinical consequences of hydrogel infiltration into the rectal wall. *Pract Radiat Oncol.* 2017;7(3):195–202.

12. Hedrick SG, Fagundes M, Case S et al. Validation of rectal sparing throughout the course of proton therapy treatment in prostate cancer patients treated with HS˚. *J Appl Clin Med Phys.* 2017;18(1):82–89.

13. Polamraju P, Bagley AF, Williamson T et al. Hydrogel spacer reduces rectal dose during proton therapy for prostate cancer: A dosimetric analysis. *Int J Part Ther.* 2019;5(4):23–31.

14. Morita M, Fukagai T, Hirayama K et al. Placement of HS hydrogel spacer for prostate cancer patients treated with iodine-125 low-dose-rate brachytherapy. *Int J Urol.* 2020;27(1):60–66.

15. Ogita M, Yamashita H, Sawayanagi S et al. Efficacy of a hydrogel spacer in three-dimensional conformal radiation therapy for prostate cancer. *Jpn J Clin Oncol.* 2020;50(3):303–309.

16. Saito M, Suzuki T, Sugama Y et al. Comparison of rectal dose reduction by a hydrogel spacer among 3D conformal radiotherapy, volumetric-modulated arc therapy, helical tomotherapy, CyberKnife and proton therapy. *J Radiat Res.* 2020;61(3):487–493.

17. Suzuki T, Saito M, Onishi H et al. Effect of a hydrogel spacer on the intrafractional prostate motion during CyberKnife treatment for prostate cancer. *J Appl Clin Med Phys. Version of Record online* 2020;10.

18. Roeske JC, Forman JD, Mesina CF 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(5):1321–1329.

19. Zelefsky MJ, Crean D, Mageras GS et al. Quantification and predictors of prostate position variability in 50 patients evaluated with multiple CT scans during conformal radiotherapy. *Radiother Oncol.* 1999;50(2):225–234.

20. https://www.jastro.or.jp/medicalpersonnel/guideline/space_oar20200410.pdf (in Japanese)

21. Kato T, Arai K, Sagara T et al. Patient-specific quality assurance for proton depth dose distribution using a multi-layer ionization chamber in a single-ring wobbling method. *Radiol Phys Technol.* 2019;12(3):305–311.

22. Moyers MF, Miller DW, Bush DA, Slater JD. Methodologies and tools for proton beam design for lung tumors. *Int J Radiat Oncol Biol Phys* 2001;49(5):1429–38.