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Development of a Vaginal Immobilization Device: A Treatment-planning Study of Carbon-ion Radiotherapy and Intensity-modulated Radiation Therapy for Uterine Cervical Cancer

YOSHIKI KUBOTA[1], TATSUYA OHNO[1], MOTOHIRO KAWASHIMA[1], KAZUTOSHI MURATA[1], NORIYUKI OKONOGI[2], SHIN-EI NODA[3], KAZUHISA TSUDA[4], MAKOTO SAKAI[1], MUTSUMI TASHIRO[1] and TAKASHI NAKANO[1]

[1]*Gunma University Heavy Ion Medical Center, Maebashi, Japan;*
[2]*National Institute of Radiological Sciences Hospital, National Institutes for Quantum and Radiological Science and Technology, Chiba, Japan;*
[3]*Department of Radiation Oncology, Saitama Medical University International Medical Center, Saitama, Japan;*
[4]*Department of Radiology, Gunma University Hospital, Maebashi, Japan*

Abstract. *Aim: We developed a vaginal immobilization device for external radiotherapy in gynaecological malignancies and evaluated its bowel dose-reduction effect during carbon-ion radiotherapy (CIRT) and intensity-modulated radiation therapy (IMRT) in patients with cervical cancer. Patients and Methods: Computed tomographic images obtained with and without the device in seven patients with cervical cancer were assessed. Treatment plans for CIRT and IMRT were generated, and dose–volume parameters (V_{20}, V_{25}, V_{35}, and D_{2cc}) of the rectum, sigmoidal colon, and bladder were evaluated. Results: The mean±standard deviation of the rectal volume in CIRT for V_{35} with and without the device were 2.1±2.1 and 13.6±4.4 ml, respectively, and those in IMRT were 2.0±2.2 and 13.7±3.8 ml, respectively; these values were significantly lower in CIRT and IMRT using this device. Conclusion: Using our novel vaginal immobilization device, high rectal doses were largely reduced in CIRT and IMRT.*

High-precision external-beam therapy for uterine cervical cancer ideally requires sparing the dose to organs at risk such as the rectum, bladder, sigmoidal colon, and pelvic bones as much as possible (1-3). For instance, it is possible to reduce the rectal dose by spacing the rectum from the target and precisely immobilizing the vaginal position.

Particle therapies such as carbon-ion radiotherapy (CIRT) and proton-beam therapy have an excellent dose conformity compared with photon-beam therapy because they have a better Bragg peak and sharper penumbra (4, 5). Intensity-modulated radiation therapy (IMRT) also has an excellent dose density (6-8). Such therapies can minimize damage to normal tissues while effectively concentrating damage to the target tumour.

Hydrogel spacers (9, 10) and balloon catheters (11) have been used to reduce rectal and bladder doses of brachytherapy in patients with gynaecological cancer. Although these devices are effective, external radiotherapy should be used to confirm their positions at the time of irradiation and the device material must be as reproducible and as solid as possible because external radiotherapy requires high positional reproducibility and durability for a treatment period of several weeks.

We developed an intravaginal device for immobilizing the cervical position and spacing the rectum from the tumour in patients with gynaecological malignancies. The device has two functional requirements: The first is to confirm the device's position using internal markers on X-ray images before irradiation, and the second is to confirm the irradiated position and dose using a GAFchromic film after irradiation. In this study, we evaluated the effects of spacing the target from the rectum and assessed the reduction of bowel dose in treatment planning for CIRT and IMRT in patients with uterine cervical cancer.

Patients and Methods

Patient selection. This study was approved by the Institutional Review Board at Gunma University Hospital (registration: UMIN000013340) and informed consent was obtained from each

Correspondence to: Yoshiki Kubota, Ph.D., Gunma University Heavy Ion Medical Center, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan. Tel: +81 272208378, Fax: +81 272208379, e-mail: y_kubota@gunma-u.ac.jp

Key Words: Carbon ion radiotherapy, intensity-modulated radiation therapy, cervical cancer, vaginal immobilization device, rectal dose.

Table I. *Patient characteristics*.

			Cervical tumour volume (ml)		Rectal volume (ml)		Sigmoidal colon volume (ml)		Bladder volume (ml)		Cervical tumour–rectum distance (mm)	
Patient number	Age (years)	Device size	With device	Without device	With device	Without device	With device	Without device	With device	Without device	With device	Without device
1	47	L	146.6	211.8	29.8	32.3	38.6	49.3	154.0	182.6	18.5	0.4
2	56	L	22.2	28.0	32.1	29.5	66.3	62.8	208.6	226.4	*	2.5
3	58	S	99.6	78.2	54.3	51.7	54.2	52.2	314.2	361.4	7.2	2.6
4	64	L	70.1	64.8	73.4	71.5	109.2	98.5	270.0	377.6	7.6	4.5
5	66	S	109.8	79.0	67.5	78.4	180.3	157.8	174.2	147.3	1.8	1.4
6	81	S	37.0	36.7	67.2	65.3	72.3	58.3	149.9	156.4	16.0	11.0
7	43	LL	59.6	58.2	51.3	57.2	64.3	55.4	190.5	285.3	10.6	4.3
Median	58	L	70.1	64.8	54.3	57.2	66.3	58.3	190.5	226.4	9.1	2.6

*There was no axial plane in which both the cervical tumour and rectum existed in the computed tomographic images with the device. Size (length×vertical width×horizontal width): S: 125.4×33.9×31.6 mm; L: 139.3×37.6×35.1 mm; LL: 159.3×37.6×35.1 mm.

patient. The study was performed in accordance with the ethical guidelines and regulations. Informed consent was obtained from each patient. The inclusion criteria were i) Histologically confirmed uterine cervical cancer, ii) no vaginal tumour invasion, iii) treatment by whole-pelvic irradiation with carbon ions, and iv) computed tomographic (CT) images were available both with and without insertion of the intravaginal device. We evaluated the data of seven consecutive patients who underwent CIRT for treatment of cervical cancer with passive irradiation from October 2013 to April 2015 at our facility. The patients' characteristics and the distances between the cervical tumour and rectum are shown in Table I. The distance between the cervical tumour and rectum was calculated as the average of the shortest distance between the cervical tumour and rectum in the axial plane where both the cervical tumour and rectum existed.

Device shape. The device [Ohno-Kubota-Tashiro (OKT) device, Japan patent P2016-32595A 2016] was made of high-density polyethylene (density of 1.16 g/cm^3), and its stopping power ratio measured by 380 MeV/u of energy with a passive carbon-ion beam at our facility was 1.023. The device is available in four sizes: SS, S, L, and LL (length: 125.4, 125.4, 139.3, and 159.3 mm, respectively; vertical width: 28.9, 33.9, 37.6, and 37.6 mm, respectively; and horizontal width: 26.8, 31.6, 35.1, and 35.1 mm, respectively). Photographs of an L-size device are shown in Figure 1. All devices contain three tungsten spheres of 1.5 mm in diameter to confirm the device position on X-ray fluoroscopy for patient positioning, as shown in Figure 2. The tungsten markers are located in separate cross sections to confirm their three-dimensional positions using orthogonal X-ray fluoroscopy, and no large artefacts are produced during CT scans. The device can be split in the vertical direction as shown in Figure 1C, and GAFchromic film is inserted to confirm the irradiated dose and position. Furthermore, the device has a fixing port on the rear end to reduce misalignment for CT or irradiation as shown in Figure 1D.

In this study, we did not assess the reproducibility of the device position and irradiated dose by GAFchromic film because the primary study focus was the dose-reduction effect of the device.

CT imaging. Treatment-planning CT images were acquired with an X-ray CT device (Aquilion LB, Self-Propelled; Canon Medical Systems, Tochigi, Japan) approximately at the end of the expiration phase as monitored with a respiratory gating system (AZ-733; Anzai Medical, Tokyo, Japan). CT images with and without insertion of the device were consecutively acquired for all patients.

Treatment planning. Target delineation: The gross tumour volume was delineated on treatment-planning CT images with reference to T2-weighted magnetic resonance imaging and gynaecological examination by two radiological oncologists. The clinical target volume (CTV) included the cervical tumour, uterus, parametrium, the upper ≥2 cm of the vagina, and the pelvic lymph node regions. The planning target volume (PTV) was created from the CTV by adding 3-mm margins in all directions. When necessary, however, the common iliac lymph node regions in the PTV were cut so that they entered the irradiation field for CIRT (15×15 cm) because the dose-reduction effect on the bowel with and without the device was primarily studied. Outer organ contours were delineated for the bladder, rectum, and sigmoidal colon. The rectosigmoidal flexure was used as the border between the rectum and sigmoidal colon.

CIRT: Treatment planning for CIRT was calculated using an XiO-N system (Elekta, Stockholm, Sweden and Mitsubishi Electric, Tokyo, Japan) that employed a pencil-beam algorithm and incorporated a dose engine for CIRT (K2-Dose). The irradiation field was generated with a passive irradiation method (12). The relative biological effectiveness (RBE) was included in the absorbed dose using a spread-out Bragg peak concept (13), and the clinical dose was defined as Grays RBE.

Two beam fields (anterior–posterior and posterior–anterior) were used in six fractions per field, and the prescription dose was 3.0 Gy RBE ×12, *i.e.* 36 Gy RBE. The dose distribution was calculated to achieve minimum doses covering 95% (D_{95}) of the PTV >95%.

IMRT: In order to evaluate the differences in the parameters of the dose–volume histogram (DVH) in CIRT and IMRT, treatment planning for IMRT was also calculated using an eclipse treatment system (Varian Medical Systems, Palo Alto, CA, USA).

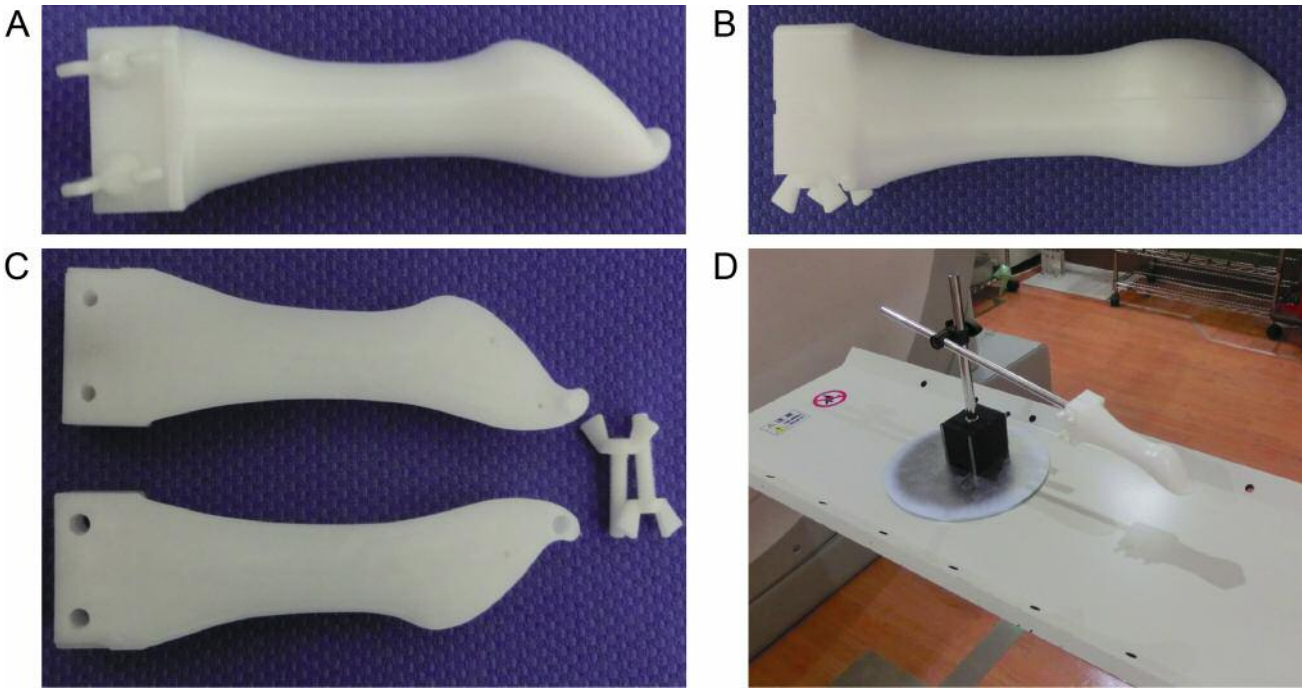

Figure 1. *Photographs of L-size device. A: Side view. B: Frontal view. C: Separated. D: Immobilized.*

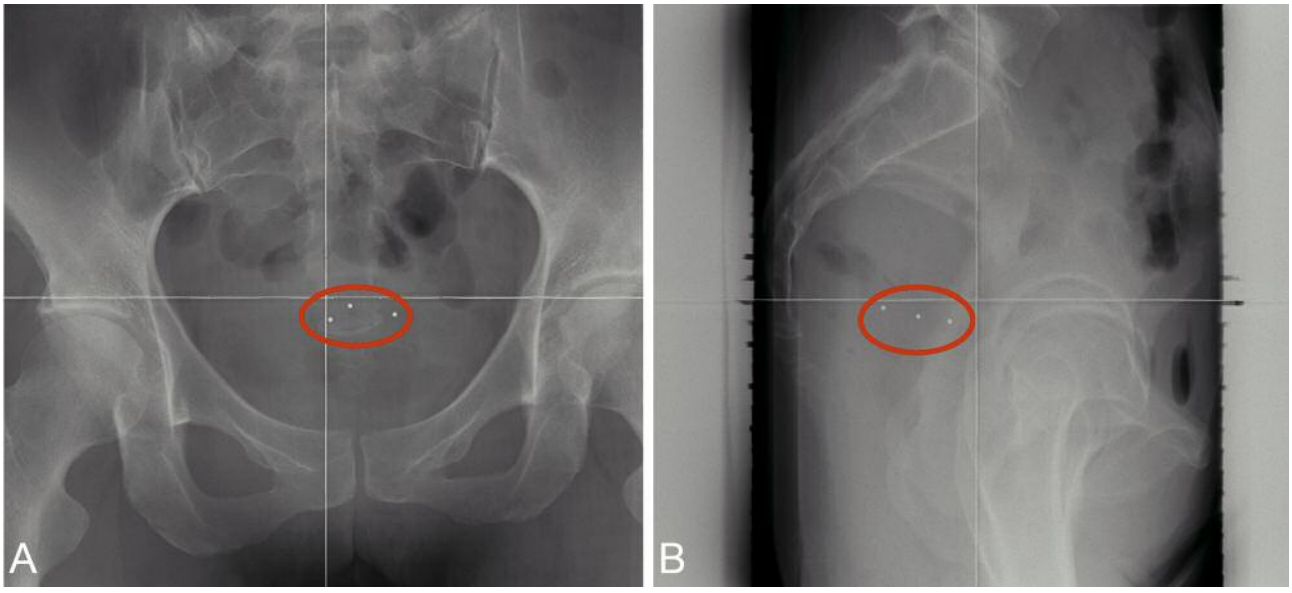

Figure 2. *Orthogonal X-ray images of a patient with insertion of the device. A: Vertical image. B: Horizontal image. Red circles show the tungsten markers.*

Nine beam fields were used, and the prescription dose was 3.0 Gy ×12, *i.e.* 36 Gy. Each field angle was chosen, and the dose distribution was calculated to achieve D95% of PTV >95% and maximum dose of PTV <110% while reducing the rectal dose as much as possible.

Evaluation of treatment planning. In order to evaluate the effectiveness of the device, the percentage volume of the rectum, sigmoidal colon, and bladder receiving 20, 25, 30, or 35 Gy RBE/Gy (V_{20}, V_{25}, V_{30}, or V_{35}, respectively) and the percentage of minimum doses covering 2 cc of the rectum, sigmoidal colon, and

Table II. *Dose–volume parameters in seven patients with and without the device in carbon-ion radiotherapy (CIRT) and intensity-modulated radiation therapy (IMRT). All parameters are shown as mean±standard deviation and range (minimum-maximum).*

	CIRT			IMRT		
	Without device	With device	*p*-Value	Without device	With device	*p*-Value
Rectum						
V_{20} (ml)	49.1±14.6 (17.7-68.8)	47.4±15.9 (25.8-71.2)	0.253	38.9±8.6 (24.5-48.4)	28.1±7.9 (16.7-36.7)	<0.001
V_{25} (ml)	29.0±8.4 (17.7-43.8)	14.1±7.4 (2.9-25.8)	<0.001	29.2±7.1 (17.7-38.2)	16.1±5.4 (7.8-21.5)	<0.001
V_{30} (ml)	22.4±6.6 (14.5-35.9)	7.5±4.4 (0.7-14.4)	<0.001	22.2±5.2 (14.5-30.2)	8.4±3.4 (3.0-13.0)	<0.001
V_{35} (ml)	13.6±4.4 (7.8-23.0)	2.1±2.1 (0.0-6.4)	<0.001	13.7±3.8 (8.1-18.3)	2.0±2.2 (0.1-7.1)	<0.001
D_{2cc} [Gy (RBE)/Gy]	36.0±0.1 (35.8-36.2)	33.4±3.0 (26.5-35.9)	0.036	37.3±0.8 (35.7-38.4)	34.4±1.6 (31.4-37.0)	0.001
Sigmoidal colon						
V_{20} (ml)	69.4±30.9 (48.3-143.1)	74.0±39.6 (36.5-165.2)	0.189	70.5±32.3 (48.3-146.3)	75.8±40.4 (37.0-168.2)	0.160
V_{25} (ml)	45.1±16.6 (26.5-80.8)	42.9±12.7 (20.2-59.9)	0.333	64.9±30.5 (43.6-136.5)	67.8±38.1 (36.6-158.6)	0.316
V_{30} (ml)	38.3±15.1 (19.1-66.8)	36.0±11.3 (15.7-50.5)	0.302	56.3±28.8 (33.1-123.9)	58.8±33.4 (28.4-137.2)	0.362
V_{35} (ml)	27.6±13.2 (9.7-47.9)	24.6±10.9 (9.5-43.0)	0.209	36.3±20.2 (25.3-85.3)	38.0±13.8 (18.5-62.7)	0.387
D_{2cc} [Gy (RBE)/Gy]	36.1±0.2 (35.8-36.3)	36.1±0.1 (35.8-36.3)	0.229	37.8±0.9 (36.0-38.8)	37.7±0.6 (36.7-38.7)	0.311
Bladder						
V_{20} (ml)	243.4±84.1 (147.3-377.1)	205.7±53.1 (149.9-298.4)	0.042	241.4±87.1 (134.5-367.8)	200.4±58.0 (149.9-308.5)	0.025
V_{25} (ml)	155.2±57.3 (67.2-216.3)	124.8±43.4 (66.1-185.8)	0.011	191.6±79.5 (88.7-320.2)	174.0±55.9 (102.4-265.7)	0.152
V_{30} (ml)	140.9±53.3 (57.1-196.4)	112.3±42.7 (51.3-167.1)	0.011	153.9±59.8 (68.2-246.0)	144.2±53.0 (78.1-245.0)	0.285
V_{35} (ml)	119.6±47.7 (43.6-171.6)	94.3±40.7 (34.6-142.2)	0.011	121.3±48.1 (45.3-175.7)	105.2±46.3 (45.3-182.8)	0.064
D_{2cc} [Gy (RBE)/Gy]	36.3±0.1 (36.1-36.4)	36.2±0.1 (36.0-36.3)	0.178	38.1±0.9 (36.1-39.0)	38.0±0.7 (37.0-39.0)	0.300

RBE: Relative biological effectiveness; VxGy (RBE)/Gy: percentage volume receiving × Gy (RBE)/Gy; D2cc: percentage of minimum dose covering 2 cc.

bladder (D_{2cc}) were calculated. Gy RBE was used as the dose unit for CIRT, and Gy was used as the dose unit for IMRT. All DVH parameters were calculated with and without the device and compared using a *t*-test with a 0.05 significance level.

Results

Examples of dose distributions for CIRT and IMRT with and without the device are shown in Figure 3. The doses to the rectum, sigmoidal colon, and bladder in CIRT and IMRT are shown in Table II. In CIRT, for the rectum, all parameters except V_{20} were significantly reduced by using the device. For the sigmoidal colon, V_{30} and V_{35} were reduced by using the device although there were no significant differences. For the bladder, all parameters except D_{2cc} were significantly reduced by using the device. In IMRT, for the rectum, all DVH parameters were significantly reduced by using the device. For the sigmoidal colon, there were no significant differences. For the bladder, V_{20} was significantly reduced by using the device. Each DVH parameter, and the DVHs for the rectum, sigmoidal colon, and bladder are shown in Figure 4.

Discussion

We evaluated the rectal dose-reduction effect of our vaginal insertion device, which spaced the cervical tumour from the bowel (especially the rectum), in patients undergoing external-beam radiotherapy for cervical cancer. From the validation in seven patients (shown in Table I), we found that the device was able to create a space of 6.5 mm; the median distance between the cervical tumour and rectum in patients without the device was 2.6 mm, and that with the device was 9.1 mm.

In the treatment-planning study, we found that the rectal dose for both CIRT and IMRT was significantly reduced using the device. Damato *et al*. reported that D_{2cc} for the rectum decreased by 22% using hydrogel injection in brachytherapy (10). Although in our study the reduction of D_{2cc} for the rectum was low, D_{2cc} decreased by 7.2% for CIRT and by 7.8% for IMRT, the reduction effect for a high dose volume was good; V_{35} was reduced by 84.6% for CIRT and by 85.4% for IMRT using our device.

In our comparison between CIRT and IMRT, the rectal volume reductions at high doses (V_{25}, V_{30}, and V_{35}) were identical. Conversely, reduction of the medium dose was observed as shown by the significant difference in V_{20} for IMRT (Table II). For the sigmoidal colon in CIRT, V_{30} and V_{35} were lower with than without the device despite the fact that the volume was larger with than without the device. The sigmoidal dose might be reduced in such cases, although there were no significant differences in the present study. For the bladder, there were significant differences in almost all cases for CIRT and in one case for IMRT. However, the cause of these differences was assumed to be the large

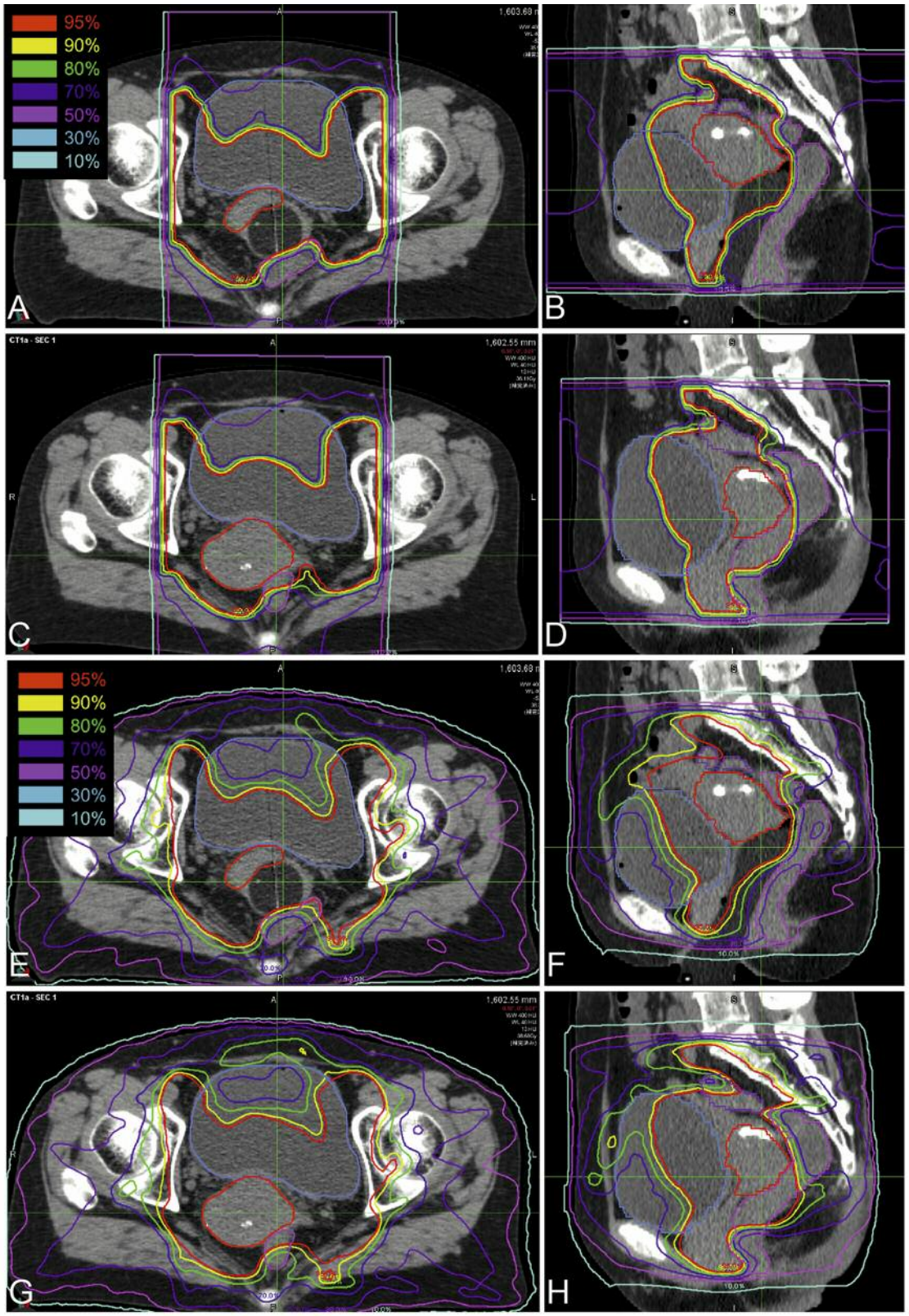

Figure 3. *Computed tomographic image and dose distribution of carbon-ion radiotherapy (A-D) and intensity-modulated radiation therapy (E-H). Cases with (A, B, E and F) and without (C, D, G and H) the device in axial (A, C, E and G) and sagittal (B, D, F and H) planes. The red, magenta, purple, and blue contours delineate the cervical tumour, rectum, sigmoidal colon, and bladder, respectively.*

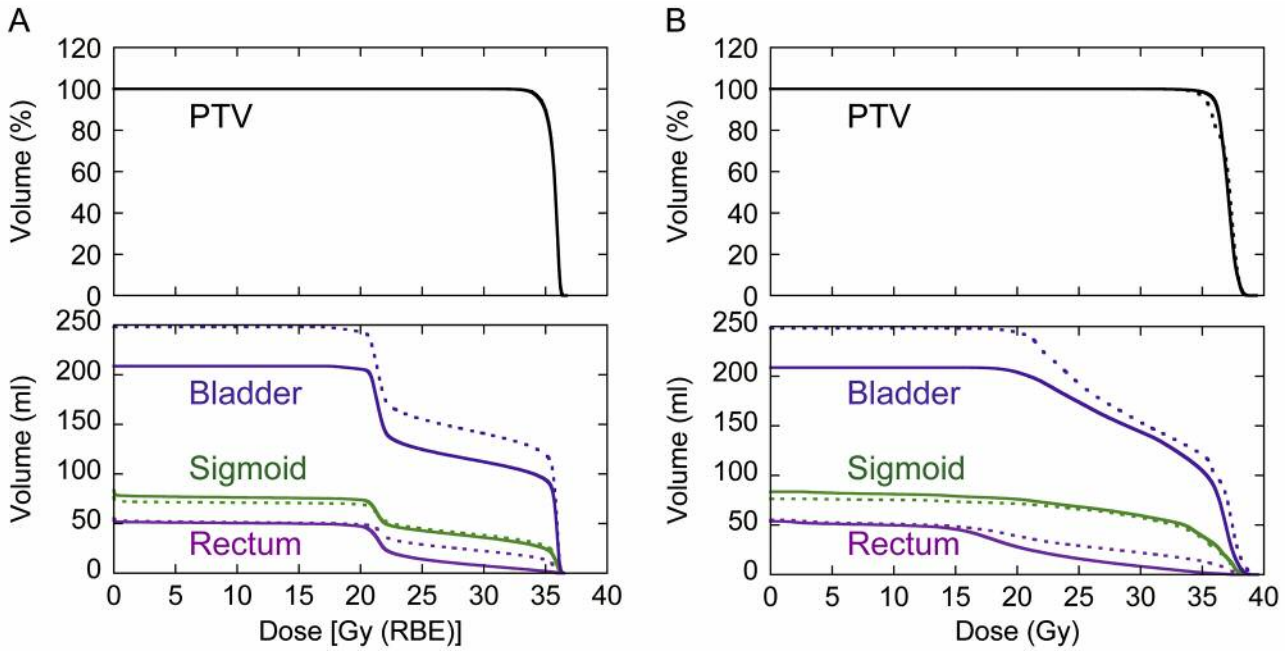

Figure 4. *Averaged dose–volume histograms of the planning target volume (PTV), rectum, sigmoidal colon, and bladder for carbon-ion radiotherapy (A) and intensity-modulated radiation therapy (B). The solid lines show cases with the device, and the dashed lines show cases without the device.*

differences in the bladder volumes because the CT images with and without device insertion were consecutively acquired without breaks. Thus, a dose-reduction effect in the bladder by the device was not found.

CIRT for passive irradiation was validated in this study. A similar effect would be observed in layer-stacking irradiation or scanning irradiation with CIRT, and these techniques might reduce the bowel dose more than passive irradiation because they have better conformity (14, 15). Additionally, a similar effect would be observed in proton therapy because the proton beams also exhibit a Bragg peak and sharp dose distribution (16-18).

When the cervical tumour and rectum are in proximity, as shown in Figure 3, the rectum receives a high dose if the treatment-planning dose is calculated with a normal margin. In such cases, the high dose to the rectum can largely be reduced by modifying the plan to avoid the rectal side. However, it is necessary to consider whether and how much of the plan to modify because the target dose would also be reduced.

In this study, the significance of the device was verified in patients without vaginal infiltration. If the tumour has infiltrated the lower part of the vagina, the whole vaginal region should be included in the CTV, and the rectal dose would thus be unlikely to decrease. If the tumour has infiltrated the anterior or posterior vaginal wall, a further individualized sparing effect might occur. However, accurate diagnosis and positional precision would be necessary in such cases.

Because the device has three markers, its position in the patient can be confirmed from X-ray fluoroscopy. Additionally, a GAFchromic film can be placed inside the device. *In vivo* dosimetry during CIRT or IMRT using this film is expected to be developed.

This study has certain limitations. Further analysis is necessary to elucidate the exact effect of the device because this study involved only seven patients. Moreover, this study was performed only for treatment planning. The changes in the bowel position that would occur with inter- or intrafractional position changes of the device are unclear. Because the bowel dose has a risk of increasing above the treatment-planning dose, verification is necessary.

Conclusion

We developed an intravaginal device for immobilizing the cervical position and spacing the rectum from tumour in patients with gynaecological malignancies. In this study, we validated the effectiveness of rectal dose reduction in RT of the uterine cervix. In CIRT and IMRT, high rectal doses were largely reduced when using the device. In IMRT, medium rectal doses were reduced when using the device.

Conflicts of Interest

The Authors declare that they have no competing interests in regard to this study.

Authors' Contributions

YK and TO coordinated the entire study. Patient clinical data collection were performed by YK, MK, KM, and KT. Data analysis was performed by YK and MS. The article was prepared by YK. Corrections and improvements were suggested by TO, NO, SN, MT, and TN. All Authors read and approved the final article.

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Availability of Data and Materials

Data are available upon reasonable request and with permission of Gunma University Heavy Ion Medical Center.

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