

Whole-pelvic radiotherapy with spot-scanning proton beams for uterine cervical cancer: a planning study

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ABSTRACT

The aim of this study was to compare the dosimetric parameters of whole-pelvic radiotherapy (WPRT) for cervical cancer among plans involving 3D conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), or spot-scanning proton therapy (SSPT). The dose distributions of 3D-CRT-, IMRT-, and SSPT-based WPRT plans were compared in 10 patients with cervical cancer. All of the patients were treated with a prescribed dose of 50.4 Gy in 1.8-Gy daily fractions, and all of the plans involved the same planning target volume (PTV) constrictions. A 3D-CRT plan involving a four-field box, an IMRT plan involving seven coplanar fields, and an SSPT plan involving four fields were created. The median PTV D95% did not differ between the 3D-CRT, IMRT and SSPT plans. The median conformity index 95% and homogeneity index of the IMRT and SSPT were better than those of the 3D-CRT. The homogeneity index of the SSPT was better than that of the IMRT. SSPT resulted in lower median V20 values for the bladder wall, small intestine, colon, bilateral femoral heads, skin, and pelvic bone than IMRT. Comparing the Dmean values, SSPT spared the small intestine, colon, bilateral femoral heads, skin and pelvic bone to a greater extent than the other modalities. SSPT can reduce the irradiated volume of the organs at risk compared with 3D-CRT and IMRT, while maintaining excellent PTV coverage. Further investigations of SSPT are warranted to assess its role in the treatment of cervical cancer.

KEYWORDS: spot scanning proton therapy, IMRT, 3D-CRT, whole-pelvic radiotherapy, cervical cancer, dosimetry

INTRODUCTION

Whole-pelvic radiotherapy (WPRT) with 3D conformal radiotherapy (3D-CRT) plays an important role in the treatment of gynecological malignancies, particularly cervical cancer. For patients with locally advanced cervical cancer, the standard treatment involves cisplatin-based chemotherapy and WPRT combined with intracavitary brachytherapy [1–3]. However, performing WPRT with 3D-CRT frequently results in gastrointestinal, genitourinary and/or hematological toxicities [4, 5]. Recently, it has been reported that

performing WPRT with intensity-modulated radiotherapy (IMRT) can reduce the frequency of adverse events. In contrast to 3D-CRT, IMRT generates non-uniform fields, which helps to achieve better target coverage and improved sparing of organs at risk (OARs). For example, IMRT can reduce the doses delivered to the small intestine, rectum and bladder [6] and is associated with significantly lower toxicity rates than 3D-CRT [7].

The use of proton beams, which exhibit a characteristic Bragg peak, results in a modest reduction in the radiation dose delivered to

normal tissues located in front of the target and a marked reduction in the dose delivered to normal tissues behind the target [8]. The PROBEAT-III (Hitachi, Ltd, Tokyo, Japan) proton beam therapy system has been used at Nagoya Proton Therapy Center since 2013. Our center has a synchrotron and three treatment rooms. The synchrotron can accelerate protons to any energy level between 70 and 250 MeV. Two treatment rooms have passive scattering nozzles with range modulation wheels, and the other treatment room is equipped with a spot-scanning system. Spot-scanning proton therapy (SSPT), in which a thin proton beam is repeatedly applied to different parts of the target until the whole target area has been covered, makes it possible to irradiate complex targets [9–11]. Due to these characteristics, SSPT might generate a superior dose distribution compared with 3D-CRT and IMRT [12–15]. Thus, the purpose of this study was to perform dosimetric comparisons of 3D-CRT-, IMRT- and SSPT-based WPRT plans for uterine cervical cancer.

MATERIALS AND METHODS

Patients

A total of 10 patients with cervical cancer underwent WPRT with 3D-CRT at the Nagoya City West Medical Center between March 2012 and July 2015. Their mean age was 53 years (range, 33–80 years). Four patients had Stage IIB disease; two patients had Stage IIIA disease; and one patient each had Stage IB, IIA, IIIB and IVa disease, according to the International Federation of Gynecology and Obstetrics criteria. All of the patients had a biopsy-proven pathological diagnosis of squamous cell carcinoma.

Study design

This was a planning study of WPRT for uterine cervical cancer. All of the plans were created using computed tomography (CT) images of 10 patients who were treated with 3D-CRT. IMRT and SSPT plans were created for each patient. Each plan was generated using the same contours and the same planning target volume (PTV) constrictions. The prescribed WPRT dose was 50.4 Gy in 1.8-Gy daily fractions in all patients.

Simulation and contouring

The CT scans were obtained with a slice thickness of 2 mm, using a 16-row multidetector CT (Aquilion LB; Toshiba Medical Systems, Tochigi, Japan), with the patient in the supine position. Contouring of the target volumes and normal structures was performed in MIM Maestro (version 6.4, MIM Software, Cleveland, Ohio, USA). The contours created in MIM Maestro were exported to each treatment planning system.

PTV and OAR definitions

The gross tumor volume (GTV) included any gross disease that was visible on contrast-enhanced CT and/or T2-weighted magnetic resonance images (T2WI) and any lesions that were detected during clinical examinations. The Radiation Therapy Oncology Group (RTOG)/Japan Clinical Oncology Group recommendations were used in combination to guide the contouring of the clinical target volume (CTV) [16–19]. The CTV included both the primary tumor site (CTV primary) and the regional lymph nodes (CTV LNs). The

CTV primary consisted of the GTV, uterine cervix, uterine corpus, parametrium, ovaries and the upper part of the vagina. The upper part of the vagina contained half or two-thirds of the vagina, depending on the extent of the patient's disease. The CTV LN included the common iliac, external and internal iliac, obturator, and parasacral nodes. The internal target volume (ITV) included the CTV primary plus 0.5–1.0 cm internal margins, and the CTV LN. No internal margins were added to the CTV LN because the lymph nodes barely move during radiotherapy. The PTV was defined as the ITV plus a 0.5-cm isotropic margin.

The OARs, including the rectum, rectal wall, bladder, bladder wall, small intestine, colon, bilateral femoral heads, skin, and pelvic bone, were contoured. The rectum was contoured from the level of the sigmoid flexure to the anus. The rectal wall was contoured separately, from its outer wall to 3 mm beyond its inner wall. The bladder wall was contoured in a similar manner. Individual loops of the small intestine and colon were contoured on axial slices from 1 cm above the PTV to the lowest part of the pelvis. The small intestine and colon were contoured en bloc (they were treated as a 'bowel bag'). The skin was contoured from its surface to a depth of 3 mm on axial slices between 1 cm above the PTV and 1 cm below the ischial tuberosity. The pelvic bone was contoured from the L5 vertebral body to the ischial tuberosity.

3D-CRT planning

3D-CRT plans with a four-field arrangement were generated using the Pinnacle³ treatment planning system (Philips Medical Systems, Eindhoven, The Netherlands), in which the superposition algorithm was used. The four fields consisted of opposing anteroposterior/posteroanterior and lateral fields and were irradiated with 10-MV photons as follows: (i) superior border: upper edge of L5; (ii) lateral border: 1.5 cm lateral to the greater sciatic notch; (iii) inferior border: the lower edge of the obturator foramen; (iv) anterior border: 0.5 cm anterior to the symphysis pubis; and (v) posterior border: the junction of S2/S3. The irradiation device was a Novalis TX (Brainlab AG, Feldkirchen, Germany). In treatment planning, the lower constraint for the PTV was 95% of the prescribed dose in 95% of the PTV. The small intestine volumes receiving 40 Gy (V40) and the pelvic bone volumes receiving 20 Gy (V20) were kept as low as possible without compromising the PTV constraints.

IMRT planning

IMRT plans were generated using iPlan RT (version 4.1, Brainlab AG), in which the pencil beam algorithm was used. The plans involved the use of seven coplanar fields with fixed gantry angles of 30, 100, 140, 180, 220, 260 and 330 degrees. An X-ray energy of 10 MV and dynamic multileaf collimators were used. The PTV dose constraints were as follows: (i) D95% (dose received by 95% of the volume of the PTV): ≥95%; (ii) maximum dose: ≤115%, limited to within the PTV. The planning constraints for normal tissues were as follows: (i) bowel bag: V40 (volume receiving 40 Gy) <40%; maximum dose: <50 Gy; (ii) rectum: V40: <40%; maximum dose: <50 Gy; (iii) bladder: V40: <40%; maximum dose: <50 Gy; (iv) bilateral femoral heads: V30: <40%; maximum dose: <50 Gy; and (v) pelvic bone: V20: <80%. The doses for the small intestine,

colon, and skin were recorded, but no constraints were employed for these organs. The irradiation device was a Novalis TX.

SSPT planning

The SSPT plans were generated using VQA (version 3.0.5, Hitachi, Ltd), in which the pencil beam algorithm with the triple Gaussian model was used to improve the accuracy of dose calculation. The irradiation device was a PROBEAT-III. The plans involved four coplanar fields with gantry angles of 90, 150, 210 and 270 degrees and single-field optimization. Bowel gas, bowel peristalsis, and urine in the bladder affect the dose distribution of proton beams, especially for proximal beams. They lead to some uncertainty in dose distribution. After preliminarily evaluating various gantry angles, these angles were considered the most appropriate to minimize the involvement of the colon, small intestine, rectum and bladder (data not shown). The planned energy range for the SSPT treatment was 71.6–221.4 MeV in 94 steps, and the beam range varied from 4 to 30.6 cm. The minimum and maximum spot size in air was 4 and 12 mm, respectively, at the isocenter. We used a relative biological effectiveness value of 1.1 as the conversion factor when calculating the effective proton therapy dose from the physical dose in Gy, as recommended in International Commission on Radiation Units and Measurements Report (ICRU report) 78 [20]. Since the conventional geometry-based PTV concept used in photon therapy does not work well for proton therapy, the beam-specific PTV was defined for SSPT planning. The beam-specific PTV, which was expanded from the ITV, was based on the definition reported by Peter *et al.* [21] and took both lateral set-up errors and the uncertainty of the proximal/distal range calculations for each specific beam angle into consideration. Proton plans based on the beam-specific PTV concept provide better target coverage in the presence of set-up errors and range uncertainties. While the beam-specific PTV was used for SSPT planning, the PTV (geometry-based PTV) was used for evaluation. The constraints for the PTV and OAR are the same as those for 3D-CRT planning.

Verification of treatment planning system calculations

In order to validate the accuracy of the treatment planning systems, we compared dose profiles calculated by each planning system with doses actually measured. The dose profiles calculated by Pinnacle³ and iPlan were measured at a 10 cm depth in a 3D-water phantom (Blue Phantom², IBA Dosimetry GmbH, Schwarzenbruck, Germany) with a 10 × 10 cm field using a waterproof Farmer chamber (Model 30013, PTW, Freiburg, Germany). Spots of proton particles were positioned within a 10 × 10 cm field. Lateral spacing between the respective spots was 0.5 cm, which was sufficiently small for our pencil beams to produce a flat dose region. Lateral dose profiles were measured at the center of the SOBP with a solid phantom (Tough Water Phantom, Kyoto Kagaku, Kyoto, Japan) and a 2D ion chamber detector array (OCTAVIUS^{XDR}, PTW).

Evaluation of outcomes and statistics

The dose-volume data were transferred via DICOM-RT (digital imaging and communications in medicine for radiotherapy) to MIM Maestro from each treatment planning system, and dosimetric

parameters were evaluated. The equality of delivered doses among three treatment plans made with different treatment planning systems was assured by evaluating all dosimetric parameters in the MIM Maestro system. The dosimetric parameters of the 3D-CRT, IMRT and SSPT plans were compared (using the Kruskal-Wallis test adjusted for multiple comparisons using Bonferroni's method) to determine whether any of the examined parameters differed significantly. *P*-values of <0.05 were considered to be significant. In addition, the conformity index 95% (CI 95%) was defined as the ratio between the volume receiving at least 95% of the prescribed dose and the volume of the PTV. The homogeneity index (HI) (D2% – D98%/D50%) of each plan was determined. The beam-on time was defined as the time from first beam on until last beam off. All analyses were performed using the software EZR (version 1.29) [22].

RESULTS

Representative case

3D-CRT, IMRT and SSPT treatment plans for a representative patient are shown in Fig. 1. The 50 Gy (red), 40 Gy (yellow) and 20 Gy (blue) isodose lines are highlighted on each figure. The 3D-CRT plan (Fig. 1a) exhibited a square-like dose distribution, which provided good coverage of the PTV, but also resulted in the irradiation of the surrounding normal tissues. In the IMRT plan (Fig. 1b), the 50 Gy isodose lines conformed to the shape of the PTV, and the volumes of the OARs that were irradiated with the prescribed dose were reduced. The SSPT plan (Fig. 1c) yielded a better dose distribution, which spared the OARs to a greater extent, particularly in the low-dose range.

Verification of treatment planning system calculations

W_{50} (radiological width on a 50% dose level) and P_{80-20} (penumbra, defined as distance between 80 and 20% dose levels) values are shown in Tables 1 and 2. The differences between measured values and values calculated from the treatment planning systems were all within 2 mm. The dose profiles calculated by Pinnacle³ and iPlan met the acceptance criteria [23]. Although the accuracy criteria for calculation with proton beam planning systems has not yet been unified among the respective facilities, the calculation by VQA had sufficiently high accuracy for clinical use [11, 24] and met the acceptance criteria for X-rays [23].

Target coverage

The dosimetric parameters of the PTV in the 3D-CRT, IMRT and SSPT plans were analyzed (Table 3). The median values of the dose-volume histogram (DVH) parameters for the PTVs obtained for 10 patients using each of the three plans are shown in Fig. 2. We detected no differences in the D95% and D98% values (nearly equal to D_{min} in ICRU Report 83 [25]) of the PTVs between the three plans. The 3D-CRT plans resulted in relatively higher D95% values for the PTV, because it was difficult to finely adjust the delivered dose in 3D-CRT plans. The 3D-CRT plans resulted in significantly higher D50% values for the PTV than the IMRT and SSPT plans, but no difference was detected between the D50% values of IMRT and SSPT. The D2% values (nearly equal to D_{max} in ICRU Report 83 [25]) of the PTVs differed significantly between the

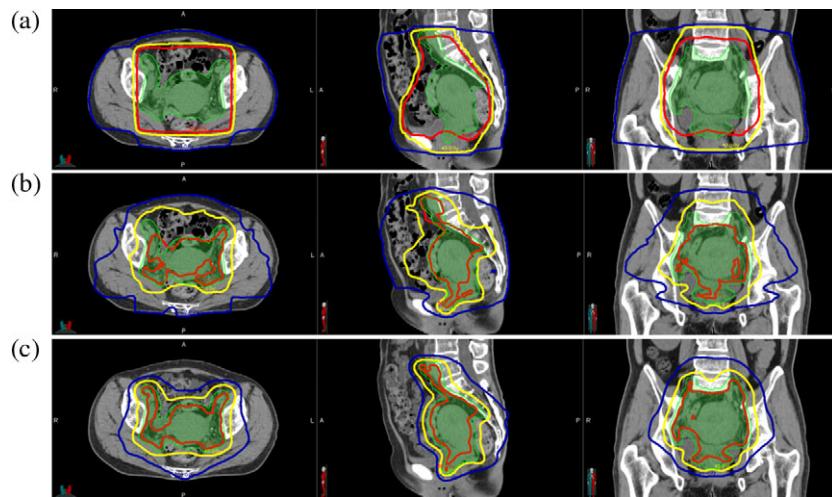


Fig. 1. Dose distributions of (a) 3D conformal radiotherapy, (b) intensity-modulated radiotherapy and (c) spot-scanning proton therapy plans. The 50 Gy (red), 40 Gy (yellow) and 20 Gy (blue) isodose lines are highlighted. The planning target volume is shown in green.

Table 1. Verification of treatment planning system calculations for 3D-CRT and IMRT

	Measured value	Calculated value in Pinacle ³	Calculated value in iPlan
W ₅₀ (mm)	110.64	109.99	109.68
P ₈₀₋₂₀ (mm)	6.72	6.38	6.12

3D-CRT = 3D conformal radiation therapy, IMRT = intensity-modulated radiation therapy, W₅₀ = radiological width on a 50% dose level, P₈₀₋₂₀ = penumbra defined as distance between 80 and 20% dose levels.

Table 2. Verification of treatment planning system calculations for SSPT

	Measured value	Calculated value in VQA
W ₅₀ (mm)	105.03	105.01
P ₈₀₋₂₀ (mm)	13.61	13.72

SSPT = spot scanning proton therapy, W₅₀ = radiological width on a 50% dose level, P₈₀₋₂₀ = penumbra defined as distance between 80 and 20% dose levels.

three plans. The CI95% of the IMRT and SSPT plans were better than that of the 3D-CRT plan, but no difference was detected between those of the IMRT and SSPT plans. The target dose HI of the SSPT plan was better than those of the 3D-CRT and IMRT plans.

OARs

The dosimetric parameters of the OARs in the 3D-CRT, IMRT and SSPT plans are shown in Table 3. The median DVH values for the rectal wall, bladder wall, small intestine, colon, bilateral femoral heads, skin, and pelvic bone obtained for 10 patients using each of

the three plans are shown in Fig. 3. Both the IMRT and SSPT plans provided better OAR dose sparing than the 3D-CRT plan. In addition, the SSPT plan protected the OARs better than the other two plans, especially in the low-dose range. The SSPT plan resulted in significantly lower V20 values for the bladder wall, small intestine, colon, bilateral femoral heads, skin, and pelvic bone. On the other hand, we did not detect any difference in the V40 values of the OARs between the IMRT and SSPT plans. The SSPT plan resulted in lower mean dose (Dmean) values for the small intestine, colon, bilateral femoral heads, skin, and pelvic bone than the IMRT plan. Dmean to the bladder wall and rectal wall was decreased with IMRT and SSPT. Representative DVH parameters for the OARs are shown in Fig. 4.

DISCUSSION

IMRT-based WPRT is being increasingly used to treat gynaecological malignancies, including locally advanced cervical cancer [26–28]. On the other hand, SSPT, a new type of proton beam therapy that achieves superior dose distributions has recently been developed [29]. Compared with conventional passive-scattering proton therapy, SSPT is more effective at treating complex targets. The use of IMRT-based WPRT in combination with proton therapy for para-aortic lymph node metastases has been reported as a treatment for gynaecological cancer [30]. The dosimetric comparison of IMRT- and SSPT-based WPRT for locally advanced cervical cancer has been reported by Marnitz *et al.* [31], while we compared three modalities (3D-CRT, IMRT and SSPT). This study demonstrated that SSPT could deliver the prescribed dose to the PTV while decreasing the doses administered to the OARs. Compared with those seen in 3D-CRT and IMRT, significantly smaller sections of the bladder wall, small intestine, colon, bilateral femoral heads, skin, and pelvic bone received low doses of radiation during SSPT.

Since the first report about the use of IMRT to treat cervical cancer by Portelance *et al.* [32], IMRT-based WPRT has become

Table 3. Dose–volume parameters of the three plans

Structure	3D-CRT			IMRT		SSPT		P			
		Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	3D-CRT vs IMRT	3D-CRT vs SSPT	IMRT vs SSPT	
PTV	D2%	(%)	103.8	(103.4–104.7)	103.0	(102.4–103.4)	100.4	(100.3–100.7)	<0.05	<0.001	<0.001
	D5%	(%)	103.3	(103.0–104.0)	102.5	(101.9–102.8)	100.3	(100.2–100.6)	<0.01	<0.001	<0.001
	D50%	(%)	101.4	(100.7–101.7)	99.9	(99.8–100.1)	99.7	(99.6–99.9)	<0.05	<0.001	0.39
	D95%	(%)	96.3	(95.5–96.8)	95.2	(94.8–95.4)	95.4	(95.3–95.6)	0.06	0.18	0.77
	D98%	(%)	90.8	(83.7–95.1)	93.4	(93.0–94.0)	93.1	(92.8–93.4)	1.00	1.00	1.00
	CI95%		2.115	(1.911–2.385)	1.057	(1.027–1.069)	1.059	(1.045–1.082)	<0.001	<0.1	1.00
	HI		0.127	(0.087–0.203)	0.095	(0.085–0.102)	0.075	(0.071–0.077)	0.74	0.056	<0.001
Rectal wall	Dmean	(Gy)	47.5	(46.4–48.7)	37.2	(35.6–38.8)	35.6	(34.5–36.7)	<0.001	<0.001	0.18
	V40	(%)	92.3	(89.0–94.1)	51.7	(44.7–58.1)	49.8	(44.7–51.8)	<0.001	<0.001	1.00
	V20	(%)	95.4	(92.9–96.9)	92.8	(87.5–95.6)	92.1	(90.2–93.2)	0.65	0.19	1.00
Bladder wall	Dmean	(Gy)	50.1	(49.7–51.0)	38.9	(36.8–41.5)	34.8	(33.8–36.8)	<0.001	<0.001	0.32
	V40	(%)	100.0	(99.5–100.0)	54.0	(48.7–61.1)	56.7	(53.6–60.5)	<0.01	<0.001	1.00
	V20	(%)	100.0	(100.0–100.0)	94.2	(89.8–99.9)	74.6	(71.6–78.6)	<0.01	<0.01	<0.05
Small intestine	Dmean	(Gy)	36.9	(34.2–40.2)	34.6	(31.9–35.9)	25.0	(23.3–30.0)	0.43	<0.01	<0.05
	V40	(%)	51.9	(42.5–63.4)	47.2	(34.6–53.9)	30.6	(24.7–41.2)	0.74	<0.05	0.16
	V20	(%)	85.3	(79.0–87.8)	79.2	(78.8–81.7)	51.1	(45.6–63.8)	0.36	<0.05	<0.05
Colon	Dmean	(Gy)	34.7	(33.5–36.4)	30.1	(28.5–32.2)	27.1	(23.4–28.0)	<0.05	<0.001	<0.05
	V40	(%)	46.6	(38.5–52.7)	39.7	(34.4–44.8)	37.1	(29.9–44.9)	0.95	0.27	1.00
	V20	(%)	82.3	(75.6–87.6)	65.1	(59.9–73.2)	49.4	(39.6–54.7)	<0.01	<0.001	<0.01
Femoral head R	Dmean	(Gy)	29.7	(29.3–30.0)	22.4	(20.9–24.8)	14.0	(13.1–16.2)	<0.001	<0.001	<0.001
	V40	(%)	1.4	(0.9–4.3)	0.1	(0.0–2.1)	0.1	(0.0–0.5)	0.62	0.19	1.00
	V20	(%)	100.0	(100.0–100.0)	58.2	(50.7–67.4)	15.6	(11.3–24.6)	<0.001	<0.001	<0.001
Femoral head L	Dmean	(Gy)	30.3	(29.2–33.3)	23.5	(20.4–24.8)	14.4	(13.8–17.0)	<0.001	<0.001	<0.001

		V40	(%)	5.6	(0.9–18.3)	0.2	(0.0–2.4)	0.1	(0.0–1.3)	0.06	<0.05	1.00
		V20	(%)	100.0	(100.0–100.0)	60.6	(46.2–69.9)	15.8	(14.8–26.2)	<0.001	<0.001	<0.001
Skin	Dmean	(Gy)	8.4	(7.6–9.3)	7.3	(6.8–8.0)	4.2	(3.8–4.6)	0.19	<0.001	<0.001	<0.001
	V20	(%)	8.7	(5.5–10.1)	6.8	(5.6–9.5)	0.1	(0.0–0.7)	1.00	<0.001	<0.001	<0.001
	V10	(%)	36.3	(32.7–40.5)	28.9	(26.4–30.9)	8.0	(7.2–9.8)	<0.05	<0.001	<0.001	<0.001
Pelvic bone	Dmean	(Gy)	36.2	(35.0–37.1)	29.8	(29.4–30.5)	25.3	(24.1–25.7)	<0.001	<0.001	<0.001	<0.001
	V40	(%)	45.1	(40.7–47.3)	25.1	(23.5–27.4)	23.3	(21.8–24.9)	<0.001	<0.001	<0.001	0.95
	V20	(%)	89.8	(85.8–91.7)	75.2	(74.8–76.7)	58.0	(55.3–59.7)	<0.001	<0.001	<0.001	<0.001

3D-CRT = 3D conformal radiation therapy, IMRT = intensity-modulated radiation therapy, SSPT = spot-scanning proton therapy, PTV = planning target volume, D2%–98% = dose received by the volume of PTV, Dmean = mean dose, V20, 40 = volume receiving dose $\geq 20/40$ Gy, CI 95% = conformity index 95%, HI = homogeneity index.

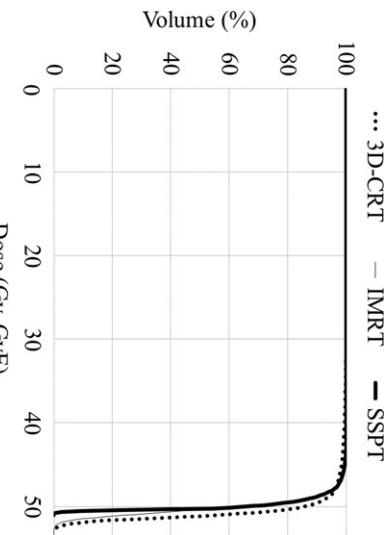


Fig. 2. Median dose–volume histogram values of the planning target volume ($n = 10$).

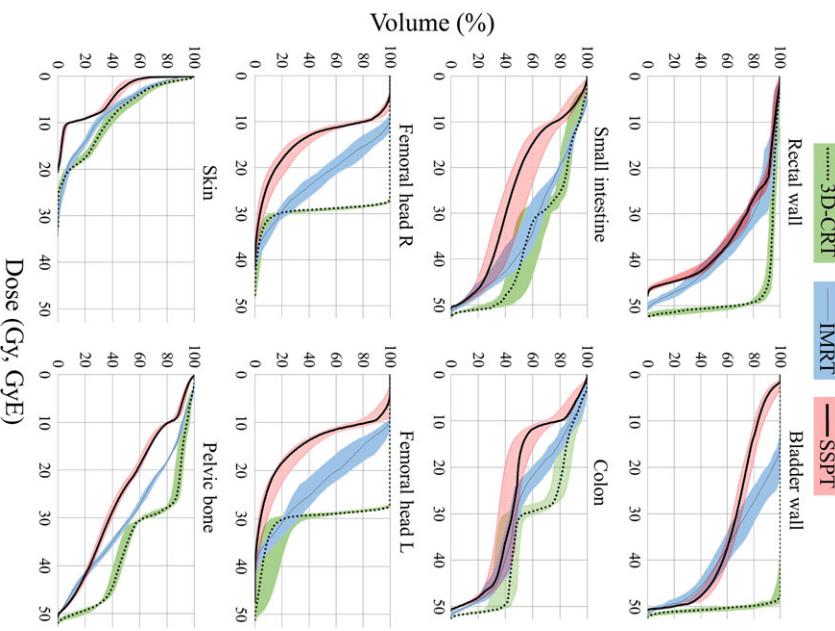


Fig. 3. Median dose–volume histogram values of the organs at risk ($n = 10$). The interquartile ranges of 3D conformal radiotherapy (green), intensity-modulated radiotherapy (blue) and spot-scanning proton therapy (red) plans are highlighted.

increasingly common. A systematic review and meta-analysis by Baolian *et al.* [33] reported that IMRT resulted in significantly smaller sections of the rectum and small bowel receiving high radiation doses (significantly lower mean percentage volumes for these

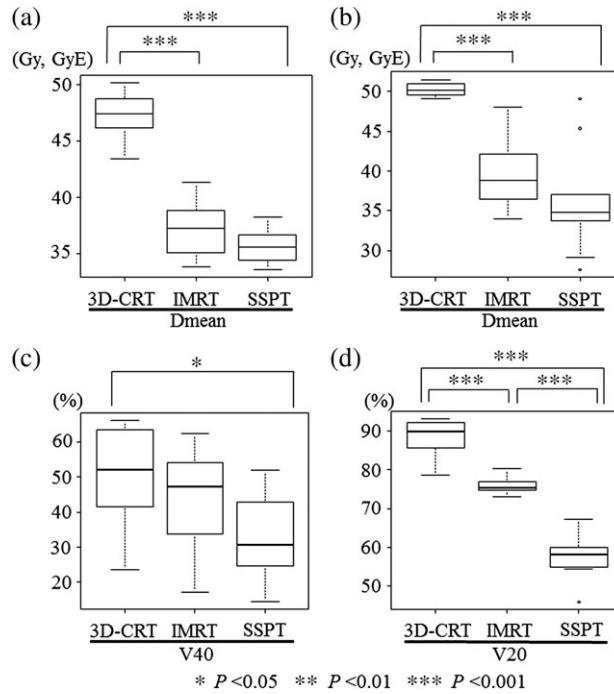


Fig. 4. Comparison of the dose–volume histogram parameters of the rectal wall (a), bladder wall (b), small intestine (c), and pelvic bone (d) among 3D conformal radiotherapy, intensity-modulated radiotherapy, and spot-scanning proton therapy plans.

structures) than 3D-CRT, but did not significantly affect the mean percentage volumes of the bladder or bone marrow. Similar results were obtained in the present study. Moreover, SSPT reduced the irradiated volume of the pelvic bone (Fig. 4d), including the bone marrow. Kevin *et al.* [34] reported a correlation between the volume of pelvic bone marrow that received 20 Gy and the development of hematological toxicities. Our study suggested that one of the benefits of SSPT-based WPRT relates to the reduced radiation doses delivered to the pelvic bone and bone marrow. Thus, the use of SSPT-based WPRT might improve the therapeutic outcomes for patients with locally advanced cervical cancer, especially when chemotherapy is added. SSPT might also make it possible to combine radiation and chemotherapy without causing additional hematological toxicities, which could lead to an improvement in the treatment completion rate.

Another potential benefit of SSPT is the reduced doses delivered to the small intestine. A prospective study of patients with locally advanced cervical cancer who were treated with chemoradiotherapy found that IMRT resulted in a lower rate of gastrointestinal toxicities than 3D-CRT [7]. In the present study, the median V40 value of the small intestine was 51.9% in 3D-CRT, 47.2% in IMRT and 30.6% in SSPT (Fig. 4c). Thus, SSPT might reduce the median V40 of the small intestine compared with 3D-CRT. Several previous studies have suggested that the V40 of the small intestine is a good predictor of the risk of acute and chronic gastrointestinal toxicities

[35, 36], so the use of SSPT might be expected to bring about a reduction in intestinal toxicities.

The RTOG 79-20 study [37] suggested that in a select group of patients the use of extended fields covering the para-aortic lymph nodes is associated with better disease-free and overall survival compared with pelvic irradiation alone. SSPT might be an effective treatment for para-aortic lymph node metastases [30]. Another potential benefit of SSPT is the fact that it makes it possible to increase the dose delivered to the tumor, while causing minimal toxicities. In cervical cancer patients who are ineligible for brachytherapy, the administration of radiation boosts to the primary cervical tumor and local lymph node metastases using SSPT might be appropriate after WPRT.

Compared with 3D-CRT, SSPT and IMRT significantly reduced the Dmean values of the rectal wall (Fig. 4a) and bladder wall (Fig. 4b). Sparing these organs during external beam radiation is important because brachytherapy delivers additional doses to the surrounding structures, including the rectum and bladder. While Marnitz *et al.* [31] reported that the Dmean to the rectum and bladder could be reduced by 7–9 Gy with SSPT, the differences between IMRT and SSPT were small in our study. This is probably due to Japanese women being relatively small and to the OARs being close to the PTV. In our study, CT images that were taken prior to 3D-CRT were used to generate plans for IMRT and SSPT. However, as no preparations were made to protect the bladder or rectum, it was hard to reduce the radiation doses delivered to these structures. The management of urine collection and the use of laxatives are desirable during IMRT- or SSPT-based WPRT, as that would suppress the internal motion of the uterus. Several previous studies have quantified internal motion and set-up uncertainty in patients with cervical cancer [38–42]. Adequate margins are required to ensure that the target volume is irradiated sufficiently. In our study, the ITV and PTV took both internal motion and set-up uncertainty into consideration.

Another limitation of our study is that the SSPT plans were created using single-field optimization, rather than multifield optimization, due to the limitations of our treatment planning system. If it had been possible to develop an Bragg peak plan using multifield optimization, it might have been easier to reduce the doses delivered to the OAR, especially the bladder and rectum. In addition, SSPT-based WPRT has another limitation regarding reliability in the dose distribution, since the position of the Bragg peak of a scanning beam is influenced by bowel gas and bowel peristalsis [31]. Because of this limitation, the dose distribution has relevant range uncertainties (the uncertainty in the dose deposition with depth) in pelvic irradiation by SSPT. So, the use of SSPT (with its advantageous sharp dose fall-off) should be carefully considered and weighed against some trade-offs (motion management, range uncertainty, and others). To ameliorate these limitations, we chose the beam angles and routes to avoid intestines. These limitations are specific to particle therapy, especially SSPT, and are less important in 3D-CRT and IMRT. Therefore, SSPT-based WPRT should be carefully used at present in the clinical setting. However, SSPT-based WPRT could be beneficial under various conditions, and future clinical trials of SSPT-based WPRT are warranted to assess its role in the treatment of cervical cancer.

CONCLUSION

Compared with 3D-CRT and IMRT, SSPT results in smaller OAR volumes being exposed to low radiation doses, while maintaining excellent PTV coverage. Further investigations of SSPT are warranted to assess its role in the treatment of cervical cancer.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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