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# Comparison of dosimetric parameters in the treatment planning of magnetic resonance imaging–based intracavitary image-guided adaptive brachytherapy with and without optimization using the central shielding technique

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## ABSTRACT

This study aimed to compare dosimetric parameters between non-optimized and optimized treatment planning (NOP and OP, respectively) of magnetic resonance imaging (MRI) –based intracavitary (IC) image-guided adaptive brachytherapy (IGABT) using the central shielding (CS) technique for cervical cancer. Fifty-three patients treated with external beam radiotherapy using CS and MRI-based IGABT with the IC approach alone were evaluated. The total high-risk clinical target volume (HR-CTV) D90 was aimed at >70 Gy equivalent dose in 2 Gy fractions (EQD2). In the small HR-CTV group ( $\leq 30 \text{ cm}^3$ ), the mean D90s for NOP/OP were 98.6/80.7 Gy. In the large ( $30.1\text{--}40 \text{ cm}^3$ ) and extensive ( $>40 \text{ cm}^3$ ) HR-CTV groups, the mean D90s were 81.9/77.5 and 71.1/73.6 Gy, respectively. The mean  $D_{2cc}$  values for organs at risks (OARs) in OP were acceptable in all groups, despite the high bladder  $D_{2cc}$  in the NOP. The correlation between HR-CTV at first brachytherapy (BT) and NOP D90 was stronger than that between HR-CTV at first BT and OP D90. The targeted HR-CTV D90 and dose constraints of  $D_{2cc}$  for OARs were both achieved in 16 NOP/47 OP patients for the bladder, 39/50 for the rectum, and 47/50 for the sigmoid colon ( $P < 0.001$ ,  $P = 0.007$ , and  $P = 0.34$ , respectively). For small tumors, the role of optimization was to reduce the  $D_{2cc}$  for OARs while maintaining the targeted D90. However, optimization was of limited value for extensive tumors. Methods of optimization in IGABT with CS for cervical cancer should be standardized while considering its effectiveness and limitations.

**Keywords:** image-guided adaptive brachytherapy; cervical cancer; optimization; D90;  $D_{2cc}$ ; central shielding

## INTRODUCTION

Brachytherapy (BT) in combination with external beam radiotherapy (EBRT) for gynecologic malignancies has significantly developed from the traditional X-ray-based treatment to a 3D image-based treatment over the past two decades. After the introduction of computed tomography (CT)-guided BT in the 1980s [1], researchers strove to improve image-based BT. Currently, magnetic resonance imaging (MRI)-based BT (referred to as MRI-based image-guided adaptive BT, IGABT) is a potential treatment strategy for gynecologic malignancies [2–4]. Since the 2000s, important target definition guidelines, including the high-risk clinical target volume (HR-CTV) as well as dose–volume parameters for MRI-based IGABT, were published by the Gynaecological (GYN) Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy and Oncology (ESTRO) working group [5, 6]. Since then, excellent treatment outcomes have been reported with IGABT [7–11].

In Japan, radiotherapy (RT) for cervical cancer has traditionally differed from that in Western countries. The most notable feature of the Japanese treatment method is the ‘central shielding (CS)’ technique, which was established in the 1970s. CS is included in the current Japanese guideline [12] and is performed for most patients during the later EBRT sessions to protect organs at risk (OARs) from overdoses.

CS is usually performed using a 3- to 4-cm wide multileaf collimator from the lower end of the anterior–posterior field; the length usually varies from patient to patient. Use of CS can reduce doses delivered to the OARs and may also result in marked dose reduction to the cervical tumor. However, previous Japanese studies on cervical cancer RT with CS using radiography-based BT prescribed to point A showed excellent outcomes [13–16]. Although IGABT has recently gained prevalence in Japan, it is commonly combined with EBRT using CS. Moreover, IGABT planning and treatment are usually performed using institution-specific protocols that are based on the previous studies [5, 7, 10, 17–19], since a standard treatment regimen (for the target organ as well as dose constraints for OARs) for using CS have not yet been established. In the process of the establishment of the appropriate treatment dose for IGABT under CS, the dosimetric parameters obtained from 3D image treatment planning using traditional non-optimized point A prescription should be evaluated and compared with those obtained after image-based optimization.

In addition to optimization, interstitial (IS) therapy is also used in IGABT. While the doses to HR-CTVs and OARs can be regulated through optimization, large residual or asymmetrically located tumors cannot be managed by intracavitary (IC) BT alone. Fokdal *et al.* reported that patients with large target volumes (HR-CTV  $\geq 30$  cm<sup>3</sup>) treated with IC/IS BT showed significantly higher local control rates than those treated with ICBT alone [20]. Their results indicated a certain benefit of this approach for large tumors. Thus, adequate evaluation of the indication of IC/IS BT with CS is also required.

In this study, dosimetric parameters in MRI-based IGABT, including both HR-CTV and OARs between non-optimized treatment planning (NOP) prescribed to point A and optimized treatment planning (OP) based on NOP, that were used in clinical treatment combined with EBRT using CS technique were compared, with the goal of evaluating the effectiveness and limitations of optimization in ICBT.

**Table 1. Patient characteristics**

| Variable                | No. of patients (Total: 53) | %  |
|-------------------------|-----------------------------|----|
| Age (years)             |                             |    |
| Median (Range)          | 67 (31–92)                  |    |
| FIGO stage              |                             |    |
| IB                      | 7                           | 13 |
| IIA                     | 5                           | 9  |
| IIB                     | 28                          | 53 |
| IIIA                    | 0                           | 0  |
| IIIB                    | 9                           | 17 |
| IVA                     | 4                           | 8  |
| Histology               |                             |    |
| Squamous cell carcinoma | 47                          | 89 |
| Adenocarcinoma          | 5                           | 9  |
| Adenosquamous carcinoma | 1                           | 2  |
| Lymph node metastases   |                             |    |
| Yes                     | 16                          | 30 |
| No                      | 37                          | 70 |
| Concurrent chemotherapy |                             |    |
| Yes                     | 45                          | 87 |
| No                      | 8                           | 13 |

FIGO = International Federation of Gynecology and Obstetrics.

## MATERIALS AND METHODS

### Patients

Fifty-three patients with histologically proven cervical cancer treated with a combination of EBRT and MRI-based IGABT with or without concurrent chemotherapy between October 2014 and February 2017 were included in this study. The patients’ characteristics are shown in Table 1. This study was approved by the Kobe University Hospital Ethical Committee (No. 170044).

### EBRT

According to the Japanese guidelines [12], EBRT generally consists of whole-pelvic irradiation (WPI) and WPI using the CS technique with a total dose of 50.4 Gy in 28 fractions (1.8 Gy/fraction). The CS width at our institution is 4 cm. For Stage I disease, EBRT generally consists of 19.8 Gy in 11 fractions or 30.6 Gy in 17 fractions of WPI using the box technique with a 10 megavolt X-ray, and 30.6 Gy in 17 fractions or 19.8 Gy in 11 fractions of WPI with the CS technique using an anterior and posterior approach. For Stage II disease, 30.6 Gy in 17 fractions of WPI and 19.8 Gy in 11 fractions of WPI with CS are generally administered. For Stage III and IVA diseases, EBRT consists of 41.4 Gy in 23 fractions of WPI and 9.0 Gy in 5 fractions of WPI with CS, or of 50.4 Gy in 28 fractions of WPI without CS.

## BT

### *Applicator and imaging*

The ‘tandem and ovoid’ applicator was used for all the patients in this study. After implantation, CT images were acquired to verify the final position of the applicator. Next, patients were transported to the MRI room, and transverse and sagittal T2-weighted images as well as diffusion-weighted images were acquired using a 3.0 Tesla MRI machine. To achieve treatment planning based on MRI without CT fusion, home-made catheters using flexible tubes for ISBT filled with normal saline solution that were compatible with MRI were used as simulated sources.

### *BT treatment planning*

BT treatment planning was performed using the Oncentra Brachy software, version 4.5.1 (Elekta AB, Stockholm, Sweden). Applicators were reconstructed using the ‘applicator placement’ method, while referring to the above-mentioned home-made simulated sources. Next, the HR-CTV and OARs (bladder, rectum, sigmoid colon, and small bowel) were delineated based on the GYN GEC ESTRO recommendation [5]. After delineation, treatment planning with the point A prescription (using NOP) was performed first, following which optimization was performed using the ‘graphical optimization’ method, and an OP was developed and used for clinical treatment. All the NOPs were recorded in the Oncentra Brachy software for comparison with OPs. Although the BT prescription was also determined following the guideline [12] with 6 Gy to point A at a single fraction, the HR-CTV D90 (defined as the minimum dose covering 90% of the target volume) was aimed for >7 Gy using optimization. A total HR-CTV D90 in combination with EBRT and BT was targeted at >70 Gy in equivalent doses in 2 Gy fractions (EQD2,  $\alpha/\beta = 10$ ). As for OARs, the preferable total  $D_{2cc}$  values (cumulative minimum doses to 2 cm<sup>3</sup>) in EQD2 for the bladder, rectum, sigmoid colon, and small bowel were <85, 75, 75, and 75 Gy ( $\alpha/\beta = 3$ ), respectively. Doses delivered via WPI using CS were not included in the dose evaluation of either the HR-CTV D90 or the OAR  $D_{2cc}$ , as was the case in previous studies [21, 22]. Generally, the first BT was performed on the same day as the start of WPI with CS, and was performed once or twice per week with 2–4 implants.

### *Details of graphical optimization*

The graphical optimization method for OP was as follows: after developing a plan prescribing 6 Gy to point A (NOP), the  $D_{2cc}$  for OARs was at first decreased on the axial image (using the ‘global’ graphical optimization method) to at least 10% below the physical dose constraints at a single fraction, which was acquired from the total and EBRT doses in EQD2. Next, dose coverage of HR-CTV was adjusted using the ‘local’ graphical optimization method to maintain >7 Gy of D90 on the axial images by referring to the reconstructed sagittal and coronal images. The obtained HR-CTV D90 and  $D_{2cc}$  for OARs from graphical optimization were converted into EQD2, and the expected total D90 and  $D_{2cc}$  values were calculated. Treatment was performed after confirming that all parameters fulfilled the targeted D90 as well as the dose constraints (in total EQD2).

## Analysis of dosimetric parameters

The mean total HR-CTV D90 and  $D_{2cc}$  for the bladder, rectum, and sigmoid colon in both NOP and OP were calculated, and the differences were analyzed. Other HR-CTV parameters (D98, D95, V100, V150 and V200) and OARS ( $D_{0.1cc}$  and  $D_{1cc}$ ) were also evaluated in the same manner. Patients were then stratified based on the size of HRCTV at first BT, and the same comparisons were performed to investigate the effect of target volume size on these parameters. Next, the correlation between HR-CTV at the first BT and dosimetric parameters of NOP and OP were compared, with a focus on the HR-CTV D90. Furthermore, the correlations between the HR-CTV D90 and  $D_{2cc}$  for OARs in NOP and OP were compared to the evaluations when using the targeted D90 and dose constraints to the OARs.

## Statistics

Statistical analyses were performed using IBM SPSS Statistics software version 24 (IBM Corp, 2016, Armonk, NY). Continuous variables were analyzed using Wilcoxon’s signed-rank test, while categorical variables were analyzed using the chi-square or Fisher’s exact test. A *P* value less than 0.05 was considered significant.  $R^2$  was used for the evaluation of the correlation between HR-CTV at first BT and dosimetric parameters.

## RESULTS

### Details of the combinations of EBRT and BT

The details of the combinations of EBRT and BT are shown in Table 2. Three patients were treated with WPI, without CS, in 2–3 BT sessions. One patient who was treated with 45 Gy of WPI in 25 fractions and 3 BT sessions was 91 years old with Stage IIB disease. The tumor response in the remaining two patients was slow; thus, 50.4 Gy of WPI in 28 fractions was delivered, and BT was delayed.

### Comparison of dosimetric parameters between NOP and OP

Table 3 shows the details of the dosimetric parameters, including comparisons of NOP with OP. Both the HR-CTV D90 and  $D_{2cc}$  for OARs

**Table 2. Details of combinations of EBRT and BT**

| WPI<br>(Gy/fractions) | WPI with CS<br>(Gy/fractions) | BT<br>(fractions) | No. of patients<br>(Total: 53) | %  |
|-----------------------|-------------------------------|-------------------|--------------------------------|----|
| 19.8/11               | 30.6/17                       | 4                 | 3                              | 6  |
| 30.6/17               | 19.8/11                       | 4                 | 33                             | 62 |
| 41.4/23               | 9.0/5                         | 3                 | 6                              | 11 |
| 41.4/23               | 9.0/5                         | 4                 | 7                              | 13 |
| 45/25                 | None                          | 3                 | 1                              | 2  |
| 45/25                 | 5.4/3                         | 3                 | 1                              | 2  |
| 50.4/28               | None                          | 2                 | 2                              | 4  |

EBRT = external beam radiotherapy, BT = brachytherapy, WPI = whole pelvic irradiation, CS = central shielding.

**Table 3. Comparison of dosimetric parameters for both HR-CTV and OARs between NOP and OP**

| Dosimetric parameters |                         | NOP          | OP           | Reduction   | P value |
|-----------------------|-------------------------|--------------|--------------|-------------|---------|
|                       |                         | Mean (SD)    |              |             |         |
| HR-CTV                | D90 (Gy)                | 89.6 (17.4)  | 78.6 (5.5)   | 11.0 (13.7) | <0.001  |
|                       | D95 (Gy)                | 82.5 (15.8)  | 73.1 (5.5)   | 9.4 (12.2)  | <0.001  |
|                       | D98 (Gy)                | 76.7 (14.4)  | 68.6 (5.3)   | 8.1 (11.0)  | <0.001  |
|                       | V100 (%)                | 97.3 (5.2)   | 97.8 (2.9)   | -0.6 (3.1)  | 0.43    |
|                       | V150 (%)                | 83.2 (13.9)  | 77.6 (8.6)   | 5.7 (9.2)   | <0.001  |
|                       | V200 (%)                | 60.6 (16.4)  | 50.6 (7.5)   | 10.0 (13.1) | <0.001  |
| Bladder               | D <sub>0.1cc</sub> (Gy) | 128.2 (35.6) | 103.8 (14.9) | 24.4 (26.9) | <0.001  |
|                       | D <sub>1cc</sub> (Gy)   | 102.5 (21.8) | 84.9 (7.7)   | 17.6 (19.1) | <0.001  |
|                       | D <sub>2cc</sub> (Gy)   | 93.4 (17.7)  | 77.8 (6.2)   | 15.5 (16.5) | <0.001  |
| Rectum                | D <sub>0.1cc</sub> (Gy) | 84.9 (19.1)  | 73.8 (13.5)  | 11.0 (14.7) | <0.001  |
|                       | D <sub>1cc</sub> (Gy)   | 69.8 (13.1)  | 62.1 (9.8)   | 7.6 (10.4)  | <0.001  |
|                       | D <sub>2cc</sub> (Gy)   | 64.3 (11.2)  | 57.6 (8.7)   | 6.7 (8.7)   | <0.001  |
| Sigmoid colon         | D <sub>0.1cc</sub> (Gy) | 76.1 (17.8)  | 65.1 (12.5)  | 11.1 (10.3) | <0.001  |
|                       | D <sub>1cc</sub> (Gy)   | 62.3 (10.6)  | 55.3 (9.4)   | 6.9 (6.4)   | <0.001  |
|                       | D <sub>2cc</sub> (Gy)   | 57.1 (8.5)   | 51.7 (8.4)   | 5.5 (5.2)   | <0.001  |

HR-CTV = high-risk clinical target volume, OARs = organs at risk, NOP = non-optimized planning, OP = optimized planning, SD = standard deviation.

in OP were significantly lower than those in NOP. Table 4 shows the group stratification according to the size of the HR-CTV at first BT and intragroup analyses of HR-CTV D90 and D<sub>2cc</sub> for OARs. Patients were stratified into three groups according to the HR-CTV at first BT ( $\leq 30 \text{ cm}^3$  was small,  $30.1\text{--}40 \text{ cm}^3$  was large, and  $>40 \text{ cm}^3$  was extensive HR-CTV). Thirty-one patients (58%) were included in the small HR-CTV group, 12 (23%) in the large group, and 10 (19%) in the extensive HR-CTV group. The mean and median HR-CTVs at first BT were  $30.9 (\pm 13.0)$  and  $27.8 \text{ cm}^3$  (range:  $9.1\text{--}66.6 \text{ cm}^3$ ), respectively. Representative cases from the small and extensive HR-CTV groups are shown in Fig. 1. The small and large groups showed significant reductions in mean doses for most parameters. However, for the large HR-CTV group, the D90 of three patients increased. In this group, six patients had  $>35 \text{ cm}^3$  of HR-CTV, and the remaining six had  $<35 \text{ cm}^3$ . All the patients with an increase in D90 had  $>35 \text{ cm}^3$  of HR-CTV. The mean D90s of the patients with  $>35 \text{ cm}^3$  of HR-CTV both in NOP/OP were 76.2/79.2 Gy, respectively ( $P = 0.39$ ). On the other hand, the mean D90s of the patients with  $<35 \text{ cm}^3$  of HR-CTV were 84.7/78.8 Gy, respectively ( $P = 0.02$ ). The extensive HR-CTV group showed an increase in D90 via optimization, with marginal significance. No differences in D<sub>2cc</sub> for OARs were observed between NOP and OP.

As for the other parameters, in total, both the HR-CTV D98/D95 and D<sub>0.1cc</sub>/D<sub>1cc</sub> for OARs values were significantly reduced by optimization, as was the case for the D90 and D<sub>2cc</sub> values (Table 3). Only the difference in V100 between NOP and OP was not significant. In the intragroup analyses, the results of HR-CTV D98/95 and D<sub>0.1cc</sub>/D<sub>1cc</sub> for

OARs showed similar tendencies to those of D90 and D<sub>2cc</sub>. As for the V100/150/200 values, only those in the extensive HR-CTV group increased in OP (Table 4).

### Correlation between HR-CTV at first BT and the dosimetric parameters of both NOP and OP

Figure 2 shows the correlation between the size of HR-CTV at first BT and the HR-CTV D90. In terms of small HR-CTVs, NOP showed extremely high D90 values, and a significant reduction was observed as the HR-CTV increased. Thirty-five patients (66%) received  $>80 \text{ Gy}$  of total D90 in EQD2, and 47 patients (89%) received more than the targeted D90 (70 Gy). Meanwhile, a minor reduction was observed in OP compared with in NOP. Twenty-two patients (42%) received  $>80 \text{ Gy}$ , and 50 patients (94%) received more than the targeted D90. The correlation between the HR-CTV at first BT and D90 in NOP was stronger than that in OP ( $R^2 = 0.555$  and  $0.283$ , respectively). As for the correlation between HR-CTV at first BT and D<sub>2cc</sub> in NOP/OP for OARs, the  $R^2$  values for the bladder, rectum, and sigmoid colon were  $0.317/0.024$ ,  $0.007/0.194$  and  $0.001/0.133$ , respectively, indicating weak (if any) correlations.

### Correlation between the HR-CTV D90 and D<sub>2cc</sub> for OARs in both NOP and OP

Figure 3 shows the correlation between HR-CTV D90 and D<sub>2cc</sub> for OARs in the form of a scatter diagram. Regarding the bladder D<sub>2cc</sub> and

**Table 4. Comparison of dosimetric parameters for both HR-CTV and OARs between NOP and OP stratified by HR-CTV at first BT (mean: 30.9 cm<sup>3</sup>, median: 27.8 cm<sup>3</sup>)**

| Group, dosimetric parameter                        |                         | NOP          | OP           | Reduction   | P value | No. of patients with decrease/increase (no change) |
|--|-------------------------|--------------|--------------|-------------|---------|--|
|  |                         | Mean (SD)    |              |             |         |  |
| Small HR-CTV ( $\leq 30\text{ cm}^3$ , $n = 31$ )  |                         |              |              |             |         |  |
| HR-CTV   | D90 (Gy)                | 98.6 (16.3)  | 80.7 (5.3)   | 18.0 (13.3) | <0.001  | 31/0   |
|  | D95 (Gy)                | 90.5 (15.1)  | 75.0 (5.5)   | 15.4 (12.0) | <0.001  | 31/0   |
|  | D98 (Gy)                | 83.8 (14.0)  | 70.4 (5.4)   | 13.5 (10.9) | <0.001  | 31/0   |
|  | V100 (%)                | 99.7 (1.1)   | 99.1 (1.4)   | 0.6 (0.9)   | <0.001  | 26/4 (2)   |
|  | V150 (%)                | 92.1 (6.1)   | 81.7 (6.7)   | 10.4 (6.7)  | <0.001  | 29/1 (1)   |
|  | V200 (%)                | 71.0 (11.4)  | 53.7 (6.8)   | 17.3 (11.6) | <0.001  | 29/1 (1)   |
| Bladder  | D <sub>0.1cc</sub> (Gy) | 144.8 (33.4) | 106.5 (15.0) | 38.3 (24.9) | <0.001  | 31/0   |
|  | D <sub>1cc</sub> (Gy)   | 112.9 (19.7) | 85.2 (7.2)   | 27.7 (17.6) | <0.001  | 31/0   |
|  | D <sub>2cc</sub> (Gy)   | 101.1 (15.8) | 77.4 (5.8)   | 23.8 (15.1) | <0.001  | 31/0   |
| Rectum   | D <sub>0.1cc</sub> (Gy) | 88.6 (19.8)  | 71.4 (13.8)  | 17.1 (14.1) | <0.001  | 30/1   |
|  | D <sub>1cc</sub> (Gy)   | 71.5 (14.4)  | 59.8 (10.5)  | 11.7 (10.5) | <0.001  | 29/2   |
|  | D <sub>2cc</sub> (Gy)   | 65.6 (12.4)  | 55.2 (9.4)   | 10.3 (8.6)  | <0.001  | 30/1   |
| Sigmoid colon                                      | D <sub>0.1cc</sub> (Gy) | 80.8 (18.5)  | 64.8 (13.6)  | 15.9 (9.2)  | <0.001  | 30/1   |
|  | D <sub>1cc</sub> (Gy)   | 63.6 (11.0)  | 53.6 (9.7)   | 10 (5.2)    | <0.001  | 30/1   |
|  | D <sub>2cc</sub> (Gy)   | 57.5 (8.7)   | 49.7 (8.5)   | 7.8 (4.1)   | <0.001  | 30/1   |
| Large HR-CTV (30.1–40 cm <sup>3</sup> , $n = 12$ ) |                         |              |              |             |         |  |
| HR-CTV   | D90 (Gy)                | 81.9 (8.3)   | 77.5 (4.2)   | 4.4 (6.0)   | 0.04    | 9/3  |
|  | D95 (Gy)                | 75.6 (7.5)   | 71.8 (4.0)   | 3.8 (5.4)   | 0.04    | 9/3  |
|  | D98 (Gy)                | 70.7 (7.0)   | 67.3 (4.1)   | 3.4 (4.7)   | 0.03    | 9/3  |
|  | V100 (%)                | 96.9 (4.1)   | 96.8 (3.3)   | 0 (1.9)     | 0.88    | 8/4  |
|  | V150 (%)                | 78.2 (9.0)   | 75.2 (7.3)   | 3.0 (7.2)   | 0.14    | 8/4  |
|  | V200 (%)                | 52.3 (6.5)   | 49.4 (5.9)   | 2.9 (6.1)   | 0.03    | 10/2   |
| Bladder  | D <sub>0.1cc</sub> (Gy) | 109.6 (26.8) | 100.4 (17.1) | 9.2 (12.2)  | 0.05    | 8/4  |
|  | D <sub>1cc</sub> (Gy)   | 92.2 (17.5)  | 84.3 (9.5)   | 7.8 (9.7)   | 0.02    | 8/4  |
|  | D <sub>2cc</sub> (Gy)   | 85.3 (14.4)  | 78.2 (7.4)   | 7.2 (8.6)   | 0.02    | 9/3  |
| Rectum   | D <sub>0.1cc</sub> (Gy) | 83.4 (20.3)  | 77.5 (14.6)  | 5.8 (12.4)  | 0.31    | 6/6  |
|  | D <sub>1cc</sub> (Gy)   | 69.6 (12.5)  | 64.6 (9.0)   | 4.9 (6.9)   | 0.12    | 7/5  |
|  | D <sub>2cc</sub> (Gy)   | 64.0 (10.7)  | 60.1 (8.0)   | 3.9 (5.8)   | 0.12    | 7/5  |
| Sigmoid colon                                      | D <sub>0.1cc</sub> (Gy) | 71.7 (19.6)  | 66.1 (9.9)   | 5.6 (6.8)   | 0.02    | 9/3  |
|  | D <sub>1cc</sub> (Gy)   | 61.7 (9.8)   | 57.7 (6.7)   | 3.9 (4.7)   | 0.01    | 10/2   |
|  | D <sub>2cc</sub> (Gy)   | 58.4 (7.6)   | 54.5 (5.9)   | 3.8 (4.5)   | 0.01    | 10/2   |

*Continued*

Table 4. Continued

| Group, dosimetric parameter                       |                         | NOP         | OP          | Reduction   | P value | No. of patients with decrease/increase (no change) |
|---|-------------------------|-------------|-------------|-------------|---------|--|
|   |                         | Mean (SD)   |             |             |         |  |
| Extensive HR-CTV ( $>40\text{ cm}^3$ , $n = 10$ ) |                         |             |             |             |         |  |
| HR-CTV  | D90 (Gy)                | 71.1 (6.1)  | 73.6 (4.4)  | -2.6 (4.5)  | 0.07    | 3/7  |
|   | D95 (Gy)                | 66.0 (5.6)  | 68.7 (4.0)  | -2.7 (3.7)  | 0.01    | 2/8  |
|   | D98 (Gy)                | 61.9 (4.8)  | 64.8 (3.9)  | -3.0 (2.9)  | 0.007   | 1/9  |
|   | V100 (%)                | 90.4 (7.7)  | 95.2 (4.0)  | -4.8 (5.0)  | 0.005   | 0/10   |
|   | V150 (%)                | 61.9 (9.3)  | 67.5 (5.8)  | -5.6 (7.2)  | 0.07    | 4/6  |
|   | V200 (%)                | 38.0 (6.0)  | 42.2 (4.2)  | -4.1 (5.9)  | 0.09    | 4/6  |
| Bladder   | D <sub>0.1cc</sub> (Gy) | 99.0 (18.8) | 99.5 (10.8) | -0.5 (16.0) | 0.71    | 4/6  |
|   | D <sub>1cc</sub> (Gy)   | 82.8 (11.3) | 84.6 (7.8)  | -1.8 (8.6)  | 0.58    | 4/6  |
|   | D <sub>2cc</sub> (Gy)   | 79.0 (14.0) | 79.0 (6.7)  | 0.2 (11.3)  | 0.72    | 5/5  |
| Rectum  | D <sub>0.1cc</sub> (Gy) | 75.2 (11.7) | 76.9 (10.5) | -1.6 (7.3)  | 0.58    | 5/5  |
|   | D <sub>1cc</sub> (Gy)   | 64.7 (8.4)  | 66.4 (6.1)  | -1.8 (5.3)  | 0.24    | 4/6  |
|   | D <sub>2cc</sub> (Gy)   | 60.5 (7.2)  | 61.6 (5.0)  | -1.1 (4.6)  | 0.45    | 4/6  |
| Sigmoid colon                                     | D <sub>0.1cc</sub> (Gy) | 67.0 (14.9) | 64.6 (12.9) | 2.4 (8.5)   | 0.33    | 7/3  |
|   | D <sub>1cc</sub> (Gy)   | 58.6 (10.8) | 57.6 (10.5) | 1.0 (5.9)   | 0.51    | 4/6  |
|   | D <sub>2cc</sub> (Gy)   | 54.6 (9.1)  | 54.3 (9.5)  | 0.4 (4.7)   | 0.8     | 5/5  |

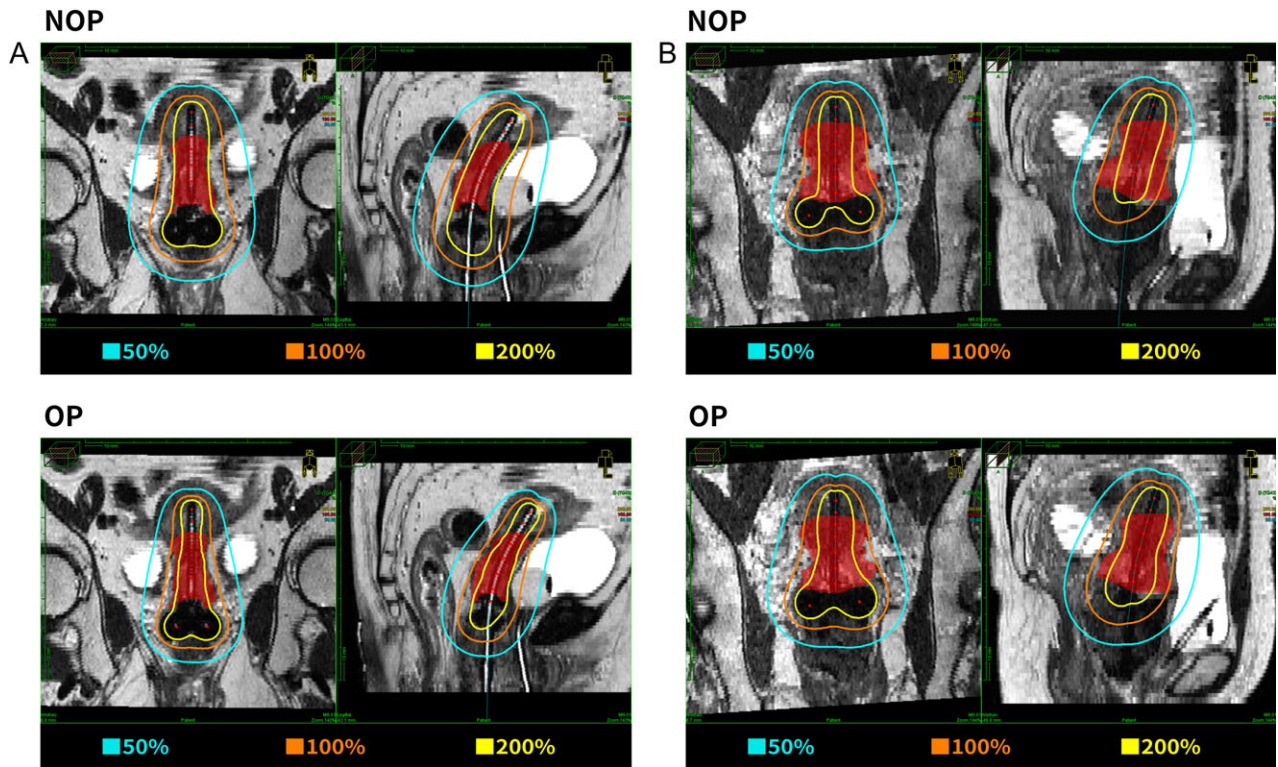
HR-CTV = high risk clinical target volume, OARs = organs at risk, NOP = non-optimized planning, OP = optimized planning, SD = standard deviation.

HR-CTV D90, 16 of the 53 points (30%) were positioned in Area 1 (the graph field that achieved both the targeted HR-CTV D90 and dose constraints of D<sub>2cc</sub> of OARs), and 37 (70%) were positioned in Area 2 (the graph field that did not achieve the target HR-CTV D90 and/or dose constraints of D<sub>2cc</sub> for OARs; equal to other than Area 1) in NOP. However, 47 (89%) and 6 (11%) points were positioned in Areas 1 and 2 in OP ( $P < 0.001$ ), respectively. As for the rectum D<sub>2cc</sub> and HR-CTV D90, 39 (74%) and 14 (26%) points were positioned in Areas 1 and 2 in NOP, respectively, while 50 (94%) and 3 (6%) were positioned in Areas 1 and 2 in OP, respectively ( $P = 0.007$ ). As for the sigmoid colon D<sub>2cc</sub> and HR-CTV D90, 46 (87%) and 7 (13%) points were positioned in Areas 1 and 2 in NOP, respectively, while 50 (94%) and 3 (6%) were positioned in Areas 1 and 2 in OP ( $P = 0.34$ ), respectively.

## DISCUSSION

The introduction of IGABT significantly influenced the treatment of cervical cancer. Before this modality became available, there were no concepts of target organs and OARs, and the point doses described in the International Commission on Radiation Units Report 38 were used merely as references [23]. The HR-CTV D90 and D<sub>2cc</sub> for OARs were established as important dosimetric parameters for IGABT in the current era. The target dose in European centers performing IGABT was

$>85\text{ Gy}$  in EQD2 for HR-CTV D90s in both high-dose or pulsed-dose-rate BT. The combination of 45 Gy in 25 fractions of WPI and 7 Gy  $\times$  4 fractions of BT, corresponding to 85 Gy in EQD2, has been used widely at these centers [5, 6, 18, 19, 24]. At our institution, the treatment strategy follows the Japanese guideline [12], which includes the use of the CS technique in EBRT. For BT, 7 Gy per fraction of high-dose-rate BT to the HR-CTV with a 6 Gy prescription to point A was adapted to be as similar as possible to that used in European institutions. According to the calculated total doses (excluding those delivered by WPI with CS), combinations of 19.8 Gy in 11 fractions of WPI and 7 Gy  $\times$  4 fractions of BT for Stage IB–IIA disease correspond to 59.1 Gy in EQD2; 30.6 Gy in 17 fractions and 7 Gy  $\times$  4 fractions correspond to 69.7 Gy for Stage IIB; and 41.4 Gy in 23 fractions and 7 Gy  $\times$  3 fractions for Stage III–IVA correspond to 70.5 Gy. Initially, these combinations of EBRT and BT stratified according to International Federation of Gynecology and Obstetrics (FIGO) stage were strictly used for MRI-based IGABT at our institution; however, as the use of this modality expanded, the combinations of 30.6 Gy in 17 fractions and 7 Gy  $\times$  4 fractions were adopted as a standard for Stage IB–IIB disease. For Stage III–IVA, 41.4 Gy in 23 fractions and 7 Gy  $\times$  4 fractions, corresponding to 80.4 Gy were adopted if the D<sub>2cc</sub> values for OARs were far below the dose constraints. Therefore, our study included patients treated with several combinations of doses and fractions of EBRT and BT at each stage.

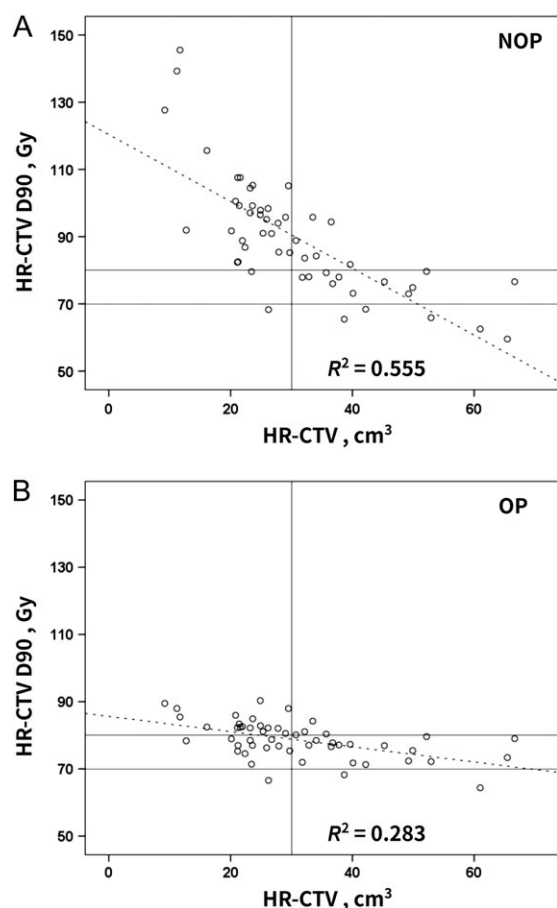


**Fig. 1. Magnetic resonance imaging-based treatment planning of small and extensive high-risk clinical target volume (HR-CTV) groups at the first brachytherapy implant.** (A) A patient with small HR-CTV (16.1 cm<sup>3</sup>) with D90s of 10.9 Gy in non-optimized treatment planning (NOP) and 8.1 Gy in optimized treatment planning (OP), respectively (total: 115.6 and 82.5 Gy in equivalent dose in 2 Gy fractions [EQD2], respectively). (B) A patient with expansive HR-CTV (52.9 cm<sup>3</sup>) with D90s of 5.8 Gy in NOP and 7.4 Gy in OP, respectively (total: 65.9 and 72.2 Gy in EQD2, respectively). Delineations of HR-CTVs of both cases are shown in red.

An important goal of optimization is to reduce the doses delivered to OARs while maintaining the target HR-CTV D90 or to increase the HR-CTV D90 while managing the OAR doses within the standard dose constraints. In our study, the mean total bladder D<sub>2cc</sub> in NOP was extremely high, necessitating optimization to reduce it. Although the HR-CTV D90 was significantly reduced by optimization as a consequence, the target D90 of 70 Gy could be maintained, and dose constraints for the bladder D<sub>2cc</sub> were achieved. Importantly, the effect of the size of the HR-CTV on optimization must be considered [25, 26] and subsequently analyzed. The HR-CTV at first BT was used for this analysis because most patients treated with ICBT alone generally had disease limited to the cervix at the time of first BT; those with extensive disease at most had proximal parametrial involvement. In such patients, significant changes in size are unlikely to occur during BT. Nomden *et al.* compared the treatment planning of four cervical cancer patients with different sizes of HR-CTV between four centers [25]. In their study, the mean HR-CTV D90 with 19.5 cm<sup>3</sup> was 96.4 Gy at the standard point A; however, the optimized HR-CTV D90 was reduced significantly to 85.4 Gy. The D<sub>2cc</sub> for OARs were also reduced via optimization; in particular, the bladder D<sub>2cc</sub> was reduced from 110.6 to 88.1 Gy. Meanwhile, the mean HR-CTV D90 with 68.0 cm<sup>3</sup> was 68.9 Gy, whereas the optimized D90 increased to 73.7 Gy without a

significant reduction in the D<sub>2cc</sub> for OARs. Consistent with the findings of Nomden *et al.*, our results for the size of the HR-CTV indicated that achieving both satisfactory D90 and acceptable D<sub>2cc</sub> for OARs in OP for limited tumors is possible, and satisfactory D90 was not achieved for extensive tumors with optimization alone. Collectively, these results indicate that the benefit of optimization is more marked in patients with small HR-CTVs than in those with extensive HR-CTVs. The mean HR-CTV D90 and D<sub>2cc</sub> for OARs in OP were also reduced in the large HR-CTV group; however, the D90 in this group showed an increase in 3 of the 12 patients, all of whom had HR-CTVs >35 cm<sup>3</sup>. In addition, comparison of D90 with HR-CTV >35 cm<sup>3</sup> between NOP and OP in this group showed a similar tendency to that in the extensive HR-CTV group. On the other hand, No D90 with HR-CTV <35 cm<sup>3</sup> increased by optimization, and comparison of D90 between NOP and OP showed a similar tendency to that in the small HR-CTV group. Although additional analyses with a larger sample size are necessary to clarify the limits of effective optimization using standard ICBT, this result indicates that HR-CTV of ~35 cm<sup>3</sup> may be borderline. For HR-CTVs >35 cm<sup>3</sup>, the IS approach helps to increase the D90 [18, 19, 25–29].

The HR-CTV D98/D95 and D<sub>0.1cc</sub>/D<sub>1cc</sub> for OARS should show changes similar to the D90 and D<sub>2cc</sub> when comparing NOP with OP.



**Fig. 2.** Correlation between high-risk clinical target volume (HR-CTV) at first brachytherapy (BT) and the HR-CTV D90 (A: non-optimized treatment planning [NOP], B: optimized treatment planning [OP]). The upper and lower horizontal lines indicate 80 and 70 Gy of HR-CTV D90, respectively. The correlation between HR-CTV at first BT and the D90 in NOP is stronger than that in OP ( $R^2 = 0.555$  and  $0.283$ , respectively).

Comparable results were obtained in our total and intragroup analyses, as shown in Table 4. Generally, only the  $D_{2cc}$  was used for bladder and rectal toxicity; however, both the  $D_{0.1cc}$  and  $D_{1cc}$  were reported to be predictive of major toxicity [30]. Therefore, these parameters should also be evaluated in terms of avoiding such toxicities, especially for patients with higher  $D_{2cc}$  values. The V100 indicates the volume covered by the prescribed dose, while the V150/200 indicates that treated with significantly higher doses. In the present study, only the V100/150/200 in the extensive HR-CTV group notably increased with optimization, which was consistent with the HR-CTV D98, D95 and D90 also increasing in the extensive HR-CTV group following optimization. When patients with extensive tumors required an increased D90 dose, a larger volume may also be irradiated with higher doses. Furthermore, larger volumes treated with higher doses (V150/V200) may be associated with severe late uterine toxicities such as necrosis. Therefore,

marked increases in V150/V200 following optimization should be noted; in such cases, the IS approach may be necessary for additional D90 delivery.

The correlation between HR-CTV at first BT and D90 in NOP were stronger than that in OP, as shown in Fig. 2. Interestingly, 35 patients (66%) received  $>80$  Gy of HR-CTV D90, with a prescription of 6 Gy to point A without optimization, even with the CS technique. Of the 35 patients, 29 were small, and 6 were a large HR-CTV group. High rates of achieving enough D90 in the small and large HR-CTV groups support the validity of the adequate treatment outcomes for cervical cancer as previously reported in Japan. Meanwhile, although six considerably low D90s in NOP  $<70$  Gy were decreased to three in OP, with an increase of D90, as a whole, D90s were remarkably homogenized by optimization with overall dose reduction. The result from Fig. 2 demonstrated that dose homogenization with dose reduction (rather than increase) occurred in OP. This illustrates the main role of optimization and was consistent with the previous studies [25, 26]. It is important to recognize that an unexpectedly insufficient dose may be delivered to the remaining tumors in the small and large HR-CTV groups following optimization due to the necessity of the reduction of  $D_{2cc}$  for OARs. It is also important to be aware that an insufficient dose can also be delivered to the remaining tumors in the extensive HR-CTV group requiring more D90 only by an optimized IC approach because the main role of optimization is not to increase the dose. Clinicians must always consider the risk of local recurrence owing to insufficient doses caused by these factors. Understanding the characteristic features of optimization helps in preventing the delivery of lower doses to the HR-CTV, and thus in avoiding a local recurrence.

Dose constraints for OARs in OP should be adhered to more strictly than those in NOP [27, 28]. As shown in Fig. 3, dose constraints for OARs vary remarkably in all NOPs, while such deviations are significantly improved in OPs. Excluding three patients who received lower doses than the targeted D90, the dose constraints to OARs were not achieved in only three patients (who received  $>85$  Gy of  $D_{2cc}$  to the bladder); constraints to both the rectum and sigmoid colon were achieved in all patients. Moreover, the mean HR-CTV D90 for all the patients was 78.6 Gy, which was significantly higher than the target D90. These results indicate that higher D90s can be targeted with current dose constraints to the OARs if precise optimization is performed. However, our clinical experience in MRI-based IGABT is relatively limited. Therefore, it is necessary to accumulate further clinical data on treatment outcomes and adverse events before determining the optimal D90. Furthermore, whether targeting D90 should be the same as that in European centers must be argued because RT for cervical cancer in Japan is different from that in Europe [18, 19].

Mastering the CS technique is important for assessing the correct D90 and  $D_{2cc}$  for OARs. Recent studies showed that increased tumor coverage was observed in the right-to-left directions when using CS [31, 32]. Therefore, additional doses (D90,  $D_{2cc}$ ) must be considered and added to the total D90 and  $D_{2cc}$  when using CS. Tamaki *et al.* performed a volumetric analysis using an HR-CTV model that resembled an elliptical column [33], in which a small-sized HR-CTV was defined as 3 cm in diameter ( $\approx 23.0$  cm³). The small-sized model received 97.3 and 95.0 Gy in EQD2, including the dose contributed by CS, when 30 Gy in 15 fractions of WPI plus 20 Gy in 10 fractions of WPI with 3

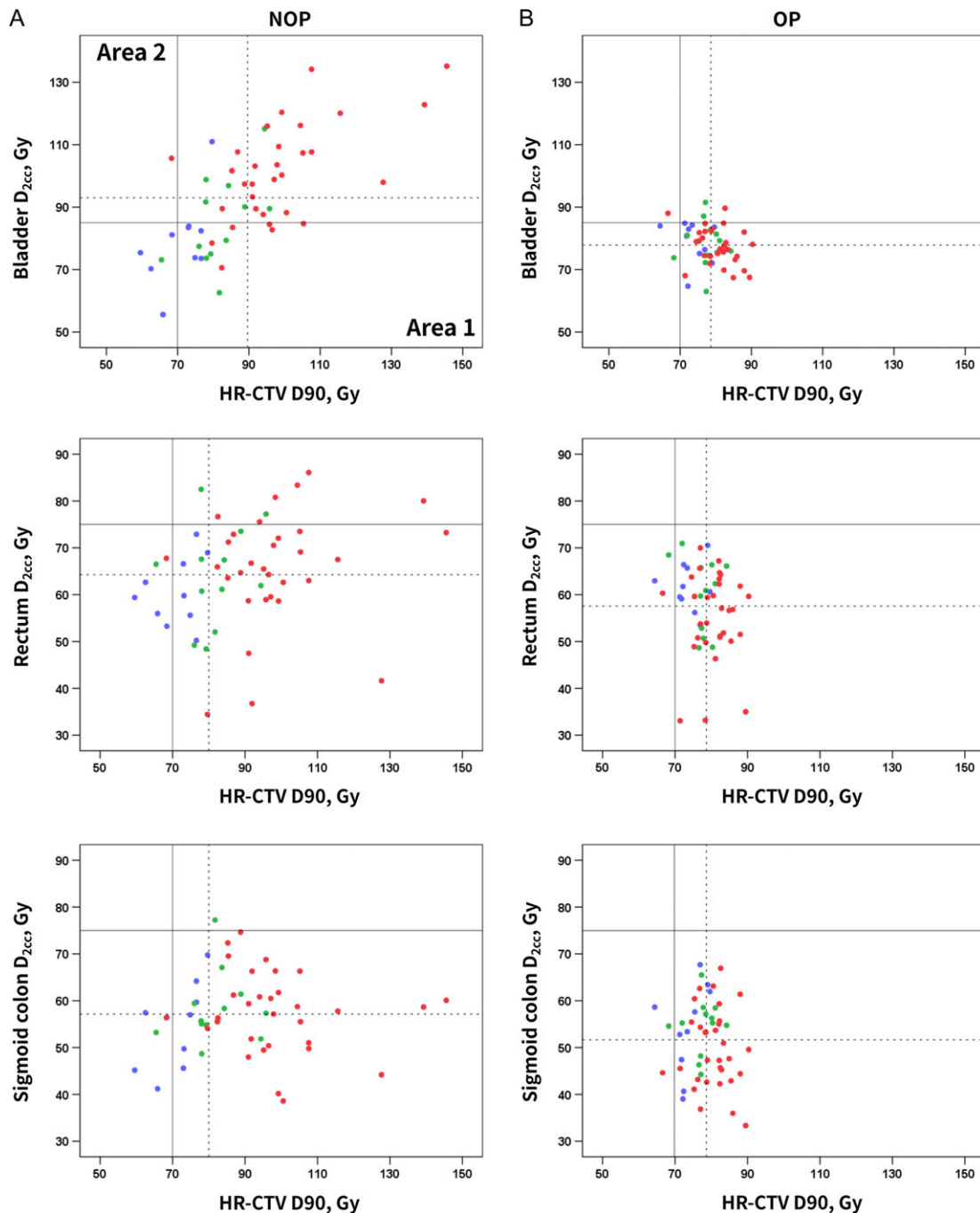


Fig. 3. Comparison of the correlation between high-risk clinical target volume (HR-CTV) D90s and  $D_{2cc}$  for organs at risk (OARS) (A: non-optimized treatment planning [NOP], B: optimized treatment planning [OP]). The vertical and horizontal solid lines indicate the targeted HR-CTV D90 and dose constraints of  $D_{2cc}$  for OARS, respectively. The vertical and horizontal dot lines indicate the mean values of HR-CTV D90 and  $D_{2cc}$  for OARS, respectively. The graph field that achieved both the target HR-CTV D90 and dose constraints of  $D_{2cc}$  of OARS was defined as Area 1. The graph field that did not achieve the target HR-CTV D90 and/or dose constraints of  $D_{2cc}$  for OARS (equal to other than Area 1) was defined as Area 2. Red, green and blue dots correspond to small, large and extensive HR-CTV groups, respectively. For the bladder, 16 points in NOP and 47 in OP were positioned in Area 1 ( $P < 0.001$ ). For the rectum, 40 points in NOP and 50 in OP were positioned in Area 1 ( $P = 0.01$ ). For the sigmoid colon, 46 points in NOP and 50 in OP were positioned in Area 1 ( $P = 0.34$ ).

and 4 cm of CS width plus 24 Gy in 4 fractions of BT to point A were administered. Using this protocol, the additional doses delivered to the HR-CTV with 3 and 4 cm of CS were 4.9 Gy (25% of the dose of WPI with CS) and 2.6 Gy (13%), respectively. Furthermore, when WPI at 30 Gy plus WPI with 4 cm of CS at 20 Gy plus BT at 24 Gy were also used for the small model, the additional dose delivered to OARs was reported to be 1.8 Gy, particularly to the bladder (9% of the dose of WPI with CS). Although doses contributed by CS to the HR-CTV and OARs should be considered in the clinical situation, these data must be adopted carefully because clinical HR-CTVs differ in size and laterality between patients, as do OAR configurations. Therefore, the doses delivered by CS should be evaluated in detail by considering the variation in the size of the HR-CTV at each implant. In addition, differences between NOP and OP should also be discussed. Precise evaluation of the dose delivered by CS with large numbers of patients could contribute to the designation of an appropriate dose to the HR-CTV in IGABT using CS.

In conclusion, sufficient HR-CTV D90s and acceptable  $D_{2cc}$  values for OARs were achieved by optimization using MRI-based IGABT for cervical cancer. The role of optimization is to reduce  $D_{2cc}$  for OARs while maintaining the target D90 for the small and large HR-CTV groups. However, the role of optimization was limited in the extensive HR-CTV group. Further evaluation of the approximate dose by CS is required, and methods of optimization in IGABT for cervical cancer when using the CS technique should be standardized, taking into account its effectiveness and limitations.

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## CONFLICT OF INTEREST

The authors state that they have no conflict of interest with respect to this study.

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## Corrigendum

Corrigendum to: Nishikawa R, Yoshida K, Ebina Y, et al. Comparison of dosimetric parameters in the treatment planning of magnetic resonance imaging-based intracavitary image-guided adaptive brachytherapy with and without optimization using the central shielding technique. *J Radiat Res* 2018: 1–11. <https://doi.org/10.1093/jrr/rry009>.

The initial Advance Access version of this paper contained some errors that have now been corrected in print and online.

In the abstract "...40/50 for the rectum, and 47/50 for the sigmoid colon ( $P < 0.001$ ,  $P = 0.01$ , and  $P = 0.34$ , respectively)." has been updated to "...39/50 for the rectum, and 47/50 for the sigmoid colon ( $P < 0.001$ ,  $P = 0.007$ , and  $P = 0.34$ , respectively)."

In the "Correlation between the HR-CTV D90 and  $D_{2cc}$  for OARs in both NOP and OP" section, the text "As for the rectum  $D_{2cc}$  and HR-CTV D90, 40 (75%) and 13 (25%) points were positioned in Areas 1 and 2 in NOP, respectively, while 50 (94%) and 3 (6%) were positioned in Areas 1 and 2 in OP, respectively ( $P = 0.01$ )."

has been updated to "As for the rectum  $D_{2cc}$  and HR-CTV D90, 39 (74%) and 14 (26%) points were positioned in Areas 1 and 2 in NOP, respectively, while 50 (94%) and 3 (6%) were positioned in Areas 1 and 2 in OP, respectively ( $P = 0.007$ )."

The author apologises for these errors.