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Computed tomography–based image-guided brachytherapy for cervical cancer: correlations between dose–volume parameters and clinical outcomes

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ABSTRACT

This study evaluated the oncologic outcomes and complications of cervical cancer patients in terms of CT-based image-guided brachytherapy (IGBT) parameters. Of 68 cervical cancer patients treated with definitive radiotherapy/concurrent chemoradiotherapy, most received whole-pelvis external beam RT (EBRT) of 40 Gy in 20 fractions, pelvic EBRT with central shield of 10 Gy in 5 fractions, and CT-based IGBT of 18 Gy in 3 fractions prescribed to point A. Cumulative EBRT and IGBT doses were calculated as the total equivalent dose in 2 Gy fractions (EQD2). The median follow-up was 31 (3–52) months. The 2-year overall survival, local control, pelvic control, and disease-free survival rates of the 68 patients were 92%, 83%, 82% and 73%, respectively. The HR-CTV D90, length from the tandem axis to left/right margin of the HR-CTV (T-LR), and HR-CTV volume were significant IGBT parameters for predicting local/pelvic control. Patients who received an HR-CTV D90 of >60 Gy, compared with ≤60 Gy, had significantly better local/pelvic control. Furthermore, 70 Gy was a marginally significant HR-CTV D90 cut-off affecting local control. T-LR was an independent IGBT parameter predicting local/pelvic control on multivariate analysis. Three patients developed Grade 3 or higher treatment-related complications. The D_{2cm^3} of organs at risk were not significant predictors of complications. Future challenges for further improving outcomes include additional interstitial needles for irregularly shaped HR-CTVs, and moderate dose escalation, especially for patients with poor tumor responses.

Keywords: cervical neoplasms; image-guided brachytherapy; computed tomography; high-risk clinical target volume

INTRODUCTION

Definitive radiotherapy (RT) consisting of external beam RT (EBRT) and intracavitary brachytherapy (ICBT) have played important roles for patients with cervical cancer [1–3]. Definitive

RT and/or concurrent chemoradiotherapy (CCRT) are now the recommended treatments for Stage I to IVA cervical cancer patients, according to treatment guidelines [4, 5].

As with EBRT, 3D treatment planning has become widely used with IGBT [6]. In 3D image-guided brachytherapy (3D-IGBT), doses are prescribed and evaluated quantitatively for the target volume as well as organs at risk (OARs). As a result, individualized treatments can be planned using 3D-IGBT, in contrast to the standard two-dimensional (2D) IGBT treatment planning, in which doses are prescribed to point A. 3D-IGBT planning is based on 3D imaging modalities such as computed tomography (CT) and/or magnetic resonance imaging (MRI), performed with inserted applicators. Appropriate contouring of both the target volume and OARs is essential for appropriate delivery of 3D-IGBT. Of particular importance is the high-risk clinical target volume (HR-CTV), which serves as a reference for both prescription and evaluation of 3D-IGBT.

The Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology (GEC-ESTRO) guidelines for 3D-IGBT for uterine cervical cancer [7, 8] and experts in this field [9] have recommended the use of T2-weighted MRI (T2WI) for the target volume delineation. However, in actual clinical practice, practical problems (such as accessibility to and limited operating time of the MRI machine) are associated with the use of MRI. Due to these practical limitations, most Japanese institutions utilize CT instead of MRI for 3D-IGBT [10], and excellent treatment results have been reported [11, 12]. The most critical issue with CT-based 3D-IGBT is inferior soft-tissue resolution on CT compared with T2WI MRI. Previous comparative studies demonstrated consistently larger HR-CTVs contoured with CT than with MRI, especially in a lateral direction [13, 14].

Dose-effect relationships in reference to the local control (LC) rate as well as the incidence and grade of complications were demonstrated in patients treated with MRI-based IGBT [15–21]. Murakami *et al.* also reported similar results with a series of CT-based IGBT [12]. These reports indicated that HR-CTV D90 is one of the most important predictors of LC [8, 12, 15, 20, 21]. To minimize the discrepancies in CT-based HR-CTV contouring and variation among physicians, consensus-based guidelines were recently developed by the Gynecological Tumor Committee Members of the Japanese Radiation Oncology Study Group (JROSG) [22].

In this study, we analyzed oncologic outcomes and complications according to various factors, including dose-volume histogram (DVH) parameters, of CT-based IGBT in cervical cancer patients treated with definitive RT/CCRT. For dose-response analyses of oncologic outcomes, we applied the CT-based HR-CTV definition proposed by the JROSG [22].

MATERIAL AND METHODS

Patients

Patient characteristics are listed in Table 1. Between November 2011 and June 2014, 90 consecutive cervical cancer patients were treated with definitive RT/CCRT at the University of the Ryukyus Hospital. From these, the following patients were excluded from the present analyses: 1 patient with condylomatous carcinoma, 1 patient with small-cell carcinoma, 8 patients treated with 2D-IGBT as part of their treatment, 9 patients with para-aortic node enlargement (>10 mm, as assessed by pretreatment CT), 2 patients who received IGBT using a cylinder applicator, and 1 patient whose CT images showed significant metallic artifacts. Therefore, the current

Table 1. Patient characteristics (n = 68)

Characteristics	No. of patients
Age	
Median (range)	58 (32–89)
FIGO stage	
IB1	14
IB2	8
IIA1	1
IIA2	1
IIB	23
IIIB	19
IVA	2
Pelvic node metastases ^a	
Yes	23
No	45
Pathology	
SCC	56
AC + ASC	12
Pretreatment tumor diameter (mm) ^b	
Median (range)	46 (24–93)
Pre-IGBT tumor diameter (mm) ^b	
Median (range)	30 (0–64)
Corpus invasion ^b	
Yes	29
No	38
Unknown	1
Pretreatment SCC antigen (ng/ml)	
Median (range)	5.3 (0.5–178)

SCC = squamous cell carcinoma, AC = adenocarcinoma, ASC = adenosquamous carcinoma, IGBT = image-guided intracavitary brachytherapy. ^aAssessed by MRI (T2-weighted images). ^bOver 10 mm in minimum diameter.

study included 68 patients. Table 1 shows the characteristics of the patients analyzed in this study.

All patients underwent pretreatment pelvic MRI (T2WI) and chest-abdomen-pelvis CT. A second MRI (T2WI) was also performed prior to the first IGBT (within 1 week). One patient did not undergo pretreatment pelvic MRI, and one patient did not have the second (pre-IGBT) MRI.

This retrospective study was approved by the ethical review board of our institution.

Radiotherapy

Details of the radiotherapy are listed in Table 2. EBRT was delivered via a 3D conformal technique using a linear accelerator (Clinac iX, Varian Medical Systems, Palo Alto, CA, USA) with a 10-MV photon beam. Treatment planning was based on CT images with a 1.25-mm slice thickness using the Aquilion LB CT scanner (Toshiba Medical Systems, Otawara, Tochigi, Japan). An EBRT dose of 50 Gy in 25 fractions was prescribed. For the majority of patients (59 patients), an initial dose of 40 Gy in 20 fractions was

delivered to the whole pelvis (WP) using a 4-field box technique; subsequently, 10 Gy in 5 fractions were delivered to the WP with a 4-cm-wide central shield (CS). For the patients whose tumors responded poorly to WP-EBRT and remained large after 40 Gy treatment, an additional WP-EBRT dose of 10 Gy without CS was delivered. One patient, whose tumor was still large after 50 Gy of WP-EBRT without CS, received additional EBRT of 6 Gy/3 fractions with reduced portals. One patient with Stage IB1 cancer received WP-EBRT of 20 Gy without CS and 30 Gy with CS; two patients received 45 Gy without CS; and one patient with active rheumatoid arthritis received 39.6 Gy of WP-EBRT.

Table 2. Details of radiotherapy

Overall treatment time (days)	
Median (range)	48 (36–74)
EBRT	
Dose to central pelvis (Gy)	
Median (range)	40 (20–56)
Dose to parametrium and pelvic wall (Gy)	
Median (range)	50 (39.6–56)
IGBT	
Total dose prescribed at point A (Gy)	
Median (range)	18 (12–24)
Total EQD2 ($\alpha/\beta = 10$) at point A (Gy)	
Median (range)	24 (14–32)
Total EQD2 ($\alpha/\beta = 10$) of HR-CTV D90 (Gy)	
Median (range)	31 (5–55)
Volume of HR-CTV at 1st IGBT (ml)	
Median (range)	28 (10–128)
Distance from tandem axis to A/P edge of the HR-CTV (mm)	
Median (range)	20 (10–44)
Distance from tandem axis to lateral edge of the HR-CTV (mm)	
Median (range)	22 (14–39)
EBRT + IGBT	
Total EQD2 at point A (Gy)	
Median (range)	64 (52–80)
Total EQD2 of HR-CTV D90 (Gy)	
Median (range)	72 (55–95)

EBRT = external beam radiotherapy, IGBT = image-guided intracavitary brachytherapy, EQD2 = the equivalent dose in 2 Gy fractions, HR-CTV = high-risk clinical target volume.

All patients received IGBT using tandem and ovoid applicators. Metallic or plastic applicators (tandem and ovoid) were utilized in the IGBT: 54 patients were treated using plastic applicators and 12 using metal applicators in all sessions; the remaining two patients were treated with both type of applicators. No patient was treated with a combination of standard intracavitary applicators and interstitial implants. IGBT was delivered using a high-dose-rate (HDR) ^{192}Ir remote afterloading system (microSelectron, Elekta, Stockholm, Sweden). IGBT was planned based on CT images with a 1.25-mm slice thickness acquired using the Aquilion LB CT scanner with inserted applicators. The dose prescribed to point A was selected according to the Manchester System. For most cases, 18 Gy in 3 fractions were delivered. One patient received 24 Gy in 4 fractions (the same patient who received 20 Gy of WP-EBRT followed by 30 Gy of WP-EBRT with CS). Two patients who received 50 Gy WP-EBRT without CS also received IGBT of 12 Gy in 2 fractions. Two patients who received 45 Gy WP-EBRT without CS also received IGBT of 20 Gy in 4 fractions of IGBT. No patient was treated with a combination of standard intracavitary applicators (tandem and ovoid) and interstitial implants. IGBT was performed once a week. EBRT and IGBT were not administered on the same day. All IGBT planning for actual treatments as well as for the present study were performed using the Oncentra MasterPlan® (Nucletron, Veenendaal, The Netherlands). Although the OARs were routinely contoured at the time of their actual treatments, the HR-CTV was not contoured. In this study, two radiation oncologists (TK, TT) performed HR-CTV delineation by mutual agreement according to the guidelines of the JROSG [22]. In the actual treatments, the dwell time or position of the source was arranged with the objective of decreasing the dose to the OARs without decreasing the prescribed dose to point A, if the minimum dose to the most irradiated 2 cm^3 ($D_{2\text{cm}^3}$) of the OARs seemed high. In 17 cases whose $D_{2\text{cm}^3}$ to the OARs was still high, even after the optimization, the prescribed dose to point A was decreased to 4–5.5 Gy per fraction. These arrangements were performed according to the physicians' discretion. In the present analyses, the minimum dose delivered to 90% (D90) of the HR-CTV and other DVH parameters were recalculated using the same dwell position and time of the source at the time of the actual treatment.

We also evaluated the oncologic outcomes according to the maximum distance between the tandem axis and the left/right margin of the HR-CTV (T-LR). Based on a dosimetric study performed by Tamaki *et al.* [23], the patients were stratified according to a T-LR cut-off of 30 mm and an anterior–posterior distance cut-off of

20 mm for directions, as those were estimated as the dosimetric edge of a total equivalent dose in 2 Gy fractions (EQD2) of 60 Gy.

Chemotherapy

Forty-seven patients were treated with concurrent chemoradiotherapy (CCRT). A weekly cisplatin dose of 40 mg/m² was administered to patients with squamous cell carcinoma (SCC). Tri-weekly doses of 50 mg/m² cisplatin combined with weekly doses of 50 mg/m² paclitaxel was administered to patients with adenocarcinoma (AC) and adenosquamous carcinoma (ASC).

Follow-up

During the treatment periods, the radiation oncologists and gynecologic oncologists performed pelvic examinations and blood tests at least once a week. After treatment completion, patients were followed up every 1–3 months by the radiation and/or gynecologic oncologists. The follow-up included a pelvic examination and Pap smear. CT scans of the abdomen and pelvis and chest X-rays (or CT scans) were performed every 6–12 months. Pelvic MRIs were not performed regularly.

A local recurrence was defined as disease progression in the uterine cervix and/or corpus and/or parametrium. Pelvic recurrence was defined as local recurrence and/or pelvic node progression. Distant metastasis was defined as development of recurrence outside the pelvis. For cases with a recurrence diagnosed pathologically, the date of the event was defined as the first date that the recurrence was suspected clinically by pelvic examination and/or diagnostic images.

Adverse events, including cystitis, proctitis and enterocolitis, were evaluated according to the National Cancer Institute Common Toxicity Criteria version 4.0 (CTCAEv4.0). Events that occurred in the sigmoid colon were considered enterocolitis. Five patients were lost to follow-up and were censored (at 3, 9, 13, 15, 18 months). The median follow-up of the patients who were not censored was 32 months (8–52 months).

Statistical analysis

Cumulative outcomes [overall survival (OS), local control (LC), pelvic control (PC) and disease-free survival (DFS)] were estimated using the Kaplan–Meier method. The outcomes were measured from the date of treatment initiation to the date the event occurred. Differences in outcomes were compared by a log-rank test. For univariate analysis, all variables were dichotomized at a median value. For multivariate analysis, we evaluated those variables with a *P*-value of <0.10 in the univariate analyses. All statistical analyses were performed using IBM SPSS Statistics version 22.0 for Windows (IBM Japan, Tokyo, Japan).

Dose parameters of IGBT, including the dose of point A, $D_{2\text{cm}^3}$ to the OARs, and HR-CTV D90 were calculated for each session. The cumulative dose of IGBT plus WP-EBRT converted to EQD2 was calculated using the linear–quadratic model with $\alpha/\beta = 10$ for tumors and $\alpha/\beta = 3$ for OARs. The WP-EBRT dose with CS was not included in the calculation.

RESULTS

Oncologic outcomes

Of the 68 patients, 20 developed recurrence: pelvic recurrence alone in 6 patients, distant metastases alone in 8, and both pelvic recurrence and distant metastasis in 6. Among the pelvic recurrence cases, 11 had local recurrence. Eight patients died: 4 due to cervical cancer, 3 due to other diseases, and 1 due to an unknown cause. Among all 68 patients, the 2-year OS, LC, PC and DFS rates were 92%, 83%, 82% and 73%, respectively (Fig. 1).

The oncologic outcomes according to the patient-related and the tumor-related variables are shown in Table 3. The 2-year LC, PC and DFS rates were significantly poorer for patients with AC/ASC than those with SCC. A large pretreatment tumor diameter had negative effects on LC and PC, but the associations did not reach statistical significance. On the other hand, tumor diameter assessed immediately before the first IGBT had significantly negative impacts on LC, PC and DFS. Neither pelvic node status nor uterine corpus invasion had an effect on the oncologic outcomes.

Table 4 shows the oncologic outcomes according to treatment-related factors, including DVH parameters. A prolonged overall treatment time (OTT) had adverse effects on LC, PC and DFS. Regarding the cumulative dose, patients were divided into two groups according to the total point A dose and HR-CTV D90 (EQD2). We compared the outcomes of patients treated with >60 Gy versus ≤60 Gy based on the reports of Murakami *et al.* [12]. Although the total point A EQD2 had no effects on outcomes, the cumulative HR-CTV D90 EQD2 was a significant predictor for all oncologic outcomes. Patients who received an HR-CTV dose of >60 Gy had significantly superior OS, LC, PC and PFS compared with those receiving ≤60 Gy. Oncologic outcomes were compared further using different cumulative HR-CTV D90 cut-off values. We found that patients who received >70 Gy achieved superior LC compared with those who received ≤70 Gy, with marginal significance. The maximum diameter from the tandem axis to the anterior/posterior margin of the HR-CTV adversely

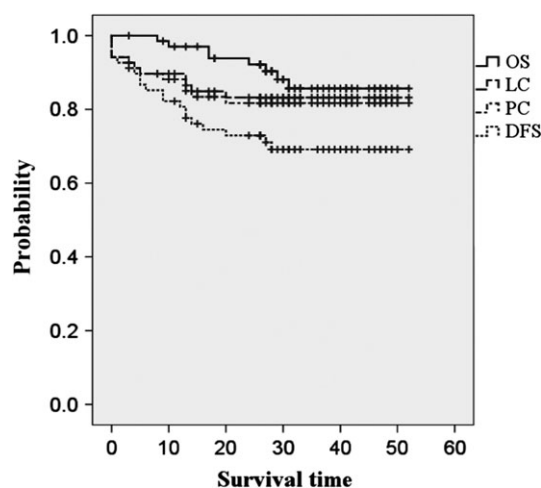


Fig. 1. Kaplan–Meier estimates for overall survival (OS), local control (LC), pelvic control (PC) and disease-free survival (DFS) in the 68 patients.

Table 3. Treatment outcomes according to patient- and tumor-related factors

Factors	<i>n</i>	2-yr OS (%)	2-year LC (%)	2-year PC (%)	2-year DFS (%)
Age (years)					
<60	35	94	86	83	73
60≤	33	90	81	81	66
		NS	NS	NS	NS
FIGO stage					
I	22	100	86	86	86
II	25	87	83	79	71
III	19	89	83	83	63
IVA	2	100	50	50	50
		NS	NS	NS	NS
Pelvic node metastases ^a					
Yes	23	96	82	78	74
No	45	90	84	84	72
		NS	NS	NS	NS
Pathology					
SCC	56	94	87	85	80
AC+ASC	12	83	67	67	42
		NS	<i>P</i> = 0.036	<i>P</i> = 0.059	<i>P</i> = 0.004
Pretreatment tumor diameter (mm) ^b					
≤ 40	21	95	91	91	76
> 40	40	92	79	77	72
		NS	NS	NS	NS
Pre-IGBT tumor diameter (mm) ^b					
≤ 30	32	100	97	94	88
30<	30	85	67	68	58
		<i>P</i> = 0.021	<i>P</i> = 0.002	<i>P</i> = 0.008	<i>P</i> = 0.007
Corpus invasion ^b					
Yes	29	88	78	78	67
No	38	95	87	84	76
		NS	NS	NS	NS
Pretreatment SCC antigen (ng/ml)					
<6.9	27	96	100	96	92
6.9≤	29	93	74	74	68
		NS	<i>P</i> = 0.006	<i>P</i> = 0.030	<i>P</i> = 0.037

OS = overall survival rate, LC = local control rate, PC = pelvic control rate, DFS = disease-free survival rate, SCC = squamous cell carcinoma, AC = adenocarcinoma, ASC = adenosquamous carcinoma, IGBT = image-guided brachytherapy. ^aOver 10 mm in shortest diameter as assessed by CT/MRI. ^bAssessed by MRI T2WI.

Table 4. Treatment outcomes according to treatment factors

Factors	<i>n</i>	2-year OS (%)	2-year LC (%)	2-year PC (%)	2-year DFS (%)
OTT (days)					
≤48	37	97	94	91	86
>48	31	85	71	71	58
		<i>P</i> = 0.068	<i>P</i> = 0.008	<i>P</i> = 0.023	<i>P</i> = 0.002
Chemotherapy administration					
CCRT	47	91	85	83	76
RT alone	21	95	80	80	66
		NS	NS	NS	NS
Total EQD2 at point A (Gy)					
>60	61	93	81	80	72
≤60	7	86	100	100	86
		NS	NS	NS	NS
Total EQD2 of HR-CTV D90 (Gy)					
>60	58	95	88	86	77
≤60	10	78	58	58	47
		<i>P</i> = 0.031	<i>P</i> = 0.005	<i>P</i> = 0.009	<i>P</i> = 0.003
>70	36	94	91	88	83
≤70	32	86	74	74	61
		NS	<i>P</i> = 0.053	NS	<i>P</i> = 0.047
Length from tandem axis to anterior/posterior edge of HR-CTV (mm)					
≤20	40	95	89	87	77
>20	28	88	74	74	67
		NS	<i>P</i> = 0.077	NS	NS
Length from tandem axis to left/right edge of HR-CTV (mm)					
≤30	60	93	88	86	76
30<	8	86	45	45	45
		NS	<i>P</i> = 0.001	<i>P</i> = 0.001	<i>P</i> = 0.003
HR-CTV Volume (ml)					
≤45	55	92	88	86	76
45<	13	92	62	62	62
		NS	<i>P</i> = 0.009	<i>P</i> = 0.017	NS

OS = overall survival rate, LC = local control rate, PC = pelvic control rate, DFS = disease-free survival, OTT = overall treatment time, CCRT: concurrent chemoradiotherapy, RT: radiotherapy, EQD2 = the equivalent dose in 2 Gy fractions.

affected the LC, with marginal significance. Patients with a T-LR >30 mm had a significantly inferior LC, PC and DFS compared with those with a T-LR ≤30 mm. Patients with an HR-CTV >45 ml demonstrated poorer LC and PC compared with those with an HR-CTV ≤45 ml.

As shown in Tables 3 and 4, those variables with *P*-values <0.1 in the univariate analyses were assessed in a Cox proportional regression analysis. According to the results of the multivariate analysis, AC/ASC and a wider tumor diameter (T-LR >30 mm) remained statistically significant factors associated with poor LC (Table 5).

Figure 2 shows local failures as a function of the HR-CTV and HR-CTV D90. A negative correlation between the volume and the dose was observed. In Figs 3 and 4, the local failures are plotted according to the length from the tandem to the anterior–posterior or lateral border of the HR-CTV and HR-CTV D90. These plots revealed that patients with a large HR-CTV and low HR-CTV D90 tended to have frequent local failures.

Complications

The cumulative EQD2 values of D_{2cm}^3 (EBRT plus IGBT) to the OARs were as follows: 69 (50–96) Gy for the bladder, 53 (38–72) Gy for the rectum, 61 (34–80) Gy for the sigmoid and 56 (32–78) Gy for the small intestine. The late complications (G1/G2/G3/G4) occurred as follows: cystitis (2/1/0/0), proctitis (1/8/0/0) and enterocolitis (3/4/4/2). There were no significant differences in the average cumulative EQD2 of the D_{2cm}^3 (EBRT plus IGBT) between patients with and those without complications with respect to each OAR. Among four cases with Grade 3 enterocolitis, only one was considered as actual radiation enteritis. The other two had peritoneal cancer dissemination, and one suffered a paralytic ileus that was potentially caused by opioid administration as part of her terminal care. The two cases of Grade 4 enterocolitis were sigmoid colon perforations requiring surgery. The cumulative EQD2 values of the D_{2cm}^3 of the sigmoid colon in these two patients were 43 Gy and 66 Gy, respectively.

DISCUSSION

This study demonstrated significantly better oncologic outcomes in cervical cancer patients who received a cumulative EQD2 of the HR-CTV D90 >60 Gy than in those who received ≤60 Gy in CT-based IGBT. The result is consistent with the results of a previously published study on CT-based IGBT [12]. Based on these findings, a cumulative EQD2 of the HR-CTV D90 should be >60 Gy for cervical cancer patients treated with CT-based IGBT. In the present series, IGBT doses were prescribed to point A irrespective of the tumor volume. The cumulative dose to point A had no impact on any oncologic outcome evaluated in this study. This finding suggests that IGBT dose prescription and evaluation using a 3D dose–volume parameter, i.e. HR-CTV D90, are essential for predicting the oncologic outcomes of cervical cancer patients treated with definitive RT/CCRT.

Some factors can lead to a decrease in the HR-CTV D90. We observed a negative correlation between the D90 and the actual HR-CTV in this study. A large HR-CTV could be one reason for the low HR-CTV D90 in patients whose IGBT doses were prescribed to point A. The present study demonstrated that a large HR-CTV had a negative effect on LC and PC. All three patients with an HR-CTV >75 ml had an HR-CTV D90 of ≤60 Gy and developed local failure. In this study, patients with AC/ASC had a poorer LC and PC compared with those with SCC, and 33% of the patients with AC/ASC received a cumulative HR-CTV D90 of ≤60 Gy. Poor and delayed responses to radiation may have affected the findings and be a reason for the unfavorable LC in the patients with AC/ASC. To overcome this negative effect, one potential solution is escalation of the EBRT dose to decrease the HR-CTV prior to IGBT. In our series, most patients received 40 Gy in 20 fractions from EBRT. Additionally, 10–16 Gy were delivered in patients with a poor response to the standard EBRT dose. Despite these efforts, we could not achieve favorable results in these patients. Therefore, EBRT dose escalation with the intention of decreasing the HR-CTV is not reasonable. Using the dose prescription with HR-CTV D90 instead of point A is considered the proper approach for

Table 5. Multivariate analysis for local control (*n* = 61)

	Risk	<i>P</i> value	HR	95% CI
Pathology	AC/ASC	0.035	11.5	1.2–111.2
Pretreatment SCC antigen (ng/ml)	≥6.9	0.078	6.1	0.8–45.3
Pre-IGBT tumor diameter (mm)	>30	0.053	9	1.0–82.7
OTT (days)	>48	0.77	1.2	0.3–5.7
Length from T to A or P of HR-CTV (mm)	>20	0.48	1.6	0.4–6.1
Length from T to L or R of HR-CTV (mm)	>30	0.047	9.7	1.0–90.5
HR-CTV (ml)	>45	0.17	0.2	0.0–1.9
Total EQD2 at HR-CTV D90 (Gy)	≤60	0.56	0.6	0.1–3.3

AC = adenocarcinoma, ASC = adenosquamous carcinoma, IGBT = image-guided brachytherapy, OTT = overall treatment time, Length from T to A or P of HR-CTV = length from tandem to anterior or posterior border of high-risk clinical target volume, Length from T to L or R of HR-CTV = length from tandem to left or right border of high-risk clinical target volume, EQD2 = the equivalent dose in 2 Gy fractions.

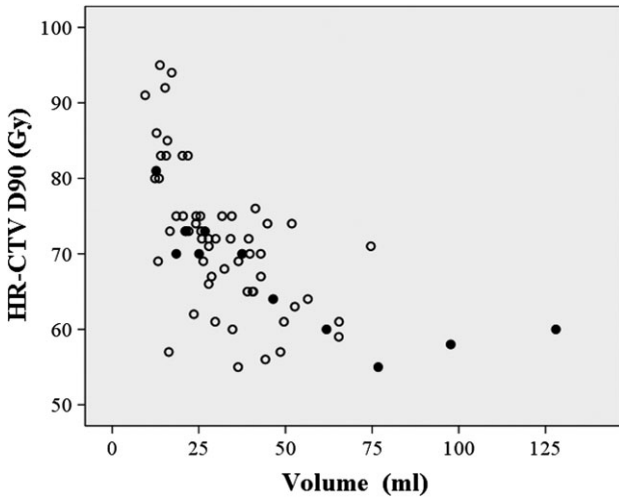


Fig. 2. Local failure as a function of the HR-CTV (volume) and HR-CTV D90 (dose). Open circles: patients with LC, Filled circles: patients with local failure.

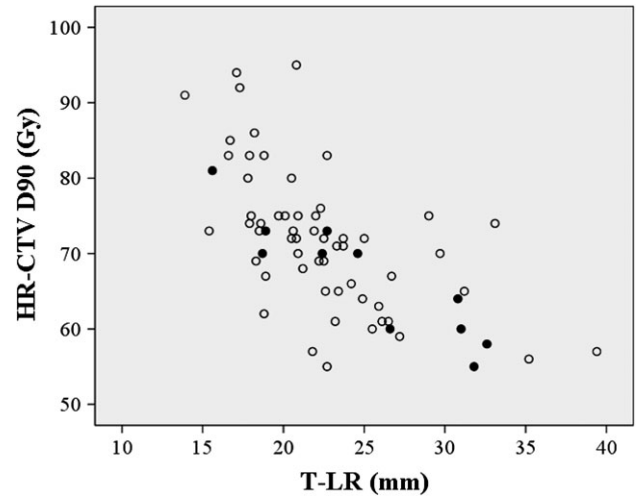


Fig. 4. A scattergram of HR-CTV D90, length from tandem axis to the lateral edge of the HR-CTV (T-LR), and local control. Open circles: patients with LC; filled circles: patients with local failure.

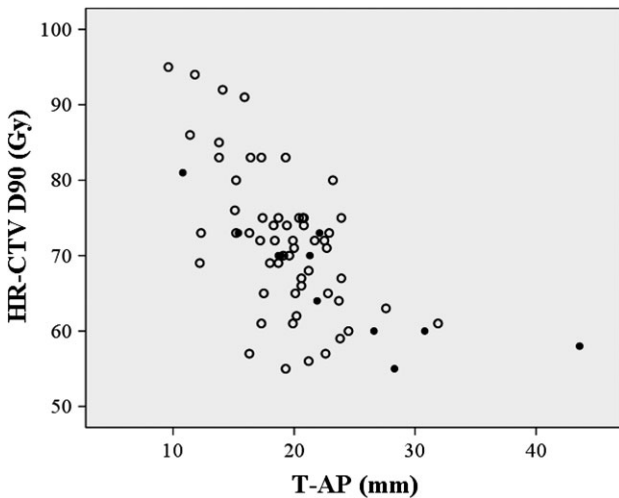


Fig. 3. A scattergram of HR-CTV D90, length from tandem axis to the antero-posterior margin of the HR-CTV (T-AP), and local control. Open circles: patients with LC; filled circles: patients with local failure.

delivering the appropriate dose to the entire tumor volume, especially for patients with large tumors at the time of IGBT. In this approach, simultaneous monitoring of the doses to OARs is mandatory [16, 17, 19, 24, 25]. The American Brachytherapy Society (ABS) guidelines [25] suggest that the D_{2cm}^3 dose constraints are 70–75 Gy for the rectum and sigmoid and ~90 Gy for the bladder. In our study, the D_{2cm}^3 for the bladder and rectum were within these tolerable limits. No patients suffered Grade 4 complications of the bladder or rectum. Therefore, dose-adaptive IGBT to maintain an HR-CTV D90 of >60 Gy for patients with a large HR-CTV might be feasible and appropriate for the majority of patients.

However, two patients in our study experienced a sigmoid colon perforation (Grade 4), despite receiving a cumulative D_{2cm}^3 to the sigmoid colon of <70 Gy. No consensus has been reached regarding dose constraints for the sigmoid colon [16]. We have to pay attention not only to DVH parameters, e.g. D_{2cm}^3 , but also to other factors, such as patient comorbidities, to minimize toxicity to the sigmoid colon.

A second factor that can negatively affect LC and PC is an asymmetrical tumor shape. The typical dose distribution of IGBT using tandem and ovoid applicators is ‘pear shaped’. With significantly asymmetrical tumors, it is difficult to encompass the entire HR-CTV within the typical dose distribution and to achieve an adequate D90. The definitive RT method used in Japan involves some specific features, with use of CS in WP-EBRT being one of the most important. CS causes different EBRT dose distribution patterns compared with those in the absence of CS. Tamaki *et al.* demonstrated a difference in the cumulative (EBRT plus IGBT) dose distribution between EBRT with CS and that without CS [23]. They demonstrated different dose distribution patterns, especially in the anterior–posterior directions. Based on these findings, we also evaluated the distances of the tandem axis to the anterior–posterior and to the lateral margin of the HR-CTV. We selected diameters of 20 mm and 30 mm as thresholds for the anterior–posterior and lateral diameters, respectively. These values were also selected based on those reported by Tamaki *et al.*, who showed that a dose of 60 Gy encompassed a diameter of 4.4 cm in the anterior–posterior direction and of 6.9 cm in the lateral direction in patients who received 40 Gy EBRT without CS, 10 Gy EBRT with CS, and 18 Gy of IGBT prescribed to point A. [23]. Murakami *et al.* revealed that the distance between the tandem axis and the lateral margin of HR-CTV (35 mm) was a significant indicator for PFS, as well as HR-CTV D90 [12]. In our study, the length from the tandem axis to the lateral edge of the HR-CTV was also found to be a significant

predictor of LC and PC. For significantly asymmetrical shaped tumors, a hybrid approach using additional interstitial sources would be a good idea to overcome this issue without increasing the dose to the OARs [26]. Ohno *et al.* reported the 5-year follow-up results in cervical cancer patients treated with CT-based IGBT [11]. The HR-CTV D90 values in their series were as follows: 69 ± 12 Gy for small tumors (<40 mm), 68 ± 6 Gy for medium-sized tumors (40–60 mm) and 67 ± 6 Gy for large tumors (>60 mm). The 5-year LC rates were excellent: 96% for small tumors, 91% for medium-sized tumors and 94% for large tumors. A combination of ICBT and interstitial brachytherapy was performed in 18% of the patients in their series. Based on these findings, coverage of the HR-CTV within an adequate dose constraint is important in addition to achieving an adequate HR-CTV D90 (e.g. 60 Gy).

The retroEMBRACE study demonstrated that a mean dose escalation from 78 Gy to 93 Gy resulted in increased LC in all patient categories [20]. The ABS guidelines recommend a cumulative EQD2 of 80–90 Gy to maximize LC [25]. In contrast, a threshold dose of 60 Gy, as demonstrated in Japanese series, including ours, seems to be unnaturally low. We consider two possible reasons for this. The first is the difference in EBRT delivery. In most Japanese institutions, including ours, CS is utilized in conjunction with the EBRT. We summed the EQD2 of 3D-IGBT and EBRT without CS EQD2 to give the cumulative HR-CTV D90, as done in previously published studies. However, Tamaki *et al.* revealed that this calculation method leads to underestimation of the cumulative dose (HR-CTV D90) [23]. Although CS of 4 cm width was utilized in our series, the actual doses delivered to the HR-CTV might be higher than those estimated using this simple calculation. The second reason involves the images utilized for IGBT. As Murakami pointed out [12], potential overestimation of the HR-CTV contoured on CT compared with MRI might have caused the dose discrepancy between the global and the Japanese series. Overestimation of the HR-CTV can lead to underestimation of the HR-CTV D90 [13, 14]. In the present study, HR-CTV was contoured on CT images in accordance with the published consensus-based guidelines [22]. The aim of the guidelines is to minimize variation in the HR-CTV among physicians and the discrepancy between CT-based and MR-based HR-CTVs. The guidelines recommend performing MRI immediately before the first ICBT as a reference, to further minimize discrepancies. In this study, some patients developed local recurrence despite receiving >60 Gy CT-based HR-CTV D90, and a cut-off dose of 70 Gy was found to have marginal significance on LC. Based on these findings, moderate dose escalation of the HR-CTV D90 (to ~70 Gy) might further improve LC with CT-based IGBT if the HR-CTV is contoured properly. A prospective study is needed to investigate the feasibility and efficacy of the dose-escalation strategy.

The present study showed that a prolonged OTT negatively affected oncologic outcomes. Tenderup *et al.* also demonstrated this finding in their 3D-IGBT series [21]. However, OTT was not found to be an independent factor in the multivariate analysis of this study. This suggested that the poorer outcomes observed were caused by other factors, e.g. the response to prior EBRT, residual tumor volume at the time of ICBT, and EBRT boost application.

There are some potential limitations in this study. It was a retrospective, single-center study involving a limited number of patients and a

limited follow-up period. The actual EBRT and IGBT dose delivered were selected according to the physicians' discretion. Although we adopted the consensus-based guidelines for CT-based HR-CTV, we still experienced some difficulties with target volume delineation in some cases.

In conclusion, the CT-based HR-CTV D90 was found to be an important prognostic indicator of LC in patients with cervical cancer treated with definitive RT/CCRT whose ICBT doses were prescribed to point A. The ICBT dose prescription with the CT-based HR-CTV D90 is essential for achieving a cumulative dose of >60 Gy, especially for patients with a large HR-CTV at the time of ICBT. To further improve the outcomes, application of additional interstitial needles for irregularly shaped HR-CTVs of certain diameters and moderate escalation of the HR-CTV D90 (to ~70 Gy) is encouraged in CT-based IGBT.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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