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BRACHYTHERAPY

Results of computer tomography-based adaptive brachytherapy in combination with whole-pelvic- and central-shielding-external beam radiotherapy for cervical cancer

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ABSTRACT

PURPOSE: To evaluate treatment results and investigate predictors of local control.

METHODS AND MATERIALS: In this retrospective study of 236 patients with cervical cancer, we administered CT-based adaptive brachytherapy (BT) in combination with whole- pelvic (WP)- and central shielding (CS)- external beam radiotherapy (EBRT) with or without chemotherapy. The study cohort comprised patients with cervical cancer treated with definitive radiotherapy (RT) or concurrent chemoradiotherapy between June 2013 and March 2019. Local control (LC), overall survival (OS), and late toxicity were evaluated. Predictive factors for LC were analyzed by univariate and multivariate analyses.

RESULTS: Median doses of WP- and CS-EBRT and BT were 30.6 Gy_{EQD2}, 19.8 Gy_{EQD2}, and 40.3 Gy_{EQD2}, respectively. The 3-year LC rates for T1b2, T2a, T2b, T3b, and T4 were 100%, 100%, 97.3%, 86.9%, and 91.7%, respectively ($p = 0.346$). The 3-year OS for Stages IB, IIB, IIIB, IIIC, and IVA were 100%, 94.8%, 82.5%, 81.7%, and 74.6%, respectively ($p = 0.037$). Rates of Grade 3–4 gastrointestinal and genitourinary toxicities were 3.8% and 1.7%, respectively. Multivariate analysis showed that T3–4, nonsquamous cell histology, and high-risk clinical target volume (CTV_{HR}) D90 of BT < $36Gy_{EQD2}$ were independently associated with significantly poorer LC.

CONCLUSIONS: The combination of WP- and CS-EBRT and CT-based IGBT with or without concurrent chemotherapy produced favorable LC outcomes with low rates of late toxicities for patients with small or medium-sized tumors. However, LC was less favorable for patients who had large T3 disease, and the use of CS requires caution in these patients.

Keywords: Uterine cervical cancer; Radiotherapy; 3D image-guided brachytherapy; Dose-volume histogram analysis

Introduction

A combination of external beam radiotherapy (EBRT) to the pelvis and brachytherapy (BT) is the standard radiotherapy (RT) approach for cervical cancer. BT plays an important role in controlling primary disease. Because the development of three-dimensional image-guided BT (3D-IGBT) using MRI or CT for treatment planning in the early 2000s (1–3), it has been increasingly used worldwide (4–6). In 3D-IGBT, doses to cervical tumors and organs at risk (OARs), such as the rectum, sigmoid colon, and bladder, can be assessed using 3D dose distributions and dose-volume histograms (DVHs). 3D-IGBT enables the delivery of a very high-dose to the tumor while minimizing doses to the OARs. Several studies have suggested that 3D-IGBT achieves favorable treatment outcomes (7–11).

Regarding BT techniques, intracavitary brachytherapy (IC-BT) using a combination of intrauterine and intravaginal applicators has long been widely used. Recently, combined intracavitary and interstitial brachytherapy (IC/IS-

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BT), which involves implanting additional interstitial needles, has been increasingly administered. IC/IS-BT has the advantage over conventional IC-BT of delivering sufficiently high-doses, especially to extensive and large tumors or those with unfavorable topography (12,13). Several studies have reported achieving favorable local control (LC) by IC/IS-BT in patients with advanced cervical cancer (11,14,15).

Late radiation toxicities in the rectum and bladder are major problems after RT for cervical cancer because EBRT and BT may deliver high-doses to these organs. In particular, in patients with small pelvises, BT applicators are often in very close proximity to the rectum and bladder, inevitably resulting in exposure of these organs to very high-doses of BT. Central-shielding (CS)-EBRT enables the reduction of doses to the rectum and bladder. Several studies have demonstrated that a combination of WP- and CS-EBRT and BT yields favorable LC and has a low incidence of late rectal and bladder toxicities (16–19). However, CS-EBRT potentially risks reducing the dose to the target volume, which may impair LC. Therefore, the contribution of BT is very important: it is imperative that sufficiently high-doses be delivered to the target volume at BT when CS-EBRT is administered (20).

In a previous study, we showed that BT contributes significantly to local tumor control when patients are treated with WP- and CS-EBRT and BT (21). In the present study, we retrospectively evaluated the treatment results and investigated predictors of LC in patients with cervical cancer treated with WP- and CS-EBRT and CT-based adaptive BT.

Methods and materials

Patients

Patients with cervical cancer who were treated with RT or concurrent chemoradiotherapy (CCRT) at our hospital between June 2013 and March 2019 were enrolled in the study in accordance with the following criteria: (1) histologically confirmed, previously untreated carcinoma of the uterine cervix; (2) $\geq$ 20 years of age; (3) thorough pretreatment evaluation by CT, MRI, and gynecological examination; (4) International Federation of Gynecology and Obstetrics (FIGO) 2018 Stage IB1–IVA; (5) treated with definitive RT or CCRT using CT-based IGBT; and (6) DVH data available. The study was approved by the institutional review board of our hospital (registration number: 2021–075). All patients underwent pretreatment diagnostic studies including physical and pelvic examinations by gynecologists and radiation oncologists, cervical biopsy, routine blood cell counts, chemistry profile, CT scans of the chest, abdomen, and pelvis, and MRI of the pelvis. Most patients also underwent 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) scan. Cervical tumor size was measured on MRI T2 weighted images. Lymph node status was diagnosed according to the findings of CT, MRI, and/or FDG-PET. A lymph node $\geq$ 1 cm in its short axis on CT or MRI and/or positive findings on FDG-PET was diagnosed as lymph node metastasis. N factor was classified as N0, N1, and N2 by UICC TNM 8th edition.

Radiotherapy

EBRT was delivered to the pelvis with 10 MV X-rays. The CTV for the WP-EBRT consisted of the primary tumor, whole uterus, bilateral parametria, at least the upper half of the vagina, and pelvic lymph nodes. Three-dimensional conformal RT with a four-field box technique was used, whereas intensity-modulated radiotherapy was not used. A dose of 1.8–2.0 Gy/fraction and five fractions/week were delivered by EBRT. The radiotherapy was based on the Japanese treatment protocols for cervical cancer (16–18). Briefly, for patients with Stage IB1–2 or IIA1 disease, 20 Gy EBRT was delivered to the WP, followed by 30 Gy CS-EBRT and BT. For patients with advanced-stage of disease, 30 Gy (for medium-sized tumors) or 40 Gy (for large tumors) WP-EBRT was delivered, followed by 20 or 10 Gy CS-EBRT and BT. When a patient had bulky pelvic lymph node(s), an additional 5–10 Gy was delivered to the lesion(s). Regarding Stage IIIC2r disease, 40 Gy EBRT was delivered to the whole abdominal para-aortic lymph node region, and an additional 10–20 Gy was delivered to the enlarged lymph node(s) to boost the dose to a total of 50–60 Gy in 25–30 fractions over 5–6 weeks.

Four weekly sessions of CT-based IGBT were initiated after completion of WP-EBRT. A high-dose-rate ^{192}Ir source was used. IC- or IC/IS-BT was performed to adapt to the tumor volume. IC/IS-BT was adopted for patients with extremely extensive or large tumors. IS needles were inserted with free-hand technique. The high-risk clinical target volume (CTV_{HR}) and OARs, including the rectum, sigmoid colon, bladder, and small bowel, were delineated on CT images in accordance with published recommendations (1–3,22) and the dose distributions and DVHs were calculated. All radiation doses were biologically converted to equivalent doses in 2 Gy (EQD2) by a linear quadratic model using an alpha/beta ratio of 10 Gy for CTV_{HR} and 3 Gy for OARs. Regarding the DVH parameters, the dose delivered to 90% and 98% of the CTV_{HR} (CTV_{HR} D90 and D98) and the minimum dose delivered to 2 cm^3 ($D2cm^3$) of the rectum, sigmoid colon, and bladder were calculated, recorded, and reported. The planned dose and dose constraints were as follows: (1) minimum CTV_{HR} D90 $\geq$ 6.5 Gy in each BT session; and (2) $D2cm^3$ of the rectum and sigmoid colon $\leq$ 70 Gy_{EQD2} and $D2cm^3$ of the bladder $\leq$ 90 Gy_{EQD2} by a combination of WP-EBRT and BT. When the dose constraints for the CTV_{HR} and OARs were not both achievable, the constraints for the OARs were prioritized. Radiotherapy was withheld if patients developed Grade 4 hematological toxicities or Grade 3–4 non-hematological toxicities as assessed by the Common Terminology Cri-

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teria for Adverse Events (CTCAE) ver. 4.0 (23). Radiotherapy was resumed when the toxicities had recovered to Grade 2.

Chemotherapy

Patients with Stage IB1–2 or IIA1 disease were treated with RT alone, whereas those with more advanced-stage disease were treated with concurrent chemoradiotherapy (CCRT) unless they were aged ≥ 75 years, had a performance status (PS) score of 3 or 4, and/or insufficient organ function. Most patients received weekly cisplatin (40 mg/m^2); however, those for whom this was considered contraindicated received monthly nedaplatin. Chemotherapy was discontinued when patients developed Grade 3–4 hematological or non-hematological toxicities and resumed when the toxicities had recovered to Grade 1.

Follow-up and evaluation

After completion of treatment, patients were followed up every 1–3 months for the first 2 years and every 3–6 months from the third year. Post-treatment evaluation and assessment of adverse events were achieved by medical interviews, physical and gynecological examinations, and blood tests at scheduled checkup visits. Patients also underwent CT and/or MRI 1 month after treatment and every 6–12 months thereafter. If a recurrence was suspected, CT, MRI, and/or FDG-PET were performed to assess disease status. Biopsies were also performed whenever possible.

The primary endpoint of the study was LC, and the secondary endpoints were overall survival (OS) and late toxicities. LC was defined as the absence of any recurrent or progressive disease in the cervix, parametrium, uterine corpus, and/or vagina. Pelvic and/or para-aortic nodal recurrence or progression within the irradiated volume was not classified as local failure. Late toxicities were defined as adverse events in the pelvis occurring more than 3 months after completing treatment. Late toxicities were classified as gastrointestinal, genitourinary, or other and were graded according to the CTCAE version 4.0. Duration of LC was measured from initiation of treatment to the date of diagnosis of local failure or the most recent follow-up. Duration of OS was measured from initiation of treatment to the date of death from any cause or the most recent follow-up. The duration of late toxicities was measured from initiation of treatment to diagnosis of toxicities or the most recent follow-up.

Statistical analysis

Statistical analysis was performed using SPSS version 26 (IBM; Armonk, NY). The rates of LC, OS, and late toxicities were calculated using the Kaplan–Meier method. Predictive factors for LC were investigated by univariate analysis using the log-rank test and multivariate analysis using the Cox proportional hazard model, with respect to the following clinicopathological and treatment factors: age (≤ 50 years or > 50 years); maximum tumor diameter (< 60 mm or ≥ 60 mm); T factor (T1–2 or T3–4), N factor (N0 or N1/2); para-aortic lymph node status (negative or positive); histology (squamous cell or non-squamous cell carcinoma); treatment (RT or CCRT); BT technique (IC-BT or IC/IS-BT); overall treatment time (< 56 days or ≥ 56 days); CTVHR volume for the first BT; and DVH parameters (CTV_{HR} D90 of BT only or of WP-EBRT plus BT). The cut-off values for CTV_{HR} volume in the first BT and DVH parameters for LC were determined using receiver operating characteristic (ROC) analysis. $p < 0.05$ was considered to denote statistical significance in univariate and multivariate analyses.

Results

Patient and treatment characteristics

The cohort of the present study comprised 236 patients. The characteristics of these patients and their treatment are summarized in Table 1. CCRT (cisplatin, 159; nedaplatin, 21) was administered to 80 patients, and the remaining 56 patients underwent RT alone. Regarding EBRT, a total dose of 39.6–60 Gy (median, 50 Gy) was delivered. A CS was inserted after delivering 19.8–45 Gy (median, 30.6 Gy) to the WP. Regarding BT, 187 patients were treated with IC-BT and 49 with IC/IS-BT. The volume of CTV_{HR} in the first BT session was 7.6–195.4 cm^3 (median, 30.0 cm^3). The median CTV_{HR} D90 and D98 of BT was calculated to be 40.3 Gy_{EQD2} (range, 19.1–76.1 Gy_{EQD2}) and, 31.9 Gy_{EQD2} (range, 15.2–61.3 Gy_{EQD2}), respectively. Regarding the cumulative dose delivered to CTV_{HR}, CTV_{HR} D90 of WP-EBRT and BT was calculated because the value was conventionally used. However, this calculation may underestimate the cumulative dose to CTV_{HR} when CS-EBRT is used. CTV_{HR} D98 of WP + CS-EBRT and BT was also calculated in this study, because, for CTV_{HR} with larger than 3 cm in width, CTV_{HR} D98 is derived by the dose outside the CS (Table 2).

Outcomes

The median duration of follow-up was 45 months (range, 2.2–90.1 months). Eighteen patients developed local recurrence during follow-up, 12 developed pelvic and/or paraaortic lymph node metastases, and 69 developed distant metastases. Regarding the sites of local recurrence, nine patients had recurrences in their uterine cervixes, two in their uterine corpuses, six in their vaginas, and three in their parametria. The 3-year LC for all patients was 92.6%. The 3-year LC according to T status was 90.9%

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Table 1

Age (years) (median, range)		62.5(29–94)
FIGO Stage	IB	18
	IIB	78
	IIIA	2
	IIIB	43
	IIIC1	71
	IIIC2	11
	IVA	13
T factor	T1b1	15
	T1b2	6
	T2a	1
	T2b	112
	T3a	4
	T3b	85
	T4	13
N facto	N0	146
	N1	79
	N2	11
Histology	SCC	200
	Non-SCC	36
Tumor size at diagnosis (cm) (median, range)		5.0(1.0–11.0)
Treatment	CCRT	180
	RT	56
EBRT dose (Gy_{EQD2}) (median, range)		
	Total	50(39.6–60)
	Whole Pelvis	30.6(19.8–45)
	Central Shielding	19.8(0–30)
BT technique	IC-BT	187
	IC/IS-BT	49
Overall treatment time (days) (median, range)		50 (35-92)

SCC = squamous cell carcinoma; CCRT = concurrent chemoradiotherapy; RT = radiotherapy; IC-BT = intracavitary brachytherapy; IC/IS-BT = combined intracavitary and interstitial brachytherapy.

Table 2

	All ($n = 236$)
CTV_{HR} D90 of BT (Gy_{EQD2}) (median, range)	40.3(19.1–76.1)
CTV_{HR} D98 of BT (Gy_{EQD2}) (median, range)	31.9(15.2–61.3)
CTV_{HR} D90 of WP-EBRT + BT (Gy_{EQD2}) (median, range)	73.8(56.0–116.1)
CTV_{HR} D98 of WP+CS-EBRT + BT (Gy_{EQD2}) (median, range)	81.6(59.4–111.3)
Rectum $D2cm^3$ (Gy_{EQD2}) (median, range)	59.4(29.0–89.1)
Bladder $D2cm^3$ (Gy_{EQD2}) (median, range)	73.4(37.3–112.7)

CTV_{HR} = high-risk clinical target volume; WP-EBRT = whole pelvic external beam radiotherapy; BT = brachytherapy; D90m = the dose delivered to 90%; D98 = the dose delivered to 98%; $D2cm^3$ = the minimum dose delivered to 2 cm^3; EQD2 = equivalent doses in 2 Gy.

for T1b1, 100% for T1b2, 100% for T2a, 97.3% for T2b, 75% for T3a, 86.9% for T3b, and 91.7% for T4 ($p = 0.346$) (Fig. 1). During follow-up, 37 patients died of cervical cancer and 4 died of other diseases. The 3-year OS according to FIGO stage was 100% for Stage IB, 94.8% for Stage IIB, 100% for Stage IIIA, 82.5% for Stage IIIB, 81.7% for Stage IIIC, and 74.6% for Stage IVA ($p = 0.037$) (Fig. 2).

The incidences of Grade 3–4 gastrointestinal and genitourinary adverse events were 3.8% and 1.7%, respectively. Two of the seven patients who developed rectovaginal fistulae and one of the four who developed vesicovaginal fistulae had Stage IVA disease with rectal or bladder invasion (Table 3).

Table 3

Adverse events	All ($n = 236$)
Gastrointestinal	
All grades	58 (24.6%)
Grade 3–4	9 (3.8%)
Genitourinary	
All grades	26 (11.0%)
Grade 3–4	4 (1.7%)

Predictors of local control

The cutoff value calculated from the ROC curve for CTV_{HR} volume for the first BT was 35 cm^3 (AUC = 0.663), whereas the cutoff values for cumulative CTV_{HR} D90 of BT only and WP-EBRT plus BT were

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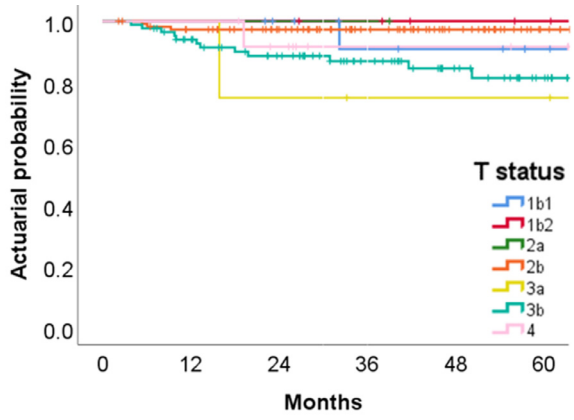
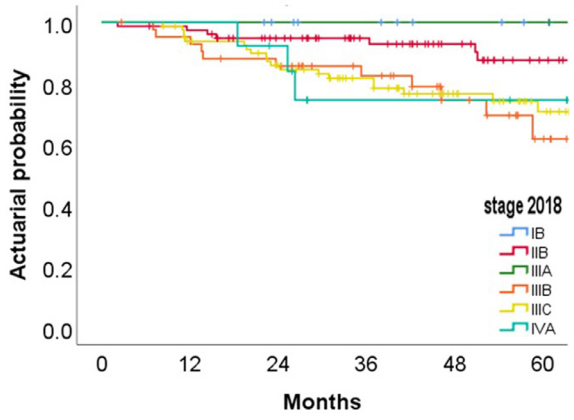


No. at risk

T1b1	14	14	14	13	13	13
T1b2	6	6	6	6	6	6
T2a	1	1	1	1	1	1
T2b	111	106	106	106	106	106
T3a	4	4	3	3	3	3
T3b	86	77	64	51	36	26
T4a	13	13	11	11	11	11

Fig. 1. Local control by T stage.



No. at risk

IB	18	18	18	18	18	18
IIB	78	75	72	72	49	33
IIIA	1	1	1	1	1	1
IIIB	43	40	35	26	22	14
IIIC	82	74	65	57	42	21
IVA	13	13	12	8	8	8

Fig. 2. Overall survival by stage.

36 Gy_{EQD2} (AUC = 0.424) and 72 Gy_{EQD2} (AUC = 0.522), respectively. Univariate analyses showed that T status, histology, CTVHR volume for the first BT, and CTV_{HR} D90 and D98 of BT only were significant predictors of LC, T3–4, nonsquamous cell histology, CTV_{HR} volume $\geq$ 35 cm^3, and CTV_{HR} D90 of BT < 36 Gy_{EQD2}, with CTV_{HR} D98 of BT < 28 Gy_{EQD2} being associated with significantly poorer LC. However, CTV_{HR} D90 of WP-EBRT plus BT was not significantly correlated with LC (Table 4). Because D90 and D98 have a strong positive correlation coefficient of 0.94 and are considered conceptually closely related variables, we selected only D90 for multivariate analysis. After multivariate analyses, T factor, histology, and CTV_{HR} D90 of BT remained significant predictors of LC (Table 5).

The relationships between CTV_{HR} volume, CTV_{HR} D90 of BT, and LC were determined using scatter plots (Fig. 3). Three-year LC for patients with CTV_{HR} volume < 35 cm^3 and CTV_{HR} D90 $\geq$ 36 Gy_{EQD2}, CTV_{HR} volume $\geq$ 35 cm^3 and CTV_{HR} D90 $\geq$ 36 Gy_{EQD2}, CTV_{HR} volume < 35 cm^3 and CTV_{HR} D90 < 36 Gy_{EQD2}, and CTV_{HR} volume $\geq$ 35 cm^3 and CTV_{HR} D90 < 36 Gy_{EQD2}, were 98%, 89%, 80%, and 78%, respectively.

Discussion

In the present study, patients with cervical cancer were treated with RT or CCRT using a combination of approximately 30 Gy WP- and 20 Gy CS-EBRT and CT-based 3D-IGBT. The median CTV_{HR} D90 of BT only was 40.3 Gy_{EQD2}. We achieved a 3-year LC of 92.6% for all patients and 96.7% and 87% for those with stage IB-IIB and III-IVA, respectively. Several studies on MRI- or CT-based 3D-IGBT have demonstrated favorable treatment outcomes. In a series from the Medical University of Vienna, the 3-year LC after CCRT and MRI-based IGBT was 100% for Stage IB, 96% for Stage IIB, and 86% for Stage IIIB, respectively (7). The RetroEMBRACE study, which was a multicenter retrospective cohort study on CT- or MRI-based IGBT, reported a 3-year LC of 91% for all patients, comprising 98% for Stage IB, 93% for Stage IIB, and 79% for Stage IIIB, respectively (9). More recently, the EMBRACE-I studies, a multicenter prospective cohort study on CCRT and MRI-based IGBT, reported a 5-year LC of 91%–98% for patients with Stages IB1–IVA (11). We consider that the results of the present study were almost similar to those of these other 3D-IGBT studies, however, the LC for patients with T3 disease was less favorable when compared with that of the EMBRACE-I study.

In the present study, univariate and multivariate analyses showed that T status, histology, and the cumulative CTV_{HR} D90 of BT were statistically significant predictors of LC (Tables 4 and 5). Regarding the dose to the cervical tumor, several 3D-IGBT studies reported the dose-response relationship of the cumulative CTV_{HR} D90 of WP-EBRT plus BT (24-26). The series in Vienna found that, in large tumors, dose escalation of CTV_{HR} D90 from 81 Gy_{EQD2} to 90 Gy_{EQD2} between two time periods resulted in improvement of LC from 71% to 90% (24). DVH analyses of the retroEMBRACE study findings demonstrated that dose escalation from 75 Gy_{EQD2} to 85 Gy_{EQD2} resulted in a 3% increase in LC for tumors of limited to intermediate size (20–30 cm^3) and a 7% increase for large tumors ($\geq$70 cm^3) CTV_{HR}. These researchers estimated that CTV_{HR} D90 of $\geq$ 85 Gy_{EQD2} delivered in 7 weeks achieved a 3-year LC of

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Table 4

Factors		3y-LC (%)	*p*-value
Age	≦50	93.3	0.726
	>50	92.3	
Tumor size	<60 mm	93.9	0.346
	≧60 mm	89.7	
T factor	T1–2	96.7	0.001
	T3–4	87.0	
N factor	N0	94.4	0.245
	N1/2	89.6	
Paraaortic lymph node	Positive	100.0	0.366
	Negative	92.2	
Histology	SCC	95.2	0.001
	Non SCC	76.4	
Treatment strategy	CCRT	91.8	0.974
	RT	95.2	
Brachytherapy technique	IC-BT	93.6	0.291
	IC/IS-BT	88.7	
Overall treatment time	<56 days	94.5	0.133
	≧56 days	84.7	
CTV_{HR} volume at first BT	<35 cc	96.1	0.001
	≧35 cc	86.3	
CTV_{HR} D90 WP+BT	<72 Gy_{EQD2}	93.0	0.852
	≧72 Gy_{EQD2}	92.9	
CTV_{HR} D98 WP+BT	<63 Gy_{EQD2}	91.5	0.336
	≧63 Gy_{EQD2}	93.4	
CTV_{HR} D90 BT	<36 Gy_{EQD2}	77.8	0.000
	≧36 Gy_{EQD2}	93.7	
CTV_{HR} D98 BT	<28 Gy_{EQD2}	78.3	0.000
	≧28 Gy_{EQD2}	94.7	

CTV_{HR} = high-risk clinical target volume; BT = brachytherapy; WP = whole pelvic external beam radiotherapy; D90 = the dose delivered to 90%; D98 = the dose delivered to 98%; EQD2 = equivalent doses in 2 Gy; SCC = squamous cell carcinoma; IC-BT = intracavitary brachytherapy; IC/IS-BT = combined intracavitary and interstitial brachytherapy.

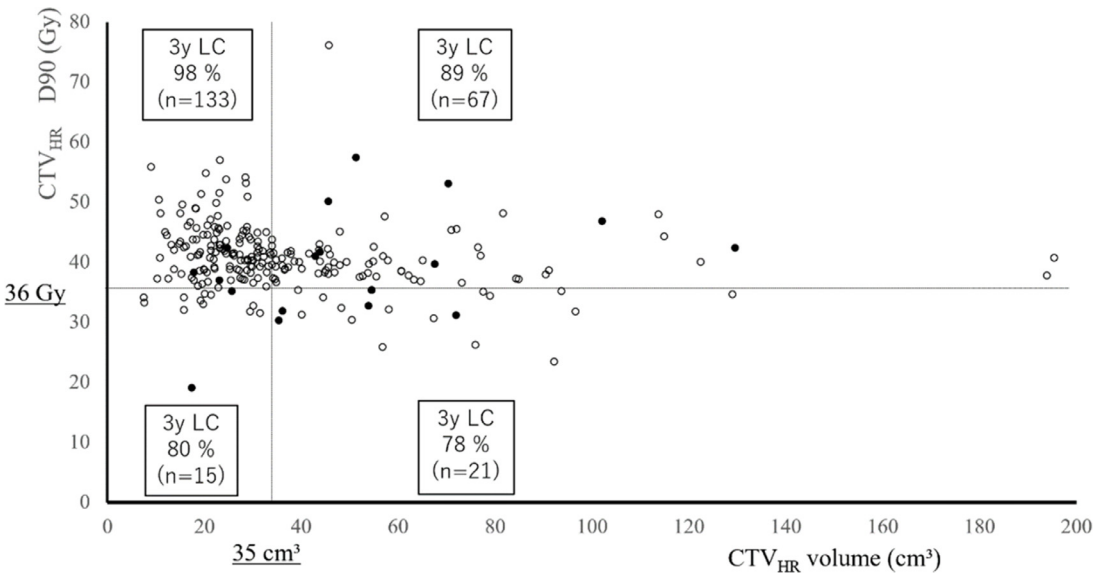

Fig. 3. Relationship between local control and CTV_{HR} volume and CTV_{HR} D90. Open and filled circles represent local control and failure, respectively. Abbreviations: CTV_{HR} = high-risk clinical target volume, LC = local control rate.

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Table 5

Factors		*p*-value
T factor	T1–2	0.014
	T3–4	
Histology	SCC	0.000
	Non SCC	
CTV_{HR} volume at first BT	<35 cc	0.056
	≧35 cc	
CTV_{HR} D90 BT	<36 Gy_{EQD2}	0.019
	≧36 Gy_{EQD2}	

CTV_{HR} = high-risk clinical target volume; BT = brachytherapy; D90 = the dose delivered to 90%; EQD2 = equivalent doses in 2 Gy; SCC = squamous cell carcinoma.

> 93–94% for tumors of limited or intermediate size and > 86% in larger tumor CTV_{HR} (26). In the EMBRACE-I study, approximately 90 Gy_{EQD2} (85–94 Gy) delivered to CTV_{HR} D90 achieved a 5-year LC of 91–92%, even in patients with Stage IIIB–IVA disease (11). Because most patients in these studies received 45–50 Gy WP-EBRT, dose escalation of BT was the main contributor to the improved LC, CTV_{HR} D90 of BT ≥ 40 Gy_{EQD2}, resulting in the high LC.

In contrast, patients in the present study were treated with a combination of WP- and CS-EBRT and BT. Previous clinical studies using WP- and CS-EBRT and BT reported the Point A dose or HR-CTV_{HR} D90 by simply adding the doses of WP-EBRT and BT while omitting the dose of CS-EBRT (15,17,18). According to this method, the median CTV_{HR} D90 of WP-EBRT plus BT in the present study was 73.8 Gy_{EQD2}, which is very low compared with the cited European and North American studies (7-11). Furthermore, no correlation was found between CTV_{HR} D90 of WP-EBRT plus BT and LC (Table 4). These results suggest that simply adding the WP-EBRT and BT doses while omitting the CS-EBRT dose may underestimate the actual dose to the CTV_{HR} (20).

Several dosimetric studies showed that the CS-EBRT dose contributes to some extent to the total dose delivered to CTV_{HR}, and the dose should not be omitted for evaluation (27–29). The lateral regions of CTV_{HR}, which are outside CS, can be covered with adequately high-doses by EBRT and BT when BT is optimally performed. In the central regions of CTV_{HR}, which are inside CS, EBRT doses are lowered by CS, but substantial doses may be delivered by BT because of the close proximity of the sources. Consequently, high enough doses for tumor control may be delivered to the central regions of CTV_{HR} (27–29). However, there are several limitations in evaluating the cumulative CTV_{HR} D90 or D98 when CS-EBRT is used. First, the presence of large dose gradients from both CS-EBRT and BT in the same regions makes it difficult to evaluate the cumulative doses (3,27,28). Second, the abovementioned hypothesis requires a good geometrical relationship between CS and the high-dose regions at BT. However, uncertainties exist regarding the interfractional variations during CS-EBRT and BT phases, which cause difficulties in the evaluation (27–29). Further studies are needed to establish a more precise formula for estimating the cumulative doses of WP- and CS-EBRT and BT to the CTV_{HR}.

The dose contribution of CS-EBRT to the dose of CTV_{HR} varies significantly by CS width (3 cm or 4 cm) and dose of CS-EBRT (10–30 Gy). When the CS width is smaller, the impact of dose reduction to CTV_{HR} is less significant (27–29). In the present study, 3-cm width CS was used, and the CS-EBRT dose was changed according to the stage and tumor size (CS-EBRT dose 30 Gy for Stage IB1–2 or Stage IIA1, 20–10 Gy for more advanced-stage disease with medium-sized or large tumor). These treatment methods and adequately high-dose delivery at BT may have resulted in the favorable LC outcomes in the present study.

However, when a tumor is large and has significant AP extension, the use of CS-EBRT has the potential risk of under dosage of CTV_{HR} (28,29). In the present study, LC for patients with T3 disease or for those with bulky disease (> 35 cc of CTV_{HR} volume at first BT) were less favorable when compared with those of the EMBRACE-I study (11). To achieve favorable LC for large Stage III-IVA tumors, the planned dose of CTV_{HR} D90 ≥ 85–90 Gy_{EQD2} is recommended (11,30,31). Therefore, CS-EBRT requires caution in patients who have large tumors with significant AP extension.

In the present study, CTV_{HR} D90 in the BT sessions were significant predictors of LC, and CTV_{HR} D90 ≥ 36 Gy_{EQD2} at BT had significantly better LC (Tables 4 and 5). In addition, CTV_{HR} D98 was strongly correlated with D90, suggesting that D98 was a significant predictor for LC as well as D90, and CTV_{HR} D98 ≥ 28 Gy_{EQD2} at BT may have had significantly better LC. These results suggested that BT makes a very important contribution to achieving LC and indicated that 90% or 98% of the CTV_{HR} should be covered with at least 6.5 Gy (approximately ~9 Gy_{EQD2}) or 5.5 Gy (approximately ~7 Gy_{EQD2}), respectively, at each BT session. Our previous study reported that local recurrence occurred outside the 6 Gy isodose line at BT (21). Interestingly, these results are almost comparable to those of the retroEMBRACE study, which demonstrated that CTV_{HR} D90 ≥ 85 Gy_{EQD2} or CTV_{HR} D98 ≥ 75 Gy_{EQD2} had better LC (26,31). Because most patients received 45–50 Gy WP-EBRT in this study, CTV_{HR} D90 ≥ 40 Gy_{EQD2} or CTV_{HR} D98 ≥ 30 Gy_{EQD2} was associated with favorable LC.

In the present study, IC/IS-BT was used for only 20% of the patients because of a personnel shortage in the early period of the study. This may have resulted in the poor LC outcomes for patients with extensive and large tumors. As described above, it is important to cover the whole tumor volume with high-dose BT using IC/IS-BT (14).

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Non-squamous cell histology was a significant predictor of LC in the current study (Tables 4 and 5). Notably, 7of the 36 patients with non-squamous cell carcinomas (6 adenocarcinomas and 1small cell carcinoma) developed local recurrence. The local recurrences were located in the uterine cervices of five of these seven patients, this region having received high-doses of radiation. Several studies have also achieved poor LC and OS of locally advanced cervical adenocarcinomas treated with RT or CCRT (32,33). Further studies are needed regarding the optimum dose to CTV_{HR} and/or the appropriate combination of RT and chemotherapy or immune therapy to achieve LC of advanced cervical adenocarcinomas. The results of several studies suggested that carbon ion radiotherapy may be an effective alternative for these radioresistant tumors (34,35).

In the current study, the rates of late Grade 3–4 gastrointestinal and genitourinary adverse events were 3.8% and 1.7%, respectively. The RetroEMBRACE study reported 5-year rates of Grade 3–5 gastrointestinal and genitourinary toxicities of 7% and 5%, respectively (9), whereas the corresponding rates in the EMBRACE-I study were 8.5% and 6.8%, respectively (11). The low incidence of severe late toxicities in the current study may have been attributable to lower doses of radiation to the rectum and bladder as a result of inserting CS during EBRT. However, because late radiation toxicities may continue to manifest long after the completion of RT, evaluation of treatment safety requires long-term follow-up (16).

This study had several limitations. First, as a retrospective single-institutional study, there was a potential selection bias. Second, there were few local recurrences, which may have limited the statistical reliability. However, in the present study, 3D-IGBT treatment planning, including delineation of CTV_{HR} and OARs and recording and reporting for DVH parameters, strictly complied with the published recommendations. Furthermore, almost all patients were strictly followed up. The present study therefore provides useful information on treatment.

Conclusions

We evaluated the treatment outcomes of a combination of WP- and CS-EBRT with 3-cm CS width and CT-based IGBT with or without concurrent chemotherapy for patients with cervical cancer. This treatment produced favorable LC outcomes with low rates of late toxicities for patients with small- or medium-sized tumors. However, LC was less favorable for patients who had large T3 disease, and the use of CS requires caution in these patients.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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