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Original Article

Local Control of Squamous Cell Carcinoma of the Cervix Treated with CT-based Three-dimensional Image-Guided Brachytherapy with or without Central Shielding

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The purposes of this retrospective study were to analyze local control of squamous cell carcinoma of the cervix treated with computed tomography (CT)-based image-guided brachytherapy (IGBT), as well as the factors affecting local control. A total of 39 patients were analyzed. The prescribed dose to the pelvis was 45-50 Gy with or without central shielding (CS). IGBT was delivered in 1-5 fractions. The total dose for high-risk clinical target volume (HR-CTV) was calculated as the biologically equivalent dose in 2-Gy fractions. The median follow-up period was 29.3 months. The 2-year overall survival and local control rates were 97% and 91%, respectively. In univariate analysis, the dose covering 90% of the HR-CTV (D_{90}) and tumor size were found to be significant factors for local control. The cutoff values of tumor size and D_{90} for local control were 4.3 cm (area under the curve [AUC] 0.75) and 67.7 Gy (AUC 0.84) in the CS group and 5.3 cm (AUC 0.75) and 73.7 Gy (AUC 0.78) in the group without CS, respectively. However, though the local control of CT-based IGBT was favorable, the results suggested that the dose required for tumor control may differ depending on the presence of CS.

Key words: cervical cancer, squamous cell cancer, brachytherapy, central shielding

The standard radiation therapy for cervical cancer is a combination of external beam radiotherapy (EBRT) and brachytherapy (BT) [1]. BT is an important component of the treatment [2], and three-dimensional image-guided BT (3D-IGBT) using computed tomography (CT) or magnetic resonance imaging (MRI) is widely employed [3,4]. Moreover, there are several reports on treatment outcomes of and risk factors for local control in IGBT of cervical cancer [5-10].

There are 2 distinct radiotherapy approaches that aim to improve outcomes: those that use central shielding (CS) and those that do not. In comparison to American and European nations [7-9,11], in Japan treatment schedules using CS are included in the guidelines [12]. Outcomes have been reported based on each treatment schedule [7-10]. The dose volume parameter, an important local control factor in cervical cancer, suggests differences in the dose required for local control depending on whether or not CS is used [7-10], and

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these differences raise questions in clinical practice.

At our institution, we have implemented treatments both with and without CS. However, to our knowledge there have been no reports examining the dose volume parameter for local control for each treatment schedule at the same facility. Therefore, one of the purposes of this study was to examine the local control rate for cervical squamous cell carcinoma as well as the factors affecting local control, including CS of CT-based 3D-IGBT. Additionally, we examined the dose volume parameters necessary for local control in each treatment schedule.

Patients and Methods

Patients. This study was approved by the institutional Ethics Committee (No. 916) of the Kagawa Prefectural Central Hospital, Kagawa. Informed consent to participate was obtained from all patients. A total of 39 patients with pathologically proven, previously untreated squamous cell carcinoma of the cervix were treated at our hospital with high-dose-rate (HDR) CT-based 3D-IGBT between August 2014 and April 2019, and were included in this study. All radiotherapy (RT) and concurrent chemoradiotherapy (CCRT) were definitive treatments. All patients underwent a pelvic examination, CT scan, MRI, and blood test. Maximum tumor diameters were measured based on the axial images of MRI. Patients with 2008 International Federation of Gynecology and Obstetrics (FIGO) Stage IB1-IVA disease were included. Patients with para-aortic node metastasis were included because this study was performed to analyze local control of the primary tumor.

Chemotherapy. Concurrent chemotherapy of cisplatin (40 mg/m^2) and nedaplatin (35 mg/m^2) was administered weekly to 30 patients (77%). CCRT was not performed in patients with insufficient organ functions or in those aged 80 years or older. Supportive treatments, such as blood transfusions, were performed during RT/CCRT.

External beam radiotherapy. EBRT was delivered by CT-based planning with 4-10 MV X-rays. The clinical target volume (CTV) for EBRT included sites such as the primary tumor, whole uterus, bilateral parametrium, at least the upper half of the vagina, and pelvic lymph nodes (common, internal, external iliac, obturator, and presacral). If the primary tumor involved the lower third of the vagina or if there were enlarged inguinal lymph nodes, the inguinal regions were also included in CTV. The planning target volume (PTV) was defined as CTV plus a 1- to 2-cm margin of primary tumor and uterus body. PTV margins for other CTV were set to 5 mm to account for daily setup errors. Three-dimensional conformal RT (3D-CRT) with an anterior—posterior parallel-opposed field or a 4-field box was used for whole pelvic (WP) irradiation. After WP irradiation, the anterior—posterior parallel-opposed field with a 4-cm-wide CS was delivered according to the Japanese guidelines [12]. The position of CS was set to the S2/3 level. We started volumetric modulated arc therapy (VMAT) for WP irradiation from April 2016. VMAT was performed using 2-4 arcs. We normalized each plan such that 100% of the prescribed dose was delivered to 95% of the PTV. The total pelvic dose administered was 45-50 Gy. For patients with lymph node metastases or inadequate tumor regression after WP irradiation, an additional boost was delivered to make the dosage 55-61 Gy.

Brachytherapy. BT was initiated after WP-EBRT and was performed weekly for a total of 1-5 sessions. A high-dose-rate (HDR) ^{60}Co source was used for the treatment. Intracavitary (IC) BT or the combination of IC and interstitial (IS) BT was performed to adapt to the tumor volume. The IS technique was considered for large (e.g., ≥4 cm) or asymmetric tumors. CT-based 3D-IGBT was performed during each BT session. The high-risk CTV (HR-CTV) and organs at risk (OARs), including the rectum and bladder, were contoured on planning CT with reference to MRI images acquired at diagnosis and just before the first BT session. The HR-CTV included the entire cervix and the residual macroscopic tumor at the time of BT [13]. OARs were delineated based on pelvic normal tissue contouring guidelines [14]. 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 HR-CTV and 3 Gy for OARs. The dwell times and dose distributions were modified manually using graphical optimization to meet our dose constraints: (i) for each BT session, HR-CTV $D_{90} \geq 6$ Gy, bladder and rectum $D_{2\,cc} < 7$ Gy (where $D_{2\,cc}$ means the dose delivered to 2 cc of OARs); (ii) total HR-CTV $D_{90} \geq 60$ Gy, bladder $D_{2\,cc} < 90$ Gy, rectum $D_{2\,cc} < 75$ Gy. In the calculation of the total HR-CTV and OAR doses, all the EQD2 values of WP-EBRT (not including CS-EBRT)

and HDR-BT were summed because CS-EBRT is considered not to contribute to the HR-CTV or OARs in the Japanese treatment schedule [6, 10].

Follow-up. Gynecologists and radiation oncologists followed up each patient every 1-3 months for the first 2 years and every 3-6 months from the third year after completion of the treatment. Tumor status and adverse events were assessed using patient interviews, physical and gynecological examinations, and blood tests. Patients generally underwent CT and/or MRI at 1-3 months after treatment to evaluate the therapeutic effects and every 6-12 months thereafter. Recurrent disease was confirmed by biopsy, though the presence of recurrence was determined when a lesion was clearly seen on imaging (CT or MRI) before the malignancy could be confirmed via biopsy. Local control (LC) duration was defined as the period between the initiation of RT and either a diagnosis of local recurrence or the date of the last follow-up. Late adverse events were defined as adverse events emerging at least 92 days after completion of RT and were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis. Differences in patient characteristics and treatment details between the CS group and the without-CS groups were compared using Fisher's exact test (categorical variables), Student's *t*-test (normally distributed continuous variables), and Wilcoxon signed-rank test (non-normally distributed continuous variables). LC was estimated using the Kaplan—Meier method. Differences between factors were examined using the log-rank test. Receiver operating characteristics (ROC) curve analysis was performed to select the most relevant threshold. The Kaplan—Meier curve was plotted with SPSS software v. 20 (IBM, Armonk, NY, USA), and other statistical analyses were performed using JMP software v. 10.0 (SAS Institute, Cary, NC, USA). A two-sided *p*-value < 0.05 was considered statistically significant.

Results

Patient characteristics are summarized in Table 1 and treatment details are provided in Table 2. Overall, patients showed a median follow-up period of 29.3 months (range 6.9-60.4 months). Further, 4 patients (10.2%) developed local recurrence. The 2-year LC rate was 91% (Fig. 1). Next, ROC analysis was used to determine each cutoff parameter, and the results of the univariate analysis of the prognostic factors for LC are summarized in Table 3. Moreover, tumor size (≥ 4.3 cm) and D_{90} (≥ 67.7 Gy) of HR-CTV were significant factors.

Thereafter, the patients were divided into 2 groups: with CS or without CS. The differences in patient background between the groups are also listed in Table 1 and Table 2. In each group, ROC analysis was used to determine each cutoff parameter for tumor size and D_{90} for local control. In the CS group, the cutoff values of tumor size and D_{90} were 4.3 cm (AUC: 0.75) and

Table 1 Patient characteristics (n = 39)

Characteristics		Total (n = 39)	With CS (n = 21) Number of patients (n)	Without CS (n = 18)	*p* value
Age (years)	Median (range)	59 (28–86)	59 (28–79)	59.5 (47–86)	0.39 *
FIGO 2008	IB1	7	5	2	–
	IIA1	3	1	2	
	IIA2	3	1	2	
	IIB	19	12	7	
	IIIB	4	1	3	
	IVA	3	1	2	
Lymph node metastasis	Positive	17	6	11	0.042 †
	Negative	22	15	7	
Histologic type	SCC	39	21	18	–
Initial tumor size (mm)	Median (range)	40 (20–76)	39 (20–58)	48 (21–76)	0.02 ¶
Para-aortic node metastasis	Positive	7	2	5	0.14 †
	Negative	32	19	13	

SCC, squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics.
*, Wilcoxon signed-rank test; †, Fisher's exact test; ¶, Student's *t*-test.

Table 2 Treatment details (n=39)

	Total (n=39)	With CS (n=21)	Without CS (n=18)	*p* value
EBRT technique				
WP (3D-CRT)	15	10	5	0.17 †
WP (VMAT)	24	11	13	
EBRT dose				
Median total dose (Gy) (range)	56 (46–61)	50 (50–60.4)	59 (46–61)	0.004 *
Median WP dose (Gy) (range)	40 (20–50.4)	30.6 (20–40)	45 (45–50.4)	<0.001 *
Median CS dose (Gy) (range)	10 (0–30)	19.8 (10–30)	0	<0.001 *
Brachytherapy				
Median number of fractions (range)	3 (1–5)	4 (2–5)	3 (1–3)	<0.001 *
IC	36	21	15	0.089 †
IC+IS	3	0	3	
Overall treatment duration (days)				
Median (range)	45 (38–63)	44 (42–52)	49.5 (38–63)	0.001 *
Chemotherapy				
No	9	3	6	0.15 †
Yes	30	18	12	
wCDDP	26	17	9	
wCDGP	4	1	3	
EQD2 of the HR-CTV D_{90} (Gy)				
Median (range)	71.9 (54–93.2)	67.8 (54–93.2)	73.1 (65.9–80.6)	0.083 ¶
EQD2 of the rectum $D_{2\,cc}$ (Gy)				
Median (range)	56.3 (34.8–74.4)	52.3 (34.8–73)	63 (48.7–74.4)	0.022 ¶
EQD2 of the bladder $D_{2\,cc}$ (Gy)				
Median (range)	72.5 (53.1–108.2)	71.1 (53.1–108.2)	72.6 (58.2–84.6)	0.88 *

WP, whole pelvis; CS, central shielding; 3D-CRT, three-dimentional conformal radiotherapy; VMAT, volumetric modulated arc therapy; IC, intracavitary; IS, interstitial; CDDP, cisplatin; CDGP, nedaplatin; HR-CTV, high-risk clinical target volume; EQD2, equivalent dose in 2 Gy; *, Wilcoxon signed-rank test; †, Fisher's exact test; ¶, Student's *t*-test.

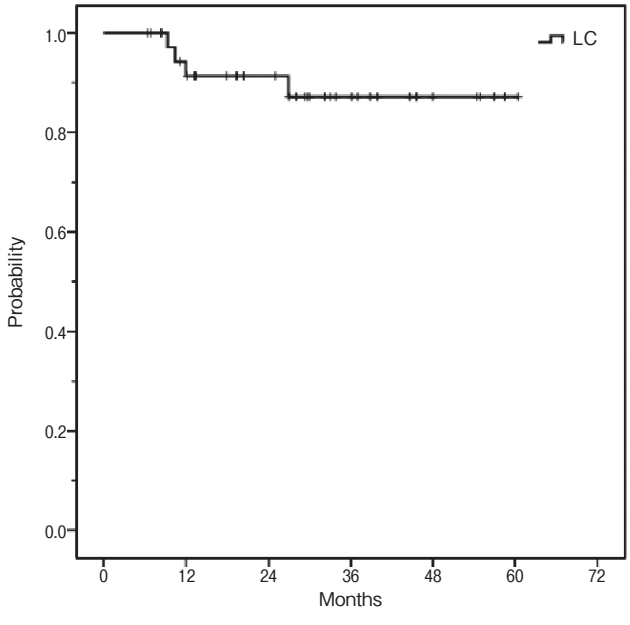

Fig. 1 Kaplan–Meier curves for local control (LC, solid line).

67.7 Gy (AUC: 0.84), respectively. In the group without CS, the cutoff values of tumor size and D_{90} were 5.3 cm (AUC: 0.75) and 73.7 Gy (AUC: 0.78), respectively. To visualize tumor size and D_{90} in local recurrent cases, scatter diagrams of the 2 groups are shown in Fig. 2A and B, where the cutoff values for these parameters are also shown. Late adverse events in the rectum, bladder, and sigmoid are shown in Table 4. Further, grades 2 and 3 proctitis were observed in 1 (rectum D_{90}: 55.1 Gy) and 2 patients (rectum D_{90}: 62.5 and 51.5 Gy), respectively. None of the patients experienced higher than grade 2 cystitis or other gastrointestinal morbidity.

Discussion

Traditionally, cervical cancer has been treated using chemotherapy and radiotherapy, and a variety of radiotherapy approaches have been considered to improve the outcomes in these patients. Here, we have confirmed similar or better outcomes than in previous reports using CT-based IGBT [7-10]. We identified D_{90}

Table 3 Univariate analyses of local recurrence within the HR-CTV (n = 39)

Factors		Local recurrence within the HR-CTV (n)		Total (n)	*p-value*
		Presence	Absence		
Age	< 54	0	14	14	0.14
	≥ 54	4	21	25	
Tumor size	< 4.3 cm	0	21	21	0.031
	≥ 4.3 cm	4	14	18	
T factor	I-IIA	0	13	13	0.22
	IIB-IV	4	22	26	
Use of chemotherapy	Yes	4	26	30	0.32
	No	0	9	9	
Ratiotherapy technique	IMRT	4	20	24	0.052
	3D-CRT	0	15	15	
Use of CS	Yes	2	19	21	0.64
	No	2	16	18	
Pelvic LN metastasis	Yes	1	16	17	0.43
	No	3	19	22	
Para-aortic LN metastasis	Yes	0	7	7	0.35
	No	4	28	32	
HR-CTV D90	< 67.7 Gy	3	7	10	0.019
	≥ 67.7 Gy	1	28	29	
Overall treatment time	< 48 days	1	22	23	0.14
	≥ 48 days	3	13	16	

CS, central shielding; LN, lymph node; HR-CTV, high-risk clinical target volume.

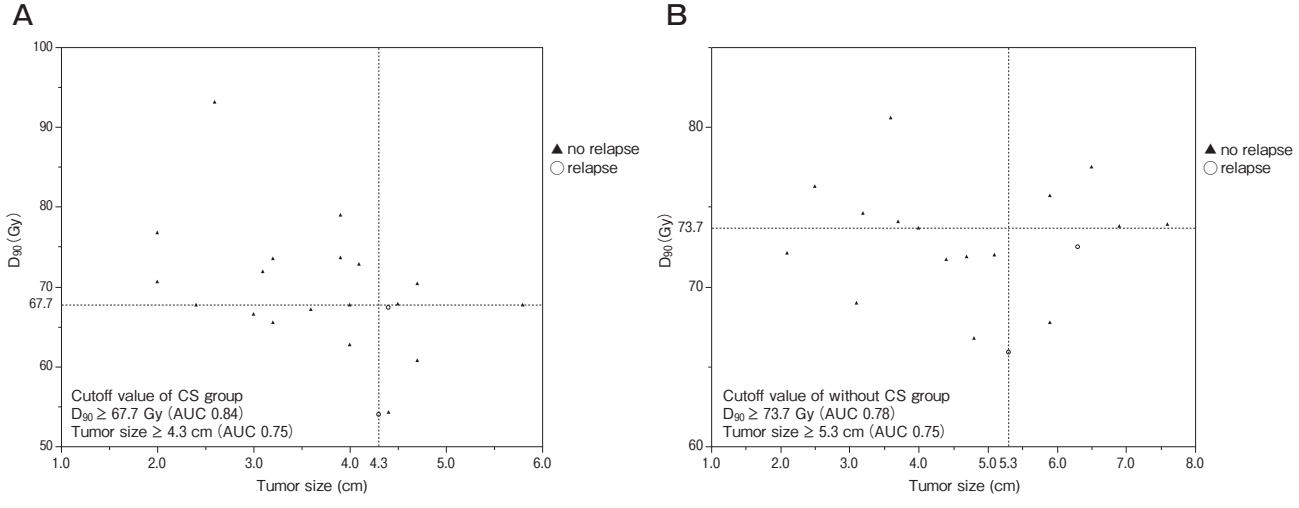

Fig. 2 Scatter diagrams for local relapse in the (**A**) CS group and (**B**) without CS group.

and tumor size as significant factors for local control using univariate analysis. Our study also suggests that the treatment intensity needs to be changed in the presence of CS.

Several studies have indicated an association between local control and tumor size. Potter *et al.* [15] reported a decrease in tumor control for tumors larger than 5 cm in treatments using MRI-based 3D-IGBT. CS was not used in their treatment schedule. On the other hand, in a study by Kawashima *et al.* [6], treatment using CT-based 3D-IGBT, with inclusion of CS, resulted in a decrease in tumor control for tumors larger

Table 4 Late adverse events (CTCAE 4.0) after radiotherapy ± chemotherapy in 39 patients

Grade	0 n (%)	1 n (%)	2 n (%)	3 n (%)	4-5 n (%)
Rectum	32 (82)	4 (10)	1 (3)	2 (5)	0 (0)
Sigmoid	36 (92)	3 (8)	0 (0)	0 (0)	0 (0)
Bladder	38 (97)	1 (3)	0 (0)	0 (0)	0 (0)
Total		8 (21)	1 (3)	2 (5)	0 (0)

CTCAE, Common Terminology Criteria for Adverse Events.

than 4.5 cm. The cutoff values determined for the CS and without-CS groups (CS -: 5.3 cm; CS +: 4.3 cm) in our study were similar to those in previous reports [6, 15].

Our present findings also confirm that the cut-off values of D_{90} for local control differ according to whether or not CS is used. Tamaki *et al.* [16, 17] reported a comparison of point A doses between the Japanese (with CS) and Western (without CS) treatment schedules using a phantom. They observed that the dose calculation based on the Japanese treatment schedule suggested a cumulative dose of WP-EBRT plus D_{90} of BT, although 13-35% of the EBRT dose with a 4 cm width CS dose contributed to tumor control. Although the cutoff value for tumor control reported by Murakami *et al.* was $D_{90} \geq 60$ Gy, it is possible that additional doses were prescribed as in the report by Tamaki and colleagues. In our study as well, the CS-EBRT dose may explain the different cutoff values between the with- and without-CS groups, as the calculation does not include the CS-EBRT contribution. However, in an IGBT that adjusts the dose distribution based on the tumor size and position, it is difficult to accurately understand the amount of the EBRT doses with CS that contributes to tumor control. The cutoff value of D_{90} calculated in our study was lower than that in the reports from the West [7-9], which could be the result of the inclusion of nonsquamous cell carcinoma samples in those studies, as opposed to the radio-sensitive squamous cell carcinoma cohort analyzed in our study. Further, reports by Kawashima *et al.* [6] and other groups [18, 19] suggest that adenocarcinoma is a significant risk factor for local control. Additionally, the present study is based on CT-based IGBT and, as reported by Viswanathan *et al.* [20], CT overestimates the volume of HR-CTV over MRI, which results in lower D_{90} values.

However, it should be noted that the present study was a retrospective study with a small sample size. Moreover, tumor size was significantly higher in the without-CS group than in the CS group. Although our results showed that $D_{90} \geq 73.7$ Gy provided more reliable local control in the without-CS group, this dose may be too high for small lesions and could lead to more adverse events in OARs. In the future, it will be necessary to formulate a treatment schedule without CS and set a target dose according to tumor size.

In conclusion, this study confirms the favorable outcome observed with CT-based IGBT. Tumor size and D_{90} were significant factors for local control. It should be understood that the use of CS complicates the current understanding regarding the treatment intensity required for local control. Finally, our study provides important findings regarding the dose required for local control both with and without CS.

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