

Survey article

Comparison of clinical outcome between computed tomography-based image-guided brachytherapy and two-dimensional-based brachytherapy for cervical cancer

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ABSTRACT

This study aimed to analyze the clinical results of radiotherapy for cervical cancer using two-dimensional (2D) intracavitary brachytherapy (ICBT) and computed tomography (CT)-based image-guided brachytherapy (IGBT) at our institution. Patients with stage IB–IVA cervical cancer who received IGBT between April 2008 and April 2014 were included in this study. In total 58 patients were assessed. The first 38 patients received IGBT with the 2D treatment plan (the 2D group), and the remaining 20 patients received CT-based IGBT (the IGBT group). The dose of point A tended to be lower in the IGBT group (mean value, 60.6 Gy vs. 62.5 Gy; $p = .07$), though the minimum dose to the 90% (D90) of the clinical target volume (CTV) was equivalent in both groups (mean value, 66.0 Gy vs. 66.2 Gy; $p = .91$). The rectum minimum dose to 2 cc (D2cc) was significantly lower in the IGBT group than in the 2D group (mean value, 61.2 Gy vs. 69.1 Gy; $p = .001$). With a median follow-up time of 60 months, the 5-year local control rates (LCRs) of the IGBT group and 2D group were 100% and 83%, respectively ($p = .12$). The 5-year incidence of rectal complications in the IGBT group and the 2D group were 11% and 29%, respectively ($p = .26$). Our study showed favorable LCR and preferred incidence of rectal complications in patients treated with CT-based IGBT.

1. Introduction

Radiotherapy for cervical cancer consists of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT). IGBT with a three-dimensional (3D) treatment plan using a computed tomography (CT) or magnetic resonance imaging (MRI) is called image-guided brachytherapy (IGBT). By using IGBT, the dose of the tumor and normal organs can be more accurately evaluated (Noda et al., 2007; Dimopoulos et al., 2009; Georg et al., 2011). We started acquiring CT images after inserting applicators in high-dose-rate IGBT from April 2008 to evaluate a dose distribution. However, until July 2012, treatment dose was determined using a two-dimensional (2D) treatment plan using two-way radiographs. We adopted IGBT with the 3D treatment plan from August 2012. In this study, we compared the dose-volume histogram (DVH) of the tumor and normal organs in the 2D treatment plan with those in CT-based IGBT plan and examined the difference between the treatment results of 2D and 3D plan.

2. Materials and methods

2.1. Eligibility criteria

Patients were considered eligible for this retrospective analysis on the basis of the following criteria: had histologically confirmed cervical cancer, did not have metastasis in a distant organ, had received EBRT and IGBT between April 2008 and April 2014 at our institution, and DVH of the tumor and normal organs can be evaluated using CT images. A total of 58 patients were included in this study. Written informed consent was obtained from each patient before treatment. This retrospective analysis was approved by the institutional review board (H29-003-2).

2.2. Radiotherapy

The whole pelvic irradiation (WPI) was performed up to a total dose of 40 Gy with a dose of 2 Gy per fraction. The central shielding (CS)

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with a 4-cm-width midline block was inserted after 40 Gy to a total dose of 50 Gy. For some patients with massive tumors, WPI was performed up to 50 Gy without CS. In EBRT, treatment plans with CT images were performed using a 3D treatment planning system. Along with the CS irradiation, ICBT was started with a remote afterloading system using HDR 60 Co source. ICBT was performed thrice with an interval of one week. In patients treated without CS, ICBT was performed twice after 50 Gy WPI. After implanting applicators, CT images with 2-mm slice thickness were obtained at each treatment in all patients. Diagnostic MRI scans were taken before the first ICBT and were used as reference images of the tumor and normal organs. The clinical target volume (CTV) was defined as the residual tumor at the time of ICBT and the whole uterine cervix. D90 (minimum dose to the 90%) of CTV, D2cc (minimum dose to 2 cc) of the rectum and bladder, was used to evaluate DVH.

From April 2008 to July 2012, the prescribed dose was determined based on the 2D treatment plan. Basically, 6 Gy was prescribed at point A (a point 2 cm cranial from the external cervical os and 2 cm lateral from the tandem) for the first 38 cases. DVH for CTV, rectum, and bladder were evaluated using CT images with applicators after treatment (the 2D group). From August 2012, the prescribed dose was determined based on the 3D treatment plan according to the D90 of the CTV in the following 20 cases. The radiation source position and the dwell time were adjusted by the doses of the CTV and risk organs. The prescribed dose was 6 Gy to D90 of CTV, and the dose constraint of D2cc of the rectum was 5.7 Gy (the IGBT group).

2.3. Chemotherapy

Patients with stage IB or IIA were treated with radiotherapy alone. Chemoradiotherapy with concomitant cisplatin (CDDP) was performed in patients with stage IIB or higher. Nedaplatin or paclitaxel was used in cases with decreased renal function. In patients who were difficult to treat by chemoradiotherapy due to old age or complications, radiotherapy alone was adopted for treatment.

2.4. Analysis

Overall survival (OS) was defined as the period from the initiation of treatment to death from any cause. Local control rates (LCR) were defined as the rates without local relapse. Local relapse was defined as a recurrence in the uterus, parametrium, or vagina. The death in the state without local recurrence was censored. Further, the incidence of adverse events in the rectum and bladder was evaluated. Adverse events were evaluated using the Common Terminology Criteria for Adverse Events version 4.0. The total doses from EBRT and IGBT were summarized and normalized to a biological equivalent dose of 2 Gy per fraction (EQD2) using the linear quadratic model with $\alpha/\beta = 10$ Gy for point A and CTV and $\alpha/\beta = 3$ Gy for the rectum and the bladder. *t*-test was used to compare the average between the two groups, and Fisher's exact test was used to compare the frequency of certain events between the two groups. The Kaplan-Meier method was used to calculate the OS, LCR, and incidence of late toxicities. For all analyses, a *p*-value < .05 was considered to be statistically significant. All factors with a *p*-value < .05 in univariate analysis (UVA) were entered into a multivariate analysis (MVA) using the Cox regression model and 95% confidence interval (CI). Statistical analyses were performed using JMP Pro 14 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient and tumor characteristics

The patient and tumor characteristics are summarized in Table 1. There was no significant difference between the 2D group and IGBT group regarding the distribution of age, histology, stage, LN metastases,

Table 1
Patient and tumor characteristics.

		All	2D group	IGBT group	<i>p</i>
n		58	38	20	
Age	Median (range)	65 (35–92)	62 (36–92)	65 (35–87)	0.61
Pathology	Sqcc	54 (93)	36 (95)	18 (90)	0.60
	Adeno	3 (5)	2 (5)	1 (5)	1.00
	Adsq	1 (2)	0 (0)	1 (5)	0.35
FIGO stage	IB	7 (12)	5 (13)	2 (10)	1.00
	IIA	2 (3)	1 (3)	1 (10)	1.00
	IIB	29 (50)	17 (45)	12 (60)	0.41
	IIIA	2 (3)	1 (3)	1 (5)	1.00
	IIIB	13 (22)	10 (26)	3 (15)	0.51
	IVA	5 (9)	4 (11)	1 (5)	0.65
LN metastasis	Positive	24 (41)	16 (42)	8 (40)	1.00
Complications	DM	7 (12)	4 (11)	3 (15)	0.68
	Anticoagulants	10 (17)	5 (13)	5 (25)	0.29

Abbreviations: Sqcc, squamous cell carcinoma; Adeno, adenocarcinoma; Adsq, adenosquamous carcinoma; DM, diabetes mellitus

Table 2
Predictive factors of rectal complication.

			UVA	MVA	
Factors		5-year incidence	<i>p</i> value	<i>p</i> value	HR (95% CI)
Age	< 65	13%	0.12	–	–
	≥ 65	32%			
FIGO stage	I–II	16%	0.07	–	–
	III–IV	36%			
Prescription	Point A	29%	0.26	–	–
	D90	11%			
Rectal dose D2cc	< 70 Gy	16%	0.006	0.007	9.0
	≥ 70 Gy	44%			(2.2–44.6)
Anticoagulants	Yes	44%	0.03	0.003	8.9
	No	18%			(1.6–49.3)
DM	Yes	43%	0.01	0.93	0.79
	No	20%			(0.79–3.9)

Abbreviations: DM, diabetes mellitus; UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; CI, confidence interval

and complications.

3.2. Treatment

WPI with CS was performed in 42 cases. WPI without CS was performed in 16 cases. ICBT was performed twice in 16 patients, thrice in 41 patients, and four times in 1 patient (stage IVA adenocarcinoma patients).

Chemotherapy was performed in 39 cases. CDDP 30 mg/m²/week was administered in 30 patients. Nedaplatin and paclitaxel was administered in 7 and 2, respectively in cases with decreased renal function. The remaining 19 patients were treated with radiotherapy alone.

3.3. Clinical outcome

The median follow-up period was 60 months (8–117 months) for all patients and 71 months (48–117 months) for survivors. The 5-year OS and LCR was 65% and 89%, respectively (Suppl. Fig. 1a, 1b). The 5-year OS rates according to FIGO classification were as follows: stage I, 100%; stage II, 68%; stage III, 53%; and stage IV, 40% (Suppl. Fig. 2a). The 5-year LCR was 96% in stages I–II and 76% in stages III–IVA (Suppl. Fig. 2b).

Table 3

Dose comparison between the 2D group and the IGBT group.

Factors	2D group		IGBT group		p
	Mean	(Range)	Mean	(Range)	
Point A	62.5Gy	(52.0Gy–72.0Gy)	60.6 Gy	(53.9Gy–66.9Gy)	0.07
CTV D90	66.2 Gy	(51.2Gy–85.5Gy)	66.0 Gy	(61.0Gy–74.9Gy)	0.91
Rectum D2cc	69.1 Gy	(51.9Gy–96.0Gy)	61.3 Gy	(50.3 Gy–70.1Gy)	0.001
Bladder D2cc	72.1 Gy	(56.8Gy–91.2Gy)	70.5 Gy	(42.0Gy–91.5Gy)	0.55

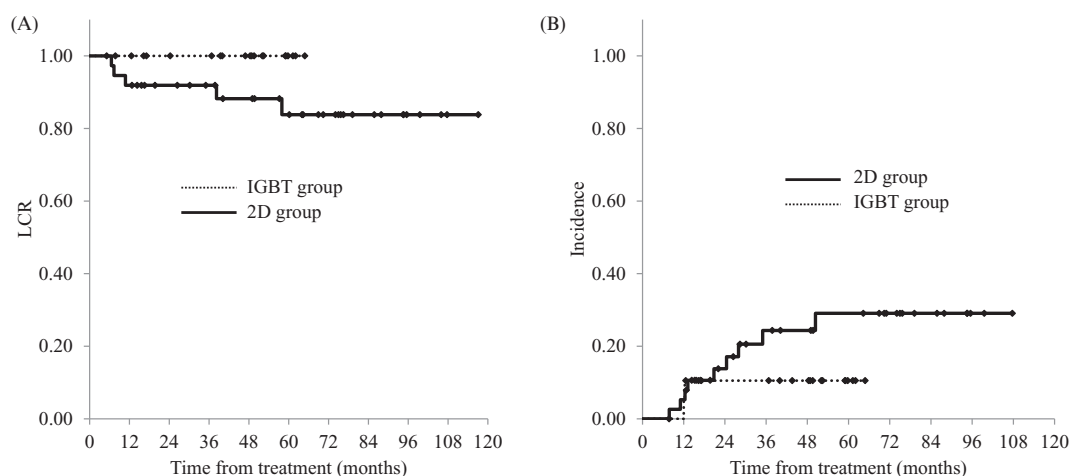


Fig. 1. a The 5-year LCRs were 83% in the 2D group and 100% in the IGBT group ($p = .11$). b The incidence of rectal complications tended to be lower in the IGBT group (5-year incidence rate in the 2D group vs the IGBT group, 29% vs 11%; $p = .26$).

3.4. Late toxicity

The 5-year incidence rates of late toxicities were 22% for the rectal complications and 8.8% for bladder complications. When it was limited to grade 3 toxicities, rectal complication was 6.3%, and bladder complication was 2.3% (Suppl. Fig. 3a and 3b). Late toxicities of grade 4 or worse were not observed.

As predictors of rectal complications, age (< 65 or > 65 years), FIGO stage (I–II or III–IV), brachytherapy technique (2D or IGBT), rectum D2cc (< 70 Gy or > 70 Gy), anticoagulant oral administration, and the complication of DM were analyzed (Table 2).

3.5. Comparison between the two-dimensional group and image-guided brachytherapy group

Table 3 shows the total doses for point A, CTV D90, rectum D2cc, and bladder D2cc in the 2D group and IGBT group. The dose of point A tended to be lower in the IGBT group than in the 2D group. However, CTV D90 was almost equivalent in both groups. The rectum D2cc, on the other hand, was significantly lower in the IGBT group than in the 2D group.

LCR tended to be better in the IGBT group than in the 2D group, but no significant difference was observed (5-year LCR in the 2D group vs. in the IGBT group, 83% vs. 100%; $p = .12$) (Fig. 1a). Although the incidence of rectal complications tended to be lower in the IGBT group than in the 2D group, the difference was not significant (5-year incidence in the 2D group vs. in the IGBT group, 29% vs. 11%; $p = .26$) (Fig. 1b).

4. Discussion

Several studies have shown that the dose of the tumor and normal organs can be more accurately evaluated with IGBT than with the 2D treatment plan (Noda et al., 2007; Dimopoulos et al., 2009; Georg et al.,

2011). In our study, there was no significant difference in CTV D90 between the 2D group and the IGBT group. However, the 5-year LCR was 100% in the IGBT group, whereas it was 83% in the 2D group. The 5-year LCRs in stage I–II and stage III–IVA cervical cancer were reported to be 85%–98% and 65%–75%, respectively (Sturdza et al., 2016; Toita et al., 2012; Arai et al., 1992). The 5-year LCRs according to FIGO stage in our study were comparable with those reported in the aforementioned studies.

Important late toxicities associated with radical radiotherapy for cervical cancer include rectal complications and bladder complications. The incidence rates of $\geq$ grade 1 and $\geq$ grade 3 rectal complications were reported to be 12%–38% and 1%–10%, respectively. The corresponding rates of bladder complication were reported to be 9.0%–23% and 0.8%–5.0%, respectively (Georg et al., 2011; Sturdza et al., 2016; Arai et al., 1992; Nakano et al., 2007; Wong et al., 2003; Rose et al., 2007). The 5-year incidence rates of $\geq$ grade 1 and grade 3 rectal and bladder complications in our study were comparable with those reported in previous studies.

Regarding the relation between the 3D dose assessment of the normal organs and incidence of late toxicities, there are several reports on rectal complications. Kato et al. (2010) examined the rectal dose according to CT images for 84 patients and reported that the mean value of rectum D2cc (EQD2) in cases with and without rectal toxicities was 72.0 Gy and 53.9 Gy, respectively (Kato et al., 2010). In our study, rectum D2cc was 61.2 Gy in the IGBT group, which was significantly lower than the rectum D2cc in the 2D group (69.2 Gy). International Commission on Radiation Units and Measurements (ICRU) report 89 showed treatment planning aims for each organ at risk (OAR) and concluded that rectum D2cc should be 70 Gy or less. Though there were no significant differences, the incidence of rectal complications tended to be lower in the IGBT group than in the 2D group, which seems to be due to the reduction in rectal dose by IGBT.

Although there are several reports on the usefulness of MRI in IGBT (Pötter et al., 2011; Sturdza et al., 2016; Derks et al., 2018), it is

difficult to introduce MRI-based IGBT in many institutions due to the unavailability of MRI or the absence of MRI-compatible applicators (Ohno et al., 2015). However, IGBT using the CT image does not require MRI availability or a new applicator, and further, the efficacy of CT-based IGBT has been previously reported (Shin et al., 2006; Kang et al., 2010; Kato et al., 2010). Our study showed that even CT-based IGBT can reduce the dose to OAR while keeping an adequate dose to CTV and suggested the possibility of reducing rectal complications.

The main limitation of this study is the small number of cases. This may be the reason the IGBT group showed a lower incidence of rectal complications than the 2D group, although this was not significantly different. Further, this study is retrospective in nature and was carried out at a single facility. However, we think our study was valuable because the follow-up period was sufficient. Moreover, few other studies have reported that DVH showed better improvement by IGBT than by the 2D plan, which was shown not by simulation but by direct comparison of the 3D image, and this led to improved treatment outcomes.

In conclusion, in this retrospective study involving 58 patients treated with either 2D or IGBT treatment for stage IB-IVA cervical cancer, CTV D90 was equal in both groups and rectum D2cc was significantly lower in the IGBT group. Favorable treatment results were obtained in the IGBT group with a 5-year LCR of 100% and a 5-year incidence of rectal complications of 11%.

Author contribution

Study concept/design: NI, KW.
 IRB application and approval: NI, KW.
 Data collection: NI, KW, IN.
 Data analysis and review: NI, KW, IN.
 Manuscript writing and editing: NI, KW, IN, YN.

Declaration of Competing Interest

No conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gore.2019.07.009>.

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