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Regular Paper

Definitive radiotherapy for primary vaginal cancer: correlation between treatment patterns and recurrence rate

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The purpose of this study was to determine the outcomes and optimal practice patterns of definitive radiotherapy for primary vaginal cancer. Between 1993 and 2012, 49 patients were treated with definitive radiotherapy for primary vaginal cancer in three hospitals. Of these, 15 patients (31%) had clinically positive regional lymph node metastasis. A total of 34 patients (70%) received external beam radiotherapy with high-dose-rate brachytherapy (interstitial or intracavitary), and 8 (16%) (with small superficial Stage I tumors) were treated with local radiotherapy. The median follow-up was 33 months (range: 1–169 months). The 3-year overall survival (OS), disease-free survival (DFS), and loco-regional control (LRC) rates were 83%, 59% and 71%, respectively. In multivariate analysis, the histological type ($P = 0.044$) was significant risk factors for LRC. In Federation of Gynecology and Obstetrics (FIGO) Stage I cases, 3 of 8 patients (38%) who did not undergo prophylactic lymph node irradiation had lymph node recurrence, compared with 2 of 12 patients (17%) who underwent prophylactic pelvic irradiation. For Stage III–IV tumors, the local recurrence rate was 50% and the lymph node recurrence rate was 40%. Patients with FIGO Stage I/II or clinical Stage N1 had a higher recurrence rate with treatment using a single modality compared with the recurrence rate using combined modalities. In conclusion, our treatment outcomes for vaginal cancer were acceptable, but external beam radiotherapy with brachytherapy (interstitial or intracavitary) was needed regardless of FIGO stage. Improvement of treatment outcomes in cases of FIGO Stage III or IV remains a significant challenge.

Keywords: high-dose-rate brachytherapy; prophylactic pelvic irradiation; radiotherapy; vaginal cancer

INTRODUCTION

Vaginal cancer is rare, comprising only about 2% of all gynecologic malignancies. Radiotherapy plays a significant role in the management of primary vaginal cancer, but there have been no prospective randomized trials for this cancer [1]. Thus, analysis of institutional retrospective data is important for obtaining a better understanding of patterns of

failure and for determining optimal treatment regimes for radiotherapy. However, most retrospective studies have had a limited number of patients and have used a variety of modalities, schedules and total doses. Therefore, the optimal dose and combinations of modalities are still poorly understood.

Here, we present a retrospective analysis of definitive radiotherapy for primary vaginal cancer at our hospital (Osaka University Hospital) and related hospitals (Osaka Rosai Hospital and the National Hospital Organization Osaka National Hospital). The goal of this study was to determine the optimal treatment practice patterns for this disease by evaluating the outcomes, toxicities, prognostic factors, and correlations of recurrence rates with the extent of radiotherapy and total dose.

MATERIALS AND METHODS

Patient characteristics

Between May 1993 and July 2012, 49 patients were treated with definitive radiotherapy for primary vaginal cancer at Osaka University Hospital, Osaka Rosai Hospital and the National Hospital Organization Osaka National Hospital. Patient characteristics and outcomes were obtained from hospital records. For patients who were no longer being followed up, we contacted them or their family by telephone. Informed consent was obtained from all patients. The study was approved by the institutional review board of Osaka University Hospital.

Patient and disease characteristics are listed in Table 1. Of the 49 patients, 21 (43%) were treated at Osaka University Hospital, 16 (33%) at Osaka Rosai Hospital, and 12 (24%) at the National Hospital Organization Osaka National Hospital. Vaginal cancer occurring 5 or more years after complete response of uterine cervical cancer was defined as primary vaginal cancer, based on the definition of the International Union Against Cancer. Therefore, four patients with a history of uterine cervical cancer and five with a history of pelvic irradiation were included in the study. Pretreatment abdominal and pelvic computed tomography (CT) scans were obtained for all patients, and a positive diagnosis was made based on a lymph node short axis >10 mm. Of the 49 patients, 15 (31%) had clinically positive regional lymph node metastasis. One patient had distant lymph node metastasis (common iliac lymph node), but was treated with radical intent. Chemotherapy was used for six patients (12%), including concurrently with radiotherapy in two cases. The other four patients received pre- or post-radiotherapy. All cases treated with chemotherapy received platinum-based regimens, including two patients given weekly cisplatin concurrently with radiotherapy and four who received pre- or post-radiotherapy with: (i) carboplatin and peplomycin; (ii) pirarubicin, cisplatin and peplomycin; (iii) nedaplatin and peplomycin; and (v) carboplatin and paclitaxel, respectively.

Table 1. Patient and disease characteristics

Characteristics	*n*	%
Age, years		
<69	25	51
≥70	24	49
Histological type		
Squamous cell carcinoma	42	86
Adenocarcinoma	6	12
Carcinosarcoma	1	2
FIGO stage		
I	20	41
II	19	39
III	7	14
IV	3	6
Clinical N stage		
N0	34	69
N1	15	31
Size, cm		
<4	31	63
≥4	18	37
Location		
Upper 2/3	30	61
Lower 1/3	11	22
Whole vagina	8	16
Chemotherapy		
Yes	6	12
No	43	88
Radiotherapy		
EBRT alone	8	16
ICBT alone	4	8
ISBT alone	3	6
EBRT + ICBT	9	19

FIGO = International Federation of Gynecology and Obstetrics, EBRT = external beam radiotherapy, ICBT = intracavitary brachytherapy, ISBT = interstitial brachytherapy.

Radiotherapy

All three hospitals had facilities for high-dose-rate (HDR) brachytherapy with a ^{192}Iridium source. The treatment strategy was almost the same in the three hospitals. Generally, patients with small, superficial tumors (tumor thickness <5 mm) were treated with local radiotherapy [brachytherapy or external beam radiotherapy (EBRT)] alone. Other tumors were treated with EBRT with brachytherapy, except in two

cases with a poor performance status. The initial 20–40 Gy was delivered to the whole pelvis, and then pelvic irradiation with a central shield was performed. If the tumor remained large (tumor thickness >5 mm) at the time of brachytherapy, HDR interstitial brachytherapy (ISBT) was performed instead of HDR intracavitary brachytherapy (ICBT). The EBRT to brachytherapy ratio and the total dose were determined on an individual basis by each physician. EBRT was administered to 42 patients (86%), including 41 with a primary lesion and regional lymph node drainage defined by the primary lesion location.

For primary tumors confined to the proximal two-thirds of the vagina, the clinical target volume (CTV) for EBRT included the areas of the obturator lymph nodes, external and internal iliac lymph nodes, and common iliac nodes. For tumors that had invaded the distal one-third of the vagina, the area of the inguinal lymph nodes was included, in addition to that of the pelvic lymph nodes. The planning target volume (PTV) for EBRT was generated using a 10-mm uniform expansion of the CTV. The prescribed doses of EBRT were at the center of the PTV. The CTV for brachytherapy comprised the whole tumor (at the time of brachytherapy) plus 5 mm in all directions, except for the posterior (rectal) margin. The posterior margin varied from 2 to 5 mm, depending on the distance to the rectal wall. Prophylactic vaginal wall irradiation was not performed. Measurement of the tumor thickness was carried out by palpation and ultrasound.

HDR-ISBT was performed in 28 patients (57%) at a median dose of 30 Gy in 5 fractions (range: 10–50 Gy in 2–10 fractions). HDR-ICBT was performed in 13 patients (27%) at a median dose of 30 Gy in 5 fractions (range: 10–38 Gy in 2–6 fractions). The ICBT dose was defined at a depth of 5 mm from the vaginal surface. In HDR-ISBT, the planning system used was either PLATO or Oncentra (Elekta, Stockholm, Sweden) was used in combination with manual modification to ensure the 100% isodose line encompassed the CTV on every slice after computer optimization using the geometrical optimization algorithm.

Practice patterns of radiotherapy are shown in Table 1. Radiotherapy using EBRT alone, ICBT alone, ISBT alone, EBRT + ICRT and EBRT + ISBT was performed in 16%, 8%, 6%, 19% and 51% of cases, respectively. Collectively, radiotherapy using a single modality and combined modalities was performed in 30% and 70% of cases, respectively.

To compare the combined dose of brachytherapy (ICBT or ISBT) and EBRT with a single modality dose (brachytherapy or EBRT alone), the total dose was calculated as the biologically equivalent dose in 2-Gy fractions (EQD_2) using the linear quadratic model. The dose to the primary tumor was the prescription dose of EBRT (excluding the fractions with central shielding) plus the prescription dose of brachytherapy. The value used for assessing effects on the tumor was $\alpha/\beta = 10$ Gy. The equation used to calculate the EQD_2 was as follows:

$$EQD_2 = EQD_{2EBRT} + EQD_{2brachytherapy}$$
$$= Nd(d + \alpha/\beta)/(2 + \alpha/\beta) + N_B d_B(d_B + \alpha/\beta)/(2 + \alpha/\beta),$$

where N is the fraction number for EBRT, d is the dose fraction for EBRT, N_B is the fraction number for brachytherapy, and d_B is the dose fraction for brachytherapy.

We divided the radiation field into three regions: primary lesion, enlarged lymph nodes and prophylactic lymph nodes, and evaluated the correlation between total EQD_2 and recurrence rates in the respective regions. Recurrence was defined as a tumor that recurred or persisted in the same region (primary, obturator, external iliac, internal iliac, common iliac or inguinal) after radiotherapy.

Statistical analysis

Overall survival (OS), disease-free survival (DFS) and loco-regional control (LRC) rates were calculated from the start of initial treatment. In evaluating LRC, common iliac LN recurrence was defined as regional recurrence. Rates were estimated using the Kaplan–Meier method, and differences between factors were examined by log-rank test. A Cox proportional hazard model was used for multivariate analysis. $P < 0.05$ or a 95% confidence interval (CI) of the hazard ratio >1.0 was considered to indicate a significant difference. All statistical analysis was performed using Stat Mate IV (ATMS Co., Ltd, Tokyo, Japan).

RESULTS

Outcome analysis

At the time of analysis, the median follow-up time of the 49 patients was 33 months (range: 1–169 months). The 3-year OS, DFS and LRC rates were 83%, 59% and 71%, respectively (Fig. 1A). According to FIGO stage, the 3-year OS for Stages I, II and III–IV patients was 81%, 86% and 83%, respectively (Fig. 1B), and the corresponding 3-year DFS was 60%, 65% and 40%, respectively (Fig. 1C). Relationships among outcomes, tumor types, and treatment factors are summarized in Table 2. The histological type ($P = 0.037$) and FIGO stage ($P = 0.026$) were significantly associated with DFS; and histological type ($P = 0.028$), FIGO stage ($P = 0.019$), and clinical N stage ($P = 0.023$) were significantly associated with LRC. In patients treated with brachytherapy, LRC did not differ significantly between patients treated with ISBT and ICBT. Multivariate analysis was performed with histological type (SCC vs others), FIGO stage (I/II vs III/IV) and clinical N stage (N0 vs N1), which were judged to be potential risk factors in univariate analysis. In multivariate analysis, the histological type (HR = 3.82, 95% CI = 1.04–13.08, $P = 0.044$) was a significant risk factor for LRC. OS showed no significant differences between different tumor types and treatment factors.

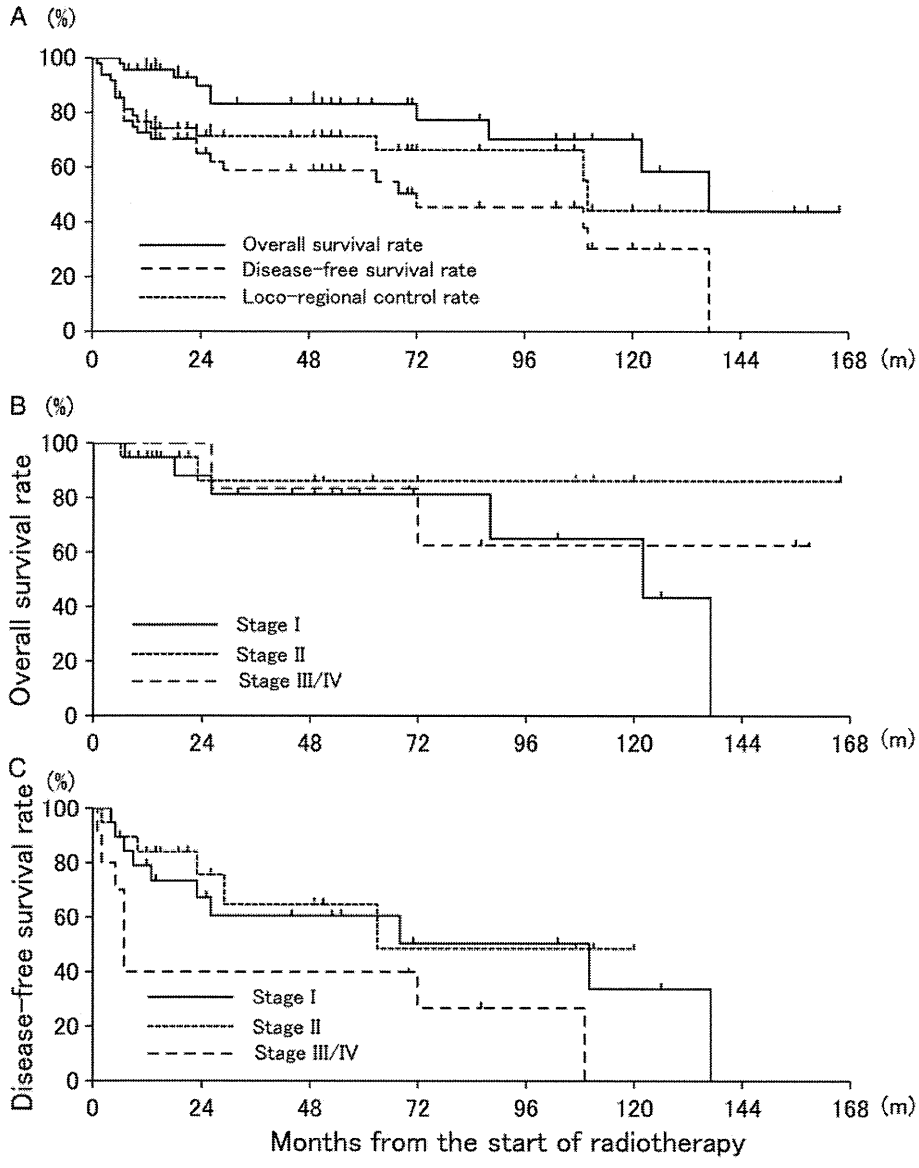

Fig. 1. (**A**) Overall survival, disease-free survival, and loco-regional control rates after definitive radiotherapy for vaginal cancer. (**B**, **C**) Overall survival and disease-free survival rates according to FIGO stage.

Correlation between total EQD_2 and recurrence rate

Correlations between total EQD_2 doses to primary lesions, enlarged lymph nodes and prophylactic lymph nodes with tumor recurrence rates for lesions of different FIGO stages are shown in Table 3. In primary lesions, recurrence clearly increased for a primary tumor with a diagnosis of Stage III or higher, despite use of a relatively high dose (median EQD_2 dose: 79 Gy). For enlarged lymph nodes, 11 cases (73%) with good control of the tumor received a total dose of >50 Gy (median EQD_2 dose: 60 Gy), whereas all four cases with recurrence received a total dose of ≤50 Gy. In FIGO Stage I cases, three of eight patients (38%) who did not undergo prophylactic lymph node irradiation had lymph node recurrence, compared with two of 12 patients (17%) who received prophylactic pelvic irradiation (median EQD_2 dose: 50 Gy), but the difference was not significant ($P = 0.29$). The rate of lymph node recurrence remained high (40%), even with prophylactic irradiation, in all Stage III or IV patients (median EQD_2 dose: 50 Gy).

Practice patterns and recurrence rate

Practice patterns (single modality vs combined therapy) were analyzed according to tumor or patient characteristics (Table 4). Patients with FIGO Stage I/II or clinical N1 stage had a higher recurrence rate in treatment with a single

Table 2. Univariate analysis of prognostic factors for OS, PFS and LRC in patients with carcinoma of the vagina treated with definitive radiotherapy.

Characteristics	*n*	3-year OS	*P*	3-year DFS	*P*	3-year LRC	*P*
		%		%		%	
Age, years			0.114		0.207		0.846
<70	25	90		66		70	
≥70	24	73		47		73	
Histological type			0.591		0.037		0.028
SCC	42	88		66		77	
Others	7	50		19		38	
FIGO stage			0.687		0.026		0.019
I/II	39	83		63		77	
III/IV	10	83		40		48	
Clinical N stage			0.395		0.100		0.023
N0	34	84		65		80	
N1	15	82		47		53	
size, cm			0.477		0.582		0.117
<4	31	82		59		77	
≥4	18	85		58		62	
Involvement of lower 1/3			0.976		0.831		0.280
NO	30	85		59		77	
YES	19	81		58		62	
Chemotherapy			0.268		0.657		0.764
NO	43	85		58		72	
Yes	6	67		63		63	
Brachytherapy			0.555		0.258		0.075
YES	41	84		61		76	
NO	8	67		50		50	

OS = overall survival rate, DFS = disease-free survival rate, LRC = loco-regional control rate, SCC = squamous cell carcinoma, FIGO = Federation of Gynecology and Obstetrics.

modality compared with that with combined modalities. However, all three patients with clinical N1 stage who had recurrence had received EBRT alone as a single modality. Additionally, these patients received ≤50 Gy to the enlarged lymph node and subsequently had recurrence in the same lesion. Age, histological type, tumor size and length of vaginal invasion did not influence the recurrence rate in either single or combined modalities.

Toxicities

Treatment-related late toxicity was evaluated using the Common Terminology Criteria for Adverse Events ver. 4.0. Six patients (12%) had Grade 3 late toxicities, including rectovaginal fistula ($n = 5$) and perforation of the sigmoid colon ($n = 1$). All of these patients were treated with ISBT, and two had a history of radiotherapy for pelvic lesions. Patients with previous pelvic irradiation had higher rates of Grade 3 complications compared with those without previous pelvic irradiation [2/5 (40%) vs 4/44 (9%), P = 0.04]. There were no vaginal complications of Grade 3 or higher and no Grade 4–5 late toxicities.

DISCUSSION

The outcomes in the current study are similar to or better than those in previous studies and showed 3-year and 5-year OS rates of 39–63% and 21–57%, respectively, for patients treated with HDR brachytherapy with or without EBRT [2, 3, 5], and rates of 0–15.8% for serious late complications [2–6]. However, the main reason for the better outcome may

Table 3. Correlation between total EQD_2 dose and tumor control according to FIGO stage

		FIGO	*n*	Mean EQD_2 ($Gy_{\alpha/\beta 10}$)	Median EQD_2 ($Gy_{\alpha/\beta 10}$)	Range	Percent recurrence (number)
Primary	Overall			65	70	38–96	18 (9/49)
		I	20	57	57	38–80	5 (1/20)
		II	19	70	70	53–96	16 (3/19)
		III–IV	10	73	79	44–90	50 (5/10)
Gross node	Overall		15	56	60	44–66	27 (4/15[a])
Prophylactic	Overall			39	50	0–60	22 (11/49)
		I[b]	8	0	0	0	38 (3/8)
		I	12	46	50	30–50	17 (2/12)
		II	19	47	50	30–60	11 (2/19)
		III–IV	10	49	50	40–60	40 (4/10)

[a]All four cases with recurrence received a total dose of 50 Gy or less. [b]Prophylactic lymph node irradiation was not performed. EQD_2 = equivalent dose in 2-Gy fractions, FIGO = Federation of Gynecology and Obstetrics.

be the shorter median follow-up period of 33 months in the current study.

The varying outcomes for the three hospitals and the lack of a pre-specified protocol were significant limitations in the analysis and interpretation of outcomes. To overcome these limitations and to compare the combined total dose in several different modalities and the extent of the radiation field, we calculated the total dose as an EQD_2 dose using the linear–quadratic model. We also divided the radiation field into three regions (primary lesion, enlarged lymph nodes, and prophylactic lymph nodes) and then evaluated the respective recurrence rates. Additionally, practice patterns (single modality vs combined therapy) were analyzed according to tumor or patient characteristics.

Patients with FIGO Stage I/II had a higher recurrence rate in a single modality. Additionally, among Stage I patients, 40% received radiotherapy for the primary lesion alone without prophylactic lymph node coverage. In cases without prophylactic lymph node irradiation, the recurrence rate in the prophylactic lesion tended to be higher, compared with cases with pelvic node irradiation (38% vs 17%) ($P = 0.29$). In a study of 21 FIGO Stage I patients treated with local radiation only (without regional node coverage), Frank *et al.* [10] found that three of nine patients (33%) treated with brachytherapy alone developed recurrent disease in the pelvis, whereas patients who had received EBRT with or without brachytherapy did not have pelvic recurrence. Collectively, these findings indicate that the optimal radiation practice is EBRT with brachytherapy (interstitial or intracavitary) regardless of FIGO stage. Patients with clinical N1 stage had a higher recurrence rate after treatment with a single modality, and all three patients with clinical N1 stage who had recurrence had received EBRT as a single modality. These patients received ≤50 Gy to the enlarged lymph node and had recurrence in the same lesion. These data indicate that recurrence in these patients was due mainly to a suboptimal EBRT dose to enlarged lymph nodes, and not to the practice pattern.

Improvement of treatment outcome in cases of FIGO Stage III or IV vaginal cancer remains a significant challenge. In previous studies, 5-year OS rates for patients with Stage III disease have ranged from 4% to 58% [2, 3, 15], with LRC rates of 57% to 69% [2,9,10]. The outcome for Stage IV disease is even worse, with survival rates of 0% to 35% [2, 3,15].

In this study, the local recurrence rate was very high (50%) with a median EQD_2 of 79 Gy, and the rate of prophylactic lymph node recurrence was also high (40%) with a median EQD_2 of 50 Gy for Stage III–IV tumors. The total dose for the primary lesion or prophylactic lymph node may be considered as the upper limit for normal tissue. However, 3D image-based HDR brachytherapy has recently been used in cervical cancer. Therefore, these results using EQD_2 of the prescribed dose require verification in studies using image-based brachytherapy.

For achievement of higher LRC, concurrent chemoradiation (CCRT) therapy has been attempted for locally advanced disease. In a study of 14 patients with vaginal cancer [including 11 (71%) with Stage II or III disease] who received CCRT with a 5-FU-based regimen, only one patient had local recurrence and died of the disease [16]. In a review of 12 patients with vaginal cancer in Stages II to IV who

Table 4. Practice pattern and recurrence rate according to tumor and patient characteristics

	Combined modalities recurrence rate		Single modality recurrence rate		
	%	Number	%	Number	*P*
Age, years					
<69	29	(6/21)	75	(3/4)	0.076
≥70	23	(3/13)	36	(4/11)	0.476
Histological type					
SCC	21	(6/30)	42	(5/12)	0.149
Others	75	(3/-4)	67	(2/3)	0.809
FIGO stage					
I/II	15	(4/26)	46	(6/13)	0.038
III/IV	50	(4/8)	100	(2/2)	0.197
Clinical N stage					
N0	18	(4/22)	42	(5/12)	0.137
N1	33	(4/12)	100	(3/3)	0.038
Size, cm					
<4	17	(4/23)	43	(3/8)	0.241
≥4	45	(5/11)	57	(4/7)	0.629
Involvement of lower 1/3					
No	19	(4/21)	44	(4/9)	0.149
Yes	38	(5/13)	50	(3/6)	0.636

SCC = squamous cell carcinonma, FIGO = International Federation of Gynecology and Obstetrics.

were treated with concurrent weekly cisplatin at a dose of 40 mg/m^2 for 5 weeks, Samant *et al.* found 5-year OS and PFS rates of 66% and 75%, respectively [17]. These findings led to the conclusion that CCRT is feasible and effective for management of primary vaginal cancer and should be considered as an option for patients being treated with curative intent [17].

Despite these promising outcomes in patients with vaginal cancer treated with CCRT, a randomized trial comparing radiation alone with radiation plus chemotherapy has not been performed in vaginal cancer. Additionally, many retrospective studies of CCRT for primary vaginal cancer are limited by the small number of patients or inclusion of other cancers, such as cervical and vulvar cancers. Therefore, further studies are needed to clarify the potential therapeutic benefits of CCRT. However, the design and execution of prospective randomized trials is challenging because of the rarity of this disease. In this study, the treatment and outcomes for vaginal cancer were acceptable, but EBRT with brachytherapy (interstitial or intracavitary) was needed regardless of FIGO stage. Thus, improvement of treatment outcome in cases of FIGO Stage III or IV remains a significant challenge.

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Preliminary results of MRI-assisted high-dose-rate interstitial brachytherapy for uterine cervical cancer

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ABSTRACT

PURPOSE: To investigate the effectiveness of our novel MRI-assisted high-dose-rate interstitial brachytherapy for uterine cervical cancer.

METHODS AND MATERIALS: Between June 2005 and June 2009, 29 previously untreated patients with cervical cancer were enrolled (2 T2b, 2 T3a, 19 T3b, and 6 T4 tumors). We implanted MRI-compatible plastic catheters using our unique ambulatory technique. The total treatment doses were 30–36 Gy (6 Gy per fraction) combined with external beam radiotherapy.

RESULTS: The median D_{90} (high-risk clinical target volume), $D_{2\ cc}$ (bladder), and $D_{2\ cc}$ (rectum) per fraction were 6.9, 5, and 4.6 Gy, respectively. The 3-year local control rates were 100%, 95%, and 83% for T2, T3, and T4 tumors, respectively. Grade 3 or 4 late complications occurred in 4 patients.

CONCLUSIONS: Our preliminary evaluation of image-based high-dose-rate interstitial brachytherapy showed favorable local treatment results with an acceptable complication rate.

Keywords: Interstitial brachytherapy; Uterine cervical cancer; Image-based brachytherapy; Dose–volume histogram

Introduction

The use of image-based brachytherapy for uterine cervical cancer is spreading. CT can visualize precise organ at risk (OAR) contouring. However, CT has limited capacity to visualize precise gross tumor volume (GTV) and clinical target volume (CTV) contouring. MRI is a better tool to visualize gynecological cancer compare with CT and helps for delineation of the contour of GTV and CTVs. United States (ABS Image-guided Brachytherapy Working Group) and European (GEC-ESTRO Working Group) brachytherapy groups established guidelines and recommendations for MRI-based intracavitary brachytherapy (ICBT) (1–3).

Some European institutes have also performed intracavitary/interstitial brachytherapy (ICISBT), in which additional needle implantation is used in cases where image-based ICBT alone is insufficient for target coverage (4, 5). Conveniently, special intracavitary applicators were designed to insert a few interstitial catheters on the side of the applicators (4, 6).

Classical multicatheter interstitial brachytherapy (ISBT) is another useful treatment modality for advanced uterine cervical cancer (7–20). Because multiple treatment catheters can be implanted in and/or around CTVs, ISBT may achieve a better CTV coverage than an intracavitary system. Some institutes have used titanium needle catheters

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to overcome the problem (20). Viswanathan *et al.* (18) pioneered the use of MRI high-dose-rate interstitial brachytherapy (HDR-ISBT) in 2004. In 2005, we designed a transrectal ultrasonography (TRUS)–guided plastic needle insertion ambulatory technique with CT/MRI planning (16, 21). Shortly after we started using this treatment technique, the Gynecological GEC-ESTRO recommendations were published. To evaluate the feasibility of this technique, we already reported a retrospective validation of dose–volume histogram (DVH) analysis according to the recommendations of the Gynecological GEC-ESTRO Working Group (16). Here, we present the DVH results and our preliminary treatment results. The purpose of the present study was to report the clinical outcome of this TRUS-guided ambulatory plastic needle insertion technique.

Methods and materials

Patient eligibility

Between June 2005 and June 2009, 35 patients with uterine cervical cancer (median age, 57 years; range, 34–83 years) were treated with ISBT at the Department of Radiation Oncology, National Hospital Organization Osaka National Hospital. The median follow-up time was 48 months (range, 9–81 months). The eligibility criteria for undergoing ISBT were bulky lesions, narrow vagina, inability to enter the cervical os, lateral extension, and lower vaginal extension, as determined according to the ABS recommendations (22). In 35 patients, 6 patients who received neoadjuvant chemotherapy were excluded.

Patients who had para-aortic lymph node (PALN) metastasis without other distant metastases were included in this study.

Catheter implantation

All patients received external beam radiotherapy (EBRT). Initially, we started EBRT using two- or four-field technique over the whole-pelvic field. The prescribed doses of whole-pelvic EBRT were 30 Gy for large T2 and T3 tumors and 40 Gy for T4 tumors. After whole-pelvic EBRT, all patients except 1 patient underwent center-shielded EBRT. The width of the midline shield was 4 cm to block the bladder and rectum. The length of the midline shield was almost two-thirds of the irradiation field to block the small bowel and bladder but not the pelvic lymph nodes. The total dose of whole-pelvic and center-shielded EBRT was 50 Gy. The boost for lymph node metastasis was an additional 6–10 Gy. Single-fraction doses were 2 Gy for the pelvic treatment field and 1.8 Gy for larger treatment fields (pelvis and PALN). ISBT was generally performed after whole-pelvic EBRT.

We performed a single catheter implantation with multi-fractionated HDR-ISBT in all patients. The concept of our ambulatory implantation technique has been previously described in detail (16, 21). A single flexible needle catheter (Fig. 1; tandem-like needle, ProGuide Sharp Needle; Nucletron an Elekta Company, Veenendaal, The Netherlands) was inserted into the uterine cavity, and the 1- to 1.5-cm tip of the needle was implanted into the uterine fundus. After implanting the tandem-like needle, a silicone custom-made cylinder was inserted into the vagina. After inserting the cylinder, we attached a custom-made vinyl template to fit the patient's perineum. It has holes to aid the implantation of the flexible needle catheters. We achieved implantation with TRUS guidance (Prosound α7; Hitachi Aloka Medical, Tokyo, Japan). The aim of implantation was to cover the low echoic area as high-risk CTV (HR CTV) using TRUS monitoring. We implanted 11–17 (median, 14) catheters. After completing implantation, the protruding connector end of the catheter was cut short enough to enable the patient to walk.

Treatment planning and treatment

All patients underwent CT and MRI examinations. CT-based planning was performed using MRI as a reference to contour HR CTV and OARs (rectum and bladder). The slice thickness of CT and MRI were united (2.5 or 3 mm) for each patient. The definition of these contours was based on the recommendations of the Gynecological GEC-ESTRO Working Group (2, 3). HR CTVs and OARs were delineated with the assistance of axial T_2-weighted MRI (Fig. 2a). Intermediate-risk CTV (IR CTV) included HR CTV plus macroscopic tumor extension at diagnosis, providing a minimal margin of 10 mm around the residual disease at the time of brachytherapy in the direction of

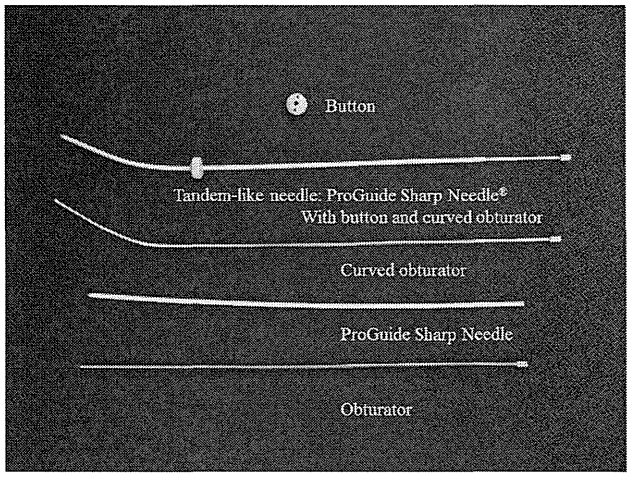

Fig. 1. Tandem-like needle was inserted into the uterine cavity and was implanted into the uterine fundus. It consists of a single flexible needle catheter (ProGuide Sharp Needle; Nucletron an Elekta Company, Veenendaal, The Netherlands), radio-opaque button, and obturator that was manually bended depending on each patient's uterine shape. After implanting the tandem-like needle, the flexible needle catheters with non-bended straight obturators were implanted from vaginal cylinder or perineal skin.

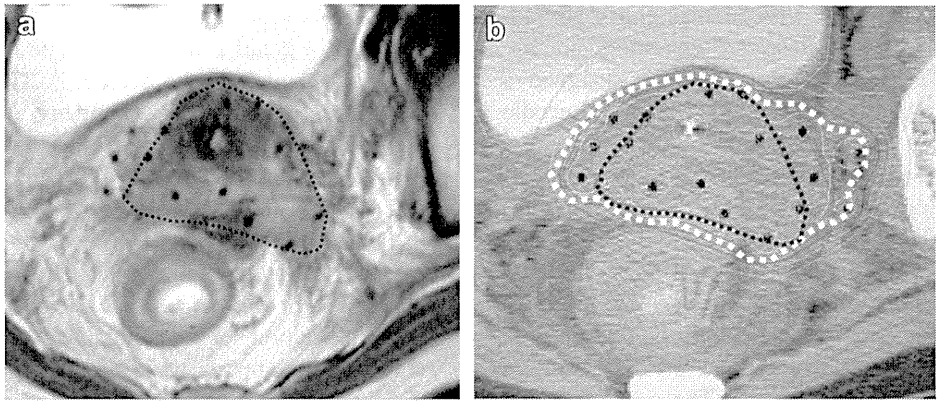

Fig. 2. (a) A MRI of a patient was taken after implantation. This image shows the contours of high-risk clinical target volume (black dotted line). (b) A CT image of the same patient was taken after implantation. The dose–distribution curve was calculated by computer optimization with manual modification. The high-risk clinical target volume (black dotted line) was well covered by the 100% prescribed isodose line (white dotted line).

potential spread. We determined the source dwell positions to cover HR CTV and an additional 15-mm cranial margin for needle displacement except when the dwell positions were inside the colon. We performed corrective action (23) for the recent 12 patients in this study. We used the center of gravity of the three metal markers implanted into the edge of the tumor as a reference. We calculated the distance between the needle tip and the center of gravity and compared it on the day of implantation and 21 and 45 h after implantation. Correction of dwell position was performed only for the third and fifth fractions because we performed CT and evaluation of displacement only after the second and fourth fractions.

Treatment planning was performed using the PLATO system (software version 14.2; Nucletron an Elekta Company) with manual modifications (Fig. 2b) (21, 24). Initially, we planned according to geometric optimization and delivered the prescribed dose to the 85% basal isodose curve; subsequently, we modified the dose distribution curve using manual modification. After achieving the isodose curve modification, we decided on the final prescription dose. In most cases, an 85% basal isodose curve was selected as the prescription dose; however, we changed the percentage depending on CTV coverage. If we wanted to expand the prescribed isodose curve, we selected <85% basal dose as the prescribed dose. If we wanted to shrink the prescribed isodose curve, we selected >85% basal dose as the prescribed dose. The single-fraction planning aim dose was 6 Gy for all patients, and the median total dose was 30 Gy per five fractions over 3 days. Two fractions were administered each day, and the time interval between the fractions was >6 h. Only two poor responders for EBRT had their planning aim dose changed to 36 Gy per six fractions over 4 days. The aim of our treatment planning was for the dose that covered 100% of the target volume (D_{100}) for HR CTV to be equal to the planning aim dose. However, we compromised the dose for HR CTV if the minimum dose received by the maximally irradiated 2-cc volumes ($D_{2\ cc}$) for OARs became too high. After the Gynecological GEC-ESTRO recommendations were published, we adopted the concept of a prescription dose that covered 90% of the target volume (D_{90}) for HR CTV. We attempted D_{90} (HR CTV) to become higher than the planning aim dose. We designated GTV plus whole uterine cavity as CTV before the Gynecological GEC-ESTRO recommendations were published. For these patients, we add the contours of HR CTV and IR CTV and calculated the DVH, retrospectively. We used microSelectron-HDR (Nucletron, an Elekta Company) for treatment and ^{192}Ir as the treatment source.

DVH analysis

DVH was calculated for HR CTV and IR CTV: the percentage of CTV covered by the prescribed dose (V_{100}), D_{90}, and D_{100}. For OARs, we calculated the minimum dose received by the maximally irradiated 0.1-, 1-, and 2-cc volumes ($D_{0.1\ cc}$, $D_{1\ cc}$, and $D_{2\ cc}$, respectively).

To sum up EBRT and ISBT doses, we used biologically equivalent doses that were calculated as equivalent 2-Gy fractions (EQD_2) using a linear quadratic model, where $\alpha/\beta = 10$ for tumors and $\alpha/\beta = 3$ for OARs. The planning aim doses for HR CTV EQD_2 were 70–80 Gy (30 Gy of ISBT plus 30–40 Gy for whole-pelvic EBRT) for patients with T2–T3 and T4 tumors. The dose–volume constraints were 67.4–77.4 Gy in $D_{2\ cc}$ EQD_2 for the rectum (30 Gy × 0.8 of ISBT plus 30–40 Gy for whole-pelvic EBRT) and 75.4–85.4 Gy for the bladder (30 Gy × 0.9 of ISBT plus 30–40 Gy for whole-pelvic EBRT).

Statistical analysis

Statistical analyses were performed using the StatView v 5.0 software program. Local control and survival rates were analyzed. Survival curves were estimated according to the Kaplan–Meier method. Student *t*, Mann–Whitney, and chi-square tests were used to compare the DVH results. A *p*-value of <0.05 was considered statistically significant.

Results

Patient characteristics

Patient characteristics are shown in Table 1. Histopathology revealed 26 squamous cell carcinomas, 1 adenosquamous carcinoma, and 2 adenocarcinomas. Using the Union for International Cancer Control (UICC) classification (2002), 2 T2b, 2 T3a, 19 T3b, and 6 T4 tumors were identified. We defined T4 tumors (five bladder invasion and one rectal invasion) as judged by palpation, CT, MRI, cystoscopy, and proctoscopy. Two stage 2B, 1 stage 3A, 18 stage 3B, 5 stage 4A, and 3 stage 4B tumors were identified. The maximum tumor diameter assessed on MRI (T_2-weighted image) before treatment was 40–50 mm for 11 patients, 51–70 mm for 10 patients, and 71–110 mm for 8 patients. There were 15 N0 and 14 N1 patients; in addition, 3 patients were classified as M1 (PALN metastasis). The median whole-pelvic and center-shielded EBRT doses were 30 Gy (range, 30–45 Gy) and 20 Gy (range, 0–20 Gy), respectively. For whole-pelvic EBRT, >40 Gy was delivered for patients with T4 or large T3b tumors. The median total dose for whole-pelvic and center-shielded EBRT was 50 Gy (range, 45–50.4 Gy). An additional boost of irradiation for pelvic lymph node metastases was performed for 11 patients (median, 6 Gy; range, 0–10 Gy). EBRT for PALN was performed for 3 patients (median, 45 Gy; range, 45–59.4 Gy). The median overall treatment time was 47 days (range, 33–62 days).

Twenty-one patients (72%) received concurrent chemotherapy (21 patients), adjuvant chemotherapy (3 patients), or both (3 patients). Eight patients did not receive chemotherapy because of older age or poor renal function due to bilateral hydronephrosis.

Table 1
Patient characteristics

Age (yr)	
Median (range)	62 (37–83)
Follow-up period (mo)	
Median (range)	48 (9–81)
Histology	
Squamous cell carcinoma	26
Adenocarcinoma	2
Adenosquamous cell carcinoma	1
T stage (UICC classification 2002)	
T2b	2
T3a	2
T3b	19
T4	6
N stage	
N0	15
N1	14
M stage (para-aortic lymph node)	
M0	26
M1	3
Stage	
2B	2
3A	1
3B	18
4A	5
4B	3
Maximum tumor diameter (mm)[a]	
40–50	11
51–70	10
71–110	8
Whole-pelvic EBRT (Gy)	
Median (range)	30 (30–45)
Center-shielded EBRT (Gy)	
Median (range)	20 (0–20)
ISBT (Gy)	
Median (range)	30 (30–36)
Chemotherapy	
+	21
–	8

EBRT = external beam radiotherapy; ISBT = interstitial brachytherapy.
[a] Assessed by MRI T_2 weighted image.

DVH results

The median HR CTV and IR CTV were 35.9 cc (range, 10.4–83.2 cc) and 83.3 cc (range, 36.7–158.4 cc), respectively. The median D_{90} and D_{100} (HR CTV) per fraction were 6.9 Gy (range, 5.5–7.5 Gy) and 5.3 Gy (range, 3.4–5.9 Gy), respectively (Table 2). The median V_{100} (HR CTV) was 99.1% (range, 83–100%). The median D_{90} and D_{100} (IR CTV) per fraction were 5.5 Gy (range, 4.4–6.4 Gy) and 3.3 Gy (range, 2.1–4.3 Gy), respectively. The median V_{100} (IR CTV) was 84% (range, 64–96.2%; Table 2).

The median D_{90} and D_{100} (HR CTV) per fraction were 5.8 Gy (range, 5.5–6.1 Gy) and 3.5 Gy (range, 3.4–4.3 Gy), respectively, for the 3 patients for whom planning took place before we adopted the Gynecological GEC-ESTRO recommendations. The results for these 3 patients were significantly lower than those for the other 26 patients ($p = 0.006$ and $p = 0.01$ for D_{90} and D_{100}, respectively [HR CTV]).

When the EBRT dose was added to the HDR-ISBT dose, the EQD_2 of the median D_{100} (HR CTV) became 63.5 Gy (range, 36.6–83.2 Gy). The EQD_2 of the median D_{90} (HR CTV) became 81.9 Gy (range, 65.5–96.6 Gy). Four

Table 2
Dose–volume histogram results of clinical target volumes for image-based interstitial brachytherapy for previously untreated uterine cervical cancer

	D_{90}, median (range)	D_{100}, median (range)	V_{100}, median (range)
HR CTV			
ISBT alone	6.9 (5.5–7.5) (Gy per fraction)	5.3 (3.4–5.9) (Gy per fraction)	99.1 (83–100) (%)
ISBT + EBRT	81.9 (65.5–96.6) (Gy EQD_2)	63.5 (36.6–83.2) (Gy EQD_2)	
IR CTV			
ISBT alone	5.5 (4.4–6.4) (Gy per fraction)	3.3 (2.1–4.3) (Gy per fraction)	84 (64–96.2) (%)

D_{90} = the dose that covered 90% of the target volume; D_{100} = the dose that covered 100% of the target volume; V_{100} = the percentage of CTV covered by the prescribed dose; HR CTV = high-risk clinical target volume; ISBT = interstitial brachytherapy; EBRT = external beam radiotherapy; EQD_2 = equivalent 2-Gy fractions; IR CTV = intermediate-risk clinical target volume; CTV = clinical target volume.

patients showed less than planning aim dose of D_{90} (HR CTV). Three of 4 patients were treated before we adopted the Gynecological GEC-ESTRO recommendations. Their D_{90} (HR CTV) were 1.8–4.5 Gy lower than the planning aim doses. We compromised the D_{90} (HR CTV) for 1 patient. She had T4 tumor, and her planning aim doses were 80 Gy; however, D_{90} (HR CTV) reduced 79.1 Gy because her $D_{2\ cc}$ (bladder) was very high (118.8 Gy).

The median $D_{2\ cc}$ (bladder) and $D_{2\ cc}$ (rectum) per fraction were 5 Gy (range, 4.2–7.5 Gy) and 4.6 Gy (range, 3.1–5.8 Gy; Table 3), respectively. The EQD_2 median $D_{2\ cc}$ (bladder) and $D_{2\ cc}$ (rectum) for all treatments were 72.6 Gy (range, 61.4–118.8 Gy) and 70 Gy (range, 56.9–86.8 Gy), respectively. The $D_{2\ cc}$ (bladder) was greater than the dose–volume constraints for 10 patients. Four of 10 patients had T4 tumors (bladder invasion), and the other 6 patients had tumors close to the bladder. The $D_{2\ cc}$ (rectum) was greater than the dose–volume constraints for 13 patients. In all patients, the tumor was close to the rectum.

The median $D_{0.1\ cc}$ (urethra) per fraction was 4.1 Gy (range, 1.8–6.1 Gy). The EQD_2 of the median $D_{0.1\ cc}$ (urethra) for all treatments was 59.7 Gy (range, 38.6–95.5 Gy).

Clinical outcomes

The 3-year local control rates were 100%, 95%, and 83% for T2, T3, and T4 tumors, respectively. The 3-year overall survival rates were 100%, 79%, and 83% for patients with T2, T3, and T4 tumors, respectively. The 3-year overall survival rates were 100%, 100%, 76%, 80%, and 100% for patients with stage 2B, 3A, 3B, 4A, and 4B tumors, respectively. The 3-year local control rates were 93% and 93% for N0 and N1 patients, respectively. The 3-year overall survival rates were 77% and 86% for N0 and N1 patients, respectively. No significant difference was observed between patients treated before and after we adopted the Gynecological GEC-ESTRO recommendations. The 3-year local control rates were 91%, 90%, and, 100% for tumors ≤50, 51–70, and >70 mm, respectively. The 3-year overall survival rates were 80%, 90%, and 73% for tumors ≤50, 51–70, and >70 mm, respectively.

The median total D_{90} (HR CTV) was 82.2 Gy (range, 65.5–96.6 Gy; EQD_2) for patients with locally controlled disease and 80.7 Gy (range, 79.6–81.9 Gy; EQD_2) for patients with locally uncontrolled disease (n.s.). No local recurrence was observed for patients whose total D_{90} (HR CTV) was >82 Gy (14 patients). Two of 15 patients (13%) whose total D_{90} (HR CTV) was <82 Gy showed local recurrence ($p = 0.16$). The median total D_{100} (HR CTV) was 63.3 Gy (range, 36.6–83.2 Gy; EQD_2) for patients with locally controlled disease and 66.1 Gy (range, 64.9–67.3 Gy; EQD_2) for patients with locally uncontrolled disease (n.s.).

The incidence of late complications was evaluated using the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). The most severe acute complication observed in this study was bleeding by the implantation procedure. Blood transfusion was necessary for 1 patient (3%) after catheter extraction.

We observed Grade ≥2 acute complications in 5 patients. Grade 3 urinary infection and Grade 3 leukopenia were observed in 2 patients each, and Grade 2 diarrhea was observed in 1 patient.

A Grade 4 late complication (rectovesicovaginal fistula) was observed in 1 patient. Grade 3 late complications were observed in 3 patients (10%; ileus: 1 patient and pelvic bone fracture: 2 patients). The 3-year Grades 3–4 late actuarial complication rates were 3% for rectal complication, 3% for bladder/urethral complication, and 8% for the other complication. Grade 2 late rectal bleeding was observed in 3 patients (10%). The $D_{2\ cc}$ (rectum) of these patients (64.4, 75, and 77.4 Gy) was not significantly different from that of the other 32 patients. No Grade ≥2 late urethral complications were observed.

Discussion

The ABS and GEC-ESTRO guidelines (1–3) emphasize the importance of image-based brachytherapy. Pötter *et al.* (25) have been using MRI-based planning for ICBT since 1998. In 2001, they started using ICISBT in cases of

Table 3
Dose–volume histogram results of organs at risk for image-based interstitial brachytherapy for previously untreated uterine cervical cancer

	$D_{0.1\ cc}$, median (range)	$D_{1\ cc}$, median (range)	$D_{2\ cc}$, median (range)
Bladder			
ISBT (Gy per fraction)	7 (6.2–17.1)	5.4 (4.6–8.5)	5 (4.2–7.5)
ISBT + EBRT (Gy EQD_2)	101.7 (87–383.7)	79.6 (66.2–137.8)	72.6 (61.4–118.8)
Rectum			
ISBT (Gy per fraction)	6.7 (5.2–8.4)	5.2 (3.4–6.3)	4.6 (3.1–5.8)
ISBT + EBRT (Gy EQD_2)	100.2 (84–125.8)	76.5 (62.6–95.5)	70 (56.9–86.8)
Urethra			
ISBT (Gy per fraction)	4.1 (1.8–6.1)		
ISBT + EBRT (Gy EQD_2)	59.7 (38.6–95.5)		

$D_{0.1\ cc}$ = the minimum dose received by the maximally irradiated 0.1 cc volume; $D_{1\ cc}$ = the minimum dose received by the maximally irradiated 1 cc volume; $D_{2\ cc}$ = the minimum dose received by the maximally irradiated 2 cc volume; ISBT = interstitial brachytherapy; EBRT = external beam radiotherapy; EQD_2 = equivalent 2-Gy fractions.

insufficient coverage by ICBT alone. As a result, the 3-year local control rates for tumors >50 mm were improved from 71% during the learning period to 90% in the MRI-based planning period (25), and large tumors (mean HR CTV, 44 cc) could be effectively treated by ICISBT (4). Their latest report showed that local control rate at 3 years was 100% for IB, 96% for IIB, and 86% for IIIB (26). From these results, MRI-based ICISBT appears to be a superior modality for large advanced tumors.

Classical ISBT is another useful treatment modality for advanced uterine cervical cancer (7–20). However, few institutes have reported the use of MRI for ISBT (16–20). Thibault *et al.* (17) reported the results of CT-based treatment planning with CT/MRI fusion. They investigated 12 primary uterine cervical cancer cases, and their 2-year local control rate was 87% for primary cases. Our present study showed that the 3-year local control rates were 100%, 95%, and 83% for T2, T3, and T4 tumors, respectively, and 91%, 90%, and 100% for tumors ≤50, 51–70, and >70 mm, respectively. These results concur with the results of Thibault *et al.* and Pötter *et al.*

Toita *et al.* (27) reported the Japanese multi-institutional treatment results of chemoradiotherapy using ICBT with a conventional, two-dimensional (2D), point A, dose-calculation method. Total EQD_2 at point A doses was 62–65 Gy. Seventy-one patients with T3 or T4 tumors were treated, and the 2-year pelvic disease progression–free rates were 85%, 72%, and 54% for tumors <50, 50–70, and ≥70 mm, respectively. Our results appear to be superior to the above results obtained using conventional treatment.

Precise contouring of HR CTV by MRI may make it possible to calculate the accurate DVH for HR CTV. It may also make it possible to precisely investigate the dose–effect relationship between local tumor control and delivered doses. Dimopoulos *et al.* (28) analyzed the DVH results of the above-mentioned study by Pötter *et al.* (25). The total D_{90} (HR CTV) of tumors >50 mm significantly improved from 79 ± 15 Gy during the learning period (local control, 71%) to 87 ± 14 Gy in the MRI-based planning period (local control, 90%), suggesting a dose–effect relationship between the local control rate and D_{90} (HR CTV). The present study showed that no local recurrences were observed for patients whose total D_{90} (HR CTV) was >82 Gy. Because the number of patients in this study was small, the study may not have the required statistical power. For example, tumor factor analysis (N stage and maximum tumor diameter) showed contradictory results. In this study, the 3-year overall survival rates were 77% and 86% for N0 and N1 patients, and the 3-year local control rates were 91%, 90%, and 100% for tumors ≤50, 51–70, and >70 mm, respectively. Therefore, further investigation is necessary.

The present study had 7 patients (24%) with Grades 2–4 late complications. In the previously mentioned Japanese multi-institutional trial, the 2-year Grades 2–4 cumulative late complication rates were 15% (27). Arai *et al.* (29) reported that for >1000 patients treated by conventional 2-dimensional ICBT and EBRT, the Grade 2–4 late complication rate was 20.2%. Their treatment doses were also similar to those of the Japanese study. Our result showed similar complication rate to above conventional ICBT studies. However, total EQD_2 at point A doses of the Japanese multi-institutional trial was 62–65 Gy, and it was lower than that of the present study. Our image-guided treatment planning may reduce the complication rate if our prescribed doses are equivalent to above studies. A French STIC prospective study of pulsed–dose-rate ICBT compared the treatment results between 2D and three-dimensional (3D) plans (30). Although point A doses were similar in both plans, Grades 2–4 late genitourinary complication rates showed significant difference between the 2D (13.1–23.1%) and 3D (7.9–13.7%) plans.

Georg *et al.* (31) reported that $D_{1\ cc}$ and $D_{2\ cc}$ (rectum) were significant factors in predicting late rectal toxicity. They demonstrated that $D_{2\ cc}$ (rectum; EQD_2) was 75 Gy for patients who had Grades 2–4 late rectal complications and 64 Gy for patients who had Grades 0–1 late rectal complication. Lee and Viswanathan (19) reported that $D_{2\ cc}$ (rectum) was 68.3 Gy for patients who had Grades 2–4 late rectal complications and 57.2 Gy for patients who had Grades 0–1 late rectal complication. Their analysis showed that 10% risk of Grades 2–4 rectal toxicity was 61.8 Gy.

The present study showed that $D_{2\ cc}$ (rectum) of 3 patients who had Grade 2 late rectal bleeding was 64.4, 75, and 77.4 Gy. All three values were higher than 61.8 Gy.

Georg *et al.* (31) reported that in the bladder, $D_{0.1\ cc}$, $D_{1\ cc}$, and $D_{2\ cc}$ were additional significant factors; however, these parameters were useful only for major toxicity. Further investigation is warranted to judge the usefulness of DVH values to predict bladder and urethral toxicity.

We believe that image-based ISBT is an effective modality for local advanced uterine cervical cancer, similar to ICISBT. The advantages of ISBT include the following: only a single catheter insertion and MRI imaging is necessary. It is more convenient for the anesthesiologist, the operating room staff, and radiation oncology staff. The technologists take only one MRI scan, and nurses prepare only one set of catheter implants. The overall treatment time is <5 days, and it may translate in better tumor control. The main disadvantage of ISBT is that it requires a greater technical skill compared with ICISBT. However, with the use of US guidance and perineal template, the implantation procedure is easier. ISBT is associated with a higher incidence of bleeding than ICISBT, which resulted in anemia requiring transfusion in some cases. Therefore, we explored the theoretical effectiveness of Doppler to reduce bleeding because vessels were clearly detected by Doppler (32). One more disadvantage is about vaginal packing to decrease the doses for the bladder and rectum. Physician can perform packing at the time of ICISBT. Against it, our ISBT technique could

not allow the packing. Improvement of the shape of cylinder may be useful to decrease the doses for OARs. Catheter displacement is an additional problem. However, we reported in our data that the median catheter displacement was 1 mm (range, −6 to 12 mm) in 3 days (23). This appears to be a minor problem, which can be resolved using corrective action.

We considered that the development of improved patient selection methods for ICBT, ICISBT, and ISBT will be useful depending on the type of tumor and patient factors. Zwahlen *et al.* (33) showed that image-guided ICBT reduced $D_{2\ cc}$ (OARs), particularly for small CTV (<16.1 cc), compared with 2D ICBT. Thus, a CTV of <16.1 cc is sufficient for ICBT. According to a report by Kirisits *et al.* (4), ICISBT is effective for a CTV of >44 cc. The median HR CTV in the present study was 31.8 cc (range, 10.4–83.2 cc). We consider that the threshold CTV volume between ICISBT and ISBT may exist somewhere between 44 and 83.2 cc. In the future, the accumulation of treatment data including DVH analysis will make it possible to decide the best modality for each patient.

Conclusion

Our preliminary analysis of MRI-assisted HDR-ISBT showed favorable local treatment results with an acceptable complication rate. DVH results may be useful to predict the treatment results. Further investigation is necessary to determine the best modality from image-based ICBT, ICISBT, and ISBT for individual patients.

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RADIATION ONCOLOGY

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Distribution patterns of metastatic pelvic lymph nodes assessed by CT/MRI in patients with uterine cervical cancer

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Abstract

Background: To investigate the three-dimensional (3D) distribution patterns of clinically metastatic (positive) lymph nodes on pretreatment computed tomography (CT)/magnetic resonance imaging (MRI) images of patients with locally advanced cervical cancer.

Methods: We enrolled 114 patients with uterine cervical cancer with positive nodes by CT/MRI (≥10 mm in the shortest diameter). Pretreatment CT/MRI data were collected at 6 institutions. The FIGO stage was IB1 in 2 patients (2%), IB2 in 6 (5%), IIA in 3 (3%), IIB in 49 (43%), IIIB in 50 (44%), and IVA in 4 (4%) patients. The median cervical tumor diameter assessed by T2-weighted MRI was 55 mm (range, 10–87 mm). The anatomical distribution of the positive nodes was evaluated on CT/MRI images by two radiation oncologists and one diagnostic radiologist.

Results: In these patients, 273 enlarged nodes were assessed as positive. The incidence of positive nodes was 104/114 (91%) for the obturator region, 31/114 (27%) for the external iliac region, 16/114 (14%) for the internal iliac region, 22/114 (19%) for the common iliac region, and 6/114 (5%) for the presacral region. The external iliac region was subdivided into four sub-regions: lateral, intermediate, medial, and caudal. The obturator region was subdivided into two sub-regions: cranial and caudal. The majority of patients had positive nodes in the cranial obturator and/or the medial external iliac region (111/114). In contrast, few had positive nodes in the lateral external iliac, caudal external iliac, caudal obturator, internal iliac and presacral regions. All cases with positive nodes in those low-risk regions also had positive nodes in other pelvic nodal regions concomitantly. The incidence of positive nodes in the low-risk regions/sub-regions was significantly related to FIGO stage ($p=0.017$) and number of positive nodes ($p<0.001$).

Conclusions: We demonstrated the 3D distribution patterns of clinical metastatic pelvic lymph nodes on pretreatment CT/MRI images of patients with locally advanced cervical cancer. These findings might contribute to future individualization of the clinical target volume of the pelvic nodes in patients with cervical cancer.

Keywords: Radiotherapy, Lymph node, Clinical target volume, Uterine cervical cancer

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Background

Radiotherapy plays very important roles in the treatment of uterine cervical cancer. Definitive radiotherapy for cervical cancer consists of external beam radiotherapy and intracavitary brachytherapy. Recently, external beam radiotherapy techniques have advanced considerably, as have those for intracavitary brachytherapy. Treatment planning for uterine cervical cancer has transitioned from a two-dimensional (2D) approach based on bony landmarks to a three-dimensional (3D) technique based on computed tomography (CT)/magnetic resonance imaging (MRI). Intensity-modulated radiotherapy (IMRT) has been proven to have a significant dosimetric advantage and less toxicity compared with conventional 2D/3D treatment planning for various malignancies, including gynecologic cancers [1]. It is essential to define the proper clinical target volume (CTV) for appropriate delivery of IMRT. Guidelines that provide a standard definition of CTV nodes are now published by the Radiation Therapy Oncology Group (RTOG) [2], UK investigators [3] and the Japan Clinical Oncology Group (JCOG) [4]. However, these guidelines were developed mainly from information on the normal anatomical pelvic lymph node distribution. The actual distribution of clinically metastatic (positive) nodes in the pelvis has not been studied in definitive radiotherapy series. If areas with a low risk of node metastases could be deleted from the CTV, toxicity could be reduced without sacrificing regional control.

The purpose of this study was to investigate the 3D distribution patterns of clinically metastatic nodes assessed by CT/MRI in patients with uterine cervical cancer.

Methods

We enrolled 114 patients with uterine cervical cancer who were diagnosed as having clinically metastatic (positive) pelvic nodes by CT/MRI (≥10 mm in the shortest diameter) and treated by definitive radiotherapy/chemoradiotherapy at 6 institutions between January 2001 and December 2007. This study conformed to the ethical principles contained in the Declaration of Helsinki [5], and was approved by the institutional review board of the principal investigator (T.T.). Lymph nodes greater than or equal to 10 mm in the shortest diameter, as assessed by CT/MRI, were defined as positive in this study. Patient characteristics are summarized in Table 1. Digitized CT/MRI images burned to CD-ROMs were collected from each institution. The images were reviewed by two radiation oncologists (G.K., T.T.) and one diagnostic radiologist (A.Y.).

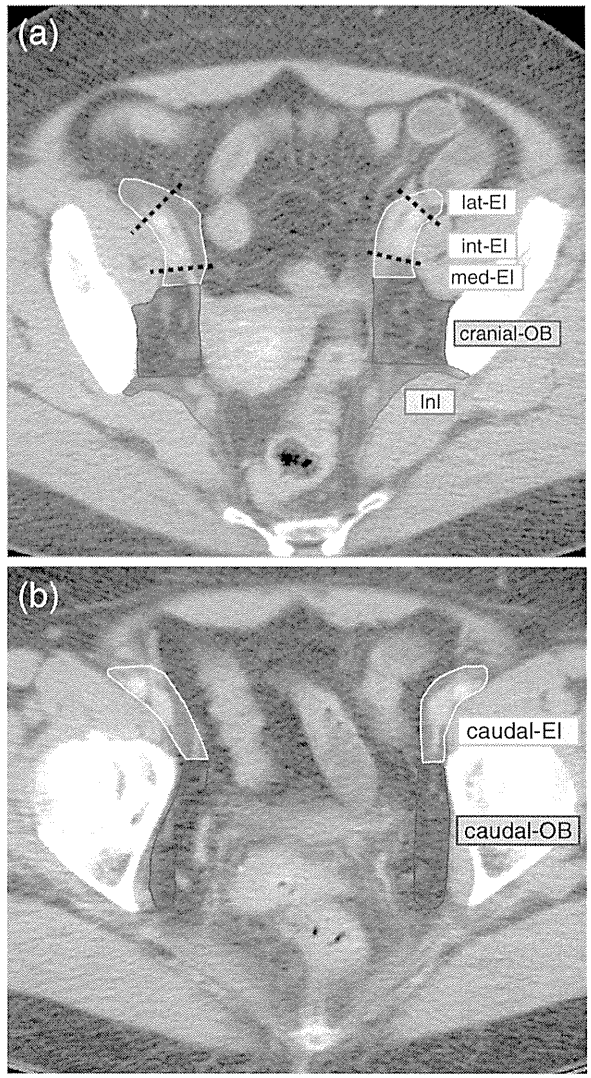
Pelvic lymph node area was divided into five anatomical regions: the obturator region, the external iliac region, the internal iliac region, the common iliac region, and the presacral region. The external iliac was further divided into four sub-regions: the medial external iliac, the intermediate external iliac, the lateral external iliac, and the caudal external iliac. The subcategories of medial external iliac, intermediate external iliac, and lateral external iliac refer to the definitions proposed by Taylor et al. [6] and Lengelé et al. [7]: medial external iliac=the dorsal area of attachment and along the external iliac vein, intermediate external iliac=the anterior area between the external iliac artery and vein, and lateral external iliac=the lateral area of the external iliac artery. These three sub-regions are all located cranial to the aspect of the femoral head. On the other hand, the caudal external iliac is located caudal to the aspect of the femoral head. The obturator was also divided into two sub-regions, with the border of the aspect of the femoral head as the external iliac: cranial obturator and caudal obturator. An atlas of these sub-regions (except for common iliac region) is presented in Figure 1 (a)-(b).

First, the number of positive nodes in each region and in the sub-regions was counted. Next, the distribution

Table 1 Patient characteristics (n=114)

Characteristic		(n)
FIGO stage		
	IB1	2
	IB2	6
	IIA	3
	IIB	49
	IIIB	50
	IVA	4
Age		
	median 52	range 26-88
Histology		
	SCC	109
	Adeno	5
Tumor size*		
	<20 mm	0
	21-40 mm	18
	41-60 mm	58
	61 mm<	38
Number of metastatic LN in the pelvis		
	1	32
	2	36
	3	23
	4	14
	≥5	9

*assessed by MRI.
FIGO=Federation Internationale de Gynecologie et de Obstetrique.
SCC=Squamous cell carcinoma.
LN=Lymph node.



OB=obturatorregion, EI = external iliac region, lat-EI = lateral external iliac region, int-EI = intermediate external iliac region, med-EI = medial external iliac region, InI= internal iliac region, PS = presacralregion

Figure 1 Atlas of the CTV nodes: regions and sub-regions. Middle-level of pelvis' for (**a**), and 'low-level of pelvis' for (**b**).

patterns of the positive nodes were analyzed in each area.

Statistical analyses were performed with the chi-square test. A probability level of 0.05 was chosen for statistical significance.

Results

There were 273 positive nodes as assessed by CT/MRI. The median number of positive nodes per patient was 2 (range, 1–7). Figure 2 shows the incidence of positive nodes in each nodal region. The area that most frequently contained positive nodes was the obturator region. In contrast, positive nodes were rarely observed in the presacral region. Table 2 shows the anatomical distribution of positive nodes in the pelvis. A solitary positive node was observed only in the obturator and the external iliac regions. In contrast, no solitary positive node was observed in the internal iliac, common iliac, and presacral regions. Within the obturator and external iliac regions, positive nodes were rarely observed in the caudal and lateral external iliac sub-regions. Ninety-seven percent of the patients (111/114) had one or more positive nodes in the cranial obturator and/or the medial external iliac regions. A solitary positive node was observed only in the cranial obturator, and medial/intermediate external iliac regions. For other regions or sub-regions, patients with positive nodes also had positive nodes concomitantly in other pelvic nodal