Radiation therapy for primary vaginal carcinoma

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Brachytherapy plays a significant role in the management of cervical cancer, but the clinical significance of brachytherapy in the management of vaginal cancer remains to be defined. Thus, a single institutional experience in the treatment of primary invasive vaginal carcinoma was reviewed to define the role of brachytherapy. We retrospectively reviewed the charts of 36 patients with primary vaginal carcinoma who received definitive radiotherapy between 1992 and 2010. The treatment modalities included high-dose-rate intracavitary brachytherapy alone (HDR-ICBT; two patients), external beam radiation therapy alone (EBRT; 14 patients), a combination of EBRT and HDR-ICBT (10 patients), or high-dose-rate interstitial brachytherapy (HDR-ISBT; 10 patients). The median follow-up was 35.2 months. The 2-year local control rate (LCR), disease-free survival (DFS), and overall survival (OS) were 68.8%, 55.3% and 73.9%, respectively. The 2-year LCR for Stage I, II, III and IV was 100%, 87.5%, 51.5% and 0%, respectively ($P = 0.007$). In subgroup analysis consisting only of T2–T3 disease, the use of HDR-ISBT showed marginal significance for favorable 5-year LCR (88.9% vs 46.9%, $P = 0.064$). One patient each developed Grade 2 proctitis, Grade 2 cystitis, and a vaginal ulcer. We conclude that brachytherapy can play a central role in radiation therapy for primary vaginal cancer. Combining EBRT and HDR-ISBT for T2–T3 disease resulted in good local control.

Keywords: primary vaginal cancer; radiation therapy; high-dose-rate brachytherapy; intracavitary brachytherapy; interstitial brachytherapy

INTRODUCTION

The most common carcinoma affecting the vagina is metastatic from other primary gynecologic and non-gynecologic sites, including the cervix, endometrium, colon and rectum, ovary, and vulva. Primary vaginal cancer is considered to be a rare entity, accounting for only 2% of gynecologic malignancies [1, 2]. To diagnose primary vaginal cancer it is necessary to fulfill the following two conditions: the cervix and vulva must be free of disease [3]; and if a hysterectomy has been performed within five years for a uterine tumor, the histopathological findings must differ from that of the uterine tumor. Squamous cell carcinomas account for the majority of primary vaginal carcinomas. Other histological subtypes of vaginal carcinomas include adenocarcinoma, adenosquamous carcinoma, small cell carcinoma, melanoma, lymphoma and sarcoma. Most patients with vaginal carcinomas are in their sixth and seventh decades of life,

with only 10% of cases occurring in patients ≤ 40 years of age; however, vaginal cancer is increasingly diagnosed in younger women, possibly because of human papillomavirus (HPV) infections [4].

There have been no prospective randomized trials with a focus on vaginal cancer treatments. Therefore, the management of vaginal cancer is not standardized, as is the treatment of cervical cancer. Small vaginal cancers, particularly those involving the apex of the vagina, may be treated successfully with surgical excision alone; however, definitive organ-sparing surgery is technically difficult for more advanced or distal lesions, which are usually treated with radiation therapy.

Before 2008, radiation therapy techniques applied to advanced primary vaginal cancer at the National Cancer Center Hospital in Tokyo, Japan, consisted of a combination of external beam radiation therapy (EBRT) and high-dose-rate intracavitary brachytherapy (HDR-ICBT), or EBRT

alone. After 2008, high-dose-rate interstitial brachytherapy (HDR-ISBT) was introduced. The purpose of this report is to retrospectively analyze the results of radiation therapy for primary vaginal cancer, and to determine whether or not the difference in radiation therapy technique affects disease control.

MATERIALS AND METHODS

The medical records of all patients treated with definitive radiation therapy for primary invasive carcinoma of the vagina at the National Cancer Center Hospital in Tokyo, Japan between February 1992 and November 2010 were reviewed retrospectively. Patients whose tumors involved the external os of the cervix or vulva were excluded [5]. Patients who had a hysterectomy for primary invasive uterine carcinoma with the same histology as vaginal cancer, patients who had distant metastases, and patients with histologic findings consistent with a sarcoma or melanoma were also excluded. Patients who had non-invasive carcinoma of the vagina, and patients who underwent EBRT post-operatively after hysterectomy for apical vaginal cancer, were excluded. A total of 36 patients with primary carcinoma of the vagina with a histopathological diagnosis of squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and small cell carcinoma were included in this study.

All patients underwent a routine metastatic work-up, including a complete blood count, renal function testing, liver function testing, chest X-ray/CT, and pelvic CT/MRI. These patients were then evaluated jointly by gynecological oncologists and radiation oncologists for the purpose of staging and to determine the optimal treatment modality. Tumor size was determined by CT/MRI imaging. For superficial disease that could not be visualized with imaging studies, tumor size was determined by physical examination. With the exception of two patients who were treated by HDR-ICBT alone, the remaining 34 patients received EBRT. The common EBRT portals included the entire vagina, as well as the paracolpium, parametrium, and draining pelvic lymph nodes up to the level of the common iliac (L4/5 junction). If the primary lesion involved the lower one-third of the vagina or there were clinically palpable inguinal nodes, the inguinal regions were also included in the EBRT fields. Superficial tumors were treated by HDR-ICBT with or without EBRT. When HDR-ICBT was used in combination with EBRT, the treatment schedule was similar to the radiation therapy schedule for the treatment of cervical cancer in Japan [6, 7]. The initial 20–40 Gy was delivered to the whole pelvis, then pelvic irradiation with a central shield ensued. The total dose delivered to the pelvic side wall was up to 50 Gy using conventional fractionation. HDR-ICBT was delivered after pelvic irradiation with a central shield at 6–10 Gy/fraction to 5 mm under the vaginal surface, for a total of 2–5 fractions.

Before 2008, HDR-ISBT was not used routinely in the treatment of vaginal cancer in our department. Advanced tumors that did not shrink sufficiently for HDR-ICBT after 40–50 Gy of pelvic irradiation were usually treated solely with EBRT with smaller boost fields of 60–70 Gy. For patients treated solely with EBRT, the median dose was 60 Gy (range, 49.6–70 Gy). For patients treated with a combination of EBRT and brachytherapy, the median EBRT dose for the central pelvis was 38 Gy (range, 20–50 Gy), the median EBRT dose for the pelvic side wall was 50 Gy (range, 36–50 Gy), the median ICBT dose was 18 Gy (range, 12–30 Gy), and the median ICBT dose per fraction was 6 Gy (range, 6–10 Gy). Of the two patients who were treated solely by ICBT, one patient was irradiated with 24 Gy in four fractions (6 Gy per fraction), and one patient was irradiated with 32 Gy in four fractions (8 Gy per fraction). After 2008, HDR-ISBT has been used routinely in the treatment of vaginal cancer in combination with EBRT. The detailed procedure for gynecological HDR-ISBT is described elsewhere [8]. In brief, a transperineal needle applicator insertion with transrectal ultrasound (TRUS) or CT image guidance was performed under general and epidural anesthesia or saddle block with the patient in the lithotomy position. After the needle applicator insertion, HDR-ISBT was performed twice daily, with each fraction 6 h apart. For advanced disease, a Syed-Neblett template™ (Alpha Omega Services, Bellflower, CA, USA) was used to sufficiently cover lateral disease spread. For localized disease with limited paracolpium or parametrium invasion, free-handed needle applicator insertion with a vaginal applicator was used with fewer needles inserted compared with the Syed-Neblett template™. The gross target volume (GTV) was defined based on the CT image obtained after needle insertion, as well as on physical examination immediately before needle insertion, the intra-operative TRUS image, and the most recent MRI. The dwell time of Ir-192 and the dose distribution of HDR-ISBT was calculated by geometric optimization and graphical modification to enclose the GTV by the prescription dose. The median HDR-ISBT dose was 24 Gy (range, 22–32 Gy) and the median HDR-ISBT dose per fraction was 6 Gy (range, 4–6 Gy). HDR-ICBT and ISBT were performed with a MicroSelectron HDR™ (Nucletron, Veenendaal, The Netherlands). Before 2010, administration of concurrent chemotherapy (cCRT) was not routinely used because there was no evidence that strongly favored utilization of cCRT for vaginal cancer; thus, the administration of cCRT was at the discretion of the attending physician and the most common agent used was cisplatin. After 2010, weekly cisplatin (40 mg/m^2) was used for bulky tumors (>4 cm) or patients with N1 disease, as is done for patients with cervical cancer.

After completion of radiotherapy, gynecological examinations were performed every 2–3 months for the initial

two years, every 4–6 months for years 3–5, and once or twice a year thereafter. Suspected persistent or recurrent disease was confirmed by a biopsy whenever possible. Treatment failures were classified as local, pelvic, or distant. Local failures were defined as persistent or recurrences located within the vagina or paracolpium. Pelvic failures were defined as recurrences in the pelvic or inguinal lymph nodes. Recurrences that involved the para-aortic nodes area were considered to be distant failures.

The local control rate (LCR), disease-free survival (DFS), and overall survival (OS) were calculated using the Kaplan Meier method [9] with all time intervals measured from the date of initiation of radiation therapy. The relationships between tumor characteristics and treatment variables, and LCR, DFS, and OS were analyzed by univariate analysis. The associations between tumor characteristics and treatment modality, and treatment modality and complications were evaluated with a chi-square test. A P-value < 0.05 was considered statistically significant. The continuous variables were dichotomized to give the lowest P-values in the log-rank test [10]. All statistical analyses were performed using SPSS^{TM} (version 18.0; SPSS, Inc., Chicago, IL, USA).

This retrospective study was approved by the Institutional Review Board.

RESULTS

There were 36 patients who met the eligibility criteria; 24 patients were alive at the time of the analysis in May 2012 and 23 patients were free from loco-regional recurrence. The median follow-up length of all living patients and those who were treated by HDR-ISBT was 35.2 months (range, 12.3–151.3 months) and 29.3 months (range, 15.9–39.4 months), respectively. The pretreatment characteristics of the 36 patients are summarized in Table 1. The median age was 59 years (range, 25–94 years). Greater than one-half of the patients presented with T1 and T2 disease. Lymph node metastasis was noted in 10 patients. Five patients had undergone a hysterectomy for benign or non-invasive disease. Five patients had adenocarcinomas, one had an adenosquamous cell carcinoma, and one had a small cell carcinoma. The remaining 29 patients were diagnosed based on pathologic evaluation as squamous cell carcinoma. The median tumor size at diagnosis was 3.6 cm (range, 1.0–11 cm). Figure 1 shows the distribution of the initial tumor location in the vagina. The involvement of the upper one-third of the vagina and lateral wall involvement were most frequent (26/36 [72.2%] and 29/36 [80.6%], respectively). Table 2 shows the methods of treatment according to T classification. All patients with T1 disease were treated by brachytherapy with or without EBRT. No ICBT was applied for patients with T3–4 disease. Either EBRT alone or a combination of EBRT and ISBT was used for patients with T3 disease, while all patients with T4 disease

were treated with EBRT alone. The tumor characteristics and treatment methods according to tumor histology are summarized in Table 3. Non-squamous cell carcinomas were more advanced compared with squamous cell carcinomas ($P = 0.006$, Table 3). Although there were no variables which were biased statistically because of the small number of patients, there was a tendency that non-squamous cell carcinomas was treated more frequently by EBRT alone than squamous cell carcinomas.

The 2-year LCR, DFS and OS were 68.8%, 55.3% and 73.9%, respectively. The 2-year LCR was 100% for Stage I, 87.5% for Stage II, 51.5% for Stage III, and 0% for Stage IV ($P = 0.007$, Table 1). The LCR was significantly unfavorable for patients with a non-squamous cell carcinoma histologic diagnosis (81.9% vs 14.3%, $P < 0.001$). In T2–T3 patients, in which EBRT alone or a combination of EBRT and HDR-ICBT/ISBT was used, HDR-ISBT had a marginally favorable LCR (88.9% vs 46.9%, $P = 0.064$, Fig. 2). In another analysis of the T1–T3 patients who had received EBRT and HDR-ICBT/ISBT, the 2-year LCR for EBRT + HDR-ICBT and EBRT + HDR-ISBT was identical (90%; $P = 0.970$). As shown in Table 1, the treatment result was not influenced by the treatment period (before or after 2008), when HDR-ISBT was introduced routinely for advanced disease.

Of the 36 patients in the current study, 17 (47.2 %) had persistent disease or recurrences; Fig. 3 shows the sites of initial failure of the 17 patients. Local recurrence was the most frequent site of recurrence.

One patient developed Grade 2 proctitis 8 months after radiation therapy and one patient developed Grade 2 cystitis 36.4 months after radiation therapy. Vaginal complications were assessed for 23 patients who did not have loco-regional recurrences (Table 4). Vaginal adhesions were noted in nine patients and were the most frequent complication; however, most of the adhesions were lysed with manual manipulation. Two patients each had vaginal atresia and strictures. A vaginal ulcer developed in one patient 17.3 months after radiation therapy, and healed with conservative treatment. No vesicovaginal or rectovaginal fistulae formed, and no patients with hemorrhagic cystitis required a blood transfusion. As shown in Table 4, the correlation between vaginal complications and administration of brachytherapy was analyzed using a chi-square test; the incidence of vaginal complications was not influenced by brachytherapy; rather there was a trend that patients treated with EBRT alone were more likely to develop vaginal adhesions ($P = 0.056$, Table 4). One patient developed a sacral bone fracture 11 months after radiation therapy.

DISCUSSION

Carcinoma of the vagina is a rare gynecological malignancy that primarily affects the elderly. Because of the

Table 1. Patient, tumor and treatment characteristics and correlation with outcome

Characteristic	*n* (%)	2-year LCR (%)	*P*	2-year DFS (%)	*P*	2-year OS (%)	*P*
Age							
<60	18 (50)	77.8	0.343	55.6	0.848	72.2	0.811
≥60	18 (50)	60		55		76.2	
Previous hysterectomy							
yes	5 (13.9)	60	0.416	60	0.928	60	0.456
no	31 (86.1)	70.3		54.6		76.2	
Stage							
I	9 (25)	100	0.007*	80	0.003*	100	0.053
II	8 (22.2)	87.5		75		62.5	
III	17 (47.2)	51.5		29.4		69.1	
IV	2 (5.6)	0		0		0	
T-Stage							
T1	9 (25)	100	0.013*	80	0.03*	100	0.051
T2	13 (36.1)	76.9		46.2		59.8	
T3	12 (33.3)	48.6		41.7		73.3	
T4	2 (5.6)	0		0		0	
N-Stage							
N0	26 (72.2)	68.5	0.804	64.9	0.062	68.4	0.071
N1	10 (27.8)	70		30		60	
Histology							
Scc	29 (80.6)	81.9	<0.001*	68.6	<0.001*	82.1	0.01*
non-Scc	7 (19.4)	14.3		0		42.9	
Tumor size							
<4 cm	20 (55.6)	80	0.133	65	0.241	74.1	0.758
≥4 cm	16 (44.4)	54.7		43.8		74	
Brachytherapy (HDR-ICBT/ISBT)							
yes	22 (61.1)	90.9	0.001*	77.3	0.001*	86.4	0.008*
no	14 (38.9)	32.1		21.4		53	
HDR-ISBT (T2–T3)							
yes	9	88.9	0.064	55.6	0.313	88.9	0.196
no	18	46.9		36.5		52.1	
Concurrent chemotherapy							
yes	7 (19.4)	64.3	0.773	28.6	0.298	71.4	0.472
no	29 (80.6)	69		62.1		74.3	
Treated period							
before 2008	23 (63.9)	60.2	0.178	51.8	0.561	68.6	0.2
after 2008	13 (36.1)	84.6		61.5		83.9	

LCR = local control rate, DFS = disease-free survival, OS = overall survival, HDR-ICBT = high-dose-rate intracavitary brachytherapy, HDR-ISBT = high-dose-rate interstitial brachytherapy.
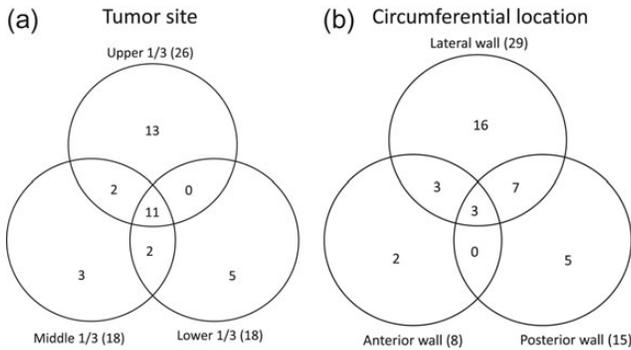
(a) Tumor site

(b) Circumferential location

Fig. 1. Distribution of initial location of the tumor in the vagina. (a) Tumor site. (b) Circumferential location.

Table 2. Methods of treatment according to T classification

Treatment methods	T1	T2	T3	T4
EBRT only	0	4	8	2
HDR-ICBT only	2	0	0	0
EBRT + HDR-ICBT	6	4	0	0
EBRT + HDR-ISBT	1	5	4	0
Concurrent chemotherapy	0	2	4	1

EBRT = external beam radiation therapy, HDR-ICBT = high-dose-rate intracavitary brachytherapy, HDR-ISBT = high-dose-rate interstitial brachytherapy.

Table 3. Tumor characteristics and treatment methods according to tumor histology

Treatment methods	Scc (29)	Non-Scc (7)	P
Age (mean)	62.5	57.9	0.441
Stage I–II	17	0	0.006*
Stage III–IV	12	7	
T-Stage T1–2	20	2	0.064
T-Stage T3–4	9	5	
N stage N0	22	4	0.37
N stage N1	7	3	
Tumor size (mean)	3.6	5.6	0.148
EBRT only	9	5	0.064
Brachytherapy ± EBRT	20	2	
Concurrent chemotherapy	6	1	0.701

EBRT = external beam radiation therapy, HDR-ICBT = high-dose-rate intracavitary brachytherapy, HDR-ISBT = high-dose-rate interstitial brachytherapy.

rarity of vaginal carcinoma, there have been no randomized clinical trials involving patients with virginal carcinoma and it is difficult to make robust treatment recommendations
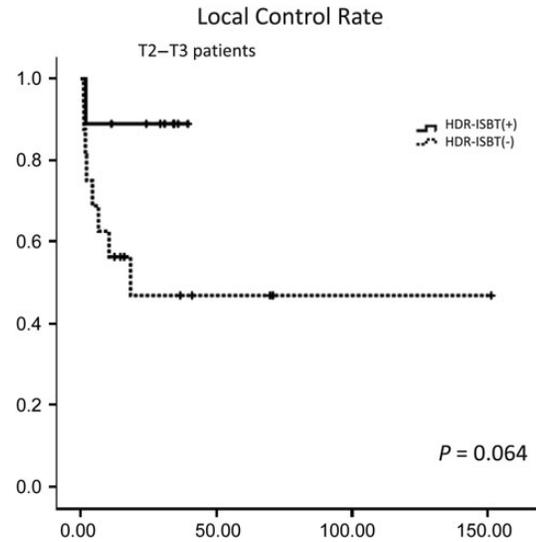

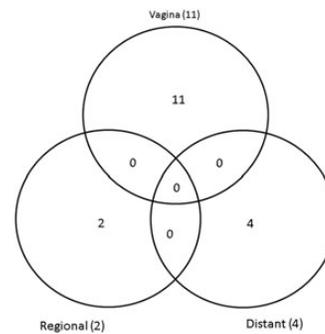**Fig. 2.** Local control rate stratified by HDR-ISBT for 25 patients with T2–3 disease.

Fig. 3. Patterns of relapse for entire patients. There were 17 relapses in this cohort. There was a local-regional component in 76% of relapses.

Table 4. Vaginal complications according to the administration of brachytherapy

		Brachytherapy		
	Total	yes (18)	no (5)	P
Vaginal adhesion	9	5	4	0.056
Vaginal atresia	2	1	1	0.395
Vaginal stricture	2	1	1	0.395
Vaginal ulcer	1	1	0	0.783

for patients with primary vaginal cancer. However, radiation therapy is considered to play a significant role in the management of primary vaginal cancer. In one of the largest series, Frank et al. [11] reported the clinical results of 193 patients with primary vaginal squamous cell

carcinomas treated with carefully tailored primary radiation therapy as showing excellent pelvic control. The 5-year pelvic disease control rate was 86% for Stage I, 84% for Stage II, and 71% for combined Stages III and IVA. The study published by Frank *et al.* [11], however, had several limitations, which are as follows: the retrospective nature of the study; the small number of patients; the heterogeneity of the patient's backgrounds; the treatment modalities used, which presumably included selection bias; and the short follow-up period. Therefore, the results have to be interpreted with caution. However, after careful analysis, several findings were derived from the current study. In the current study, the use of HDR-ISBT in patients with T2–T3 primary vaginal cancer was associated with favorable local control. This result was consistent with the report by Leung *et al.* [12], in which the addition of interstitial brachytherapy to EBRT was shown to have a significant favorable effect on clinical outcome. Seeger *et al.* [13] also reported favorable results for ISBT for primary carcinoma of the vagina and vulva, with no local recurrences of vaginal cancer with a median follow-up period of 27 months. In contrast, Nonaka *et al.* [14] reported the results of 26 patients with primary vaginal carcinoma who were treated mainly with HDR-ICBT with or without EBRT. Specifically, the 5-year pelvic control rate (PCR) for Stage I was 86%, whereas the 5-year PCR for Stages II and III was 50% and 57%, respectively [14]. Similarly, Hegemann *et al.* [15] reported the results of EBRT with or without ICBT for primary vaginal cancer and found that the median survival for Stage III/IV was unfavorable compared to Stage I/II (26.8 months and 58.1 months, respectively), suggesting that it is difficult to control thicker tumors with HDR-ICBT. In the current study, there was no difference in the LCR between HDR-ICRT and HDR-ISBT in patients withT1–T3 tumors, most likely because patient selection was performed properly; indeed, HDR-ICBT was applied only for thin tumors. The recently published American Brachytherapy Society guidelines for vaginal cancer recommend using ISBT for vaginal tumors ≥0.5 cm thick at the time of brachytherapy [16]. However, the follow-up period for those patients treated with HDR-ISBT in the current study was rather short, thus it is important to interpret this result with caution. Unfortunately, the treatment results did not differ significantly between treatment periods in this study, presumably because of the small number of patients analyzed and the short follow-up period for patients treated after 2008 (Table 1).

In seven patients with non-squamous cell carcinoma, six had Stage III and one had Stage IV disease, and only one of the patients received a combination of EBRT and HDR-ISBT, which was a relatively favorable factor for advanced disease in this analysis, while the remaining patients underwent only EBRT. As shown in Table 3, the treatment modality did not differ significantly between tumor pathologies, although non-squamous cell carcinomas were more likely to be treated by EBRT alone. The administration of chemotherapy did not differ significantly between tumor pathologies. However, non-squamous cell carcinomas were significantly more advanced at the time of initial presentation compared with squamous cell carcinomas ($P = 0.06$, Table 3). This observation explains, in part, the reason why patients with non-squamous cell carcinomas had such poor outcomes. In the current retrospective study, non-squamous cell carcinoma histology was shown to be a strongly negative factor for local control, which was consistent with the largest retrospective analysis of 301 patients with primary vaginal cancer that included 30 adenocarcinomas [17]. Specifically, the analysis showed that adenocarcinomas have twice the rates of local and metastatic relapse compared with squamous cell carcinomas. Whether or not the routine application of HDR-ISBT in patients with advanced non-squamous cell carcinomas can improve outcomes warrants an additional study.

Because of the small number of patients in the current study, it is difficult to discuss the role of chemotherapy in patients with primary vaginal carcinoma. Distant metastases were frequent in the current study, and the addition of chemotherapy concurrent with radiotherapy might add survival benefit in patients with advanced primary vaginal cancer, as occurs in patients with cervical cancer. In contrast, in vaginal cancer patients the perineum is more likely to be included in the radiation field compared with cervical cancer patients. Therefore, skin toxicities caused by chemoradiation should be prospectively assessed as well as the survival benefits.

Only a small number of patients had late complications in the current study; even HDR-ISBT and the administration of brachytherapy for vaginal cancer did not increase the incidence of complications (Table 4); however, further observation is required.

FUNDING

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