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High-dose-rate intracavitary brachytherapy for recurrent cervical cancer in the vaginal stump after hysterectomy

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ABSTRACT

This study aimed to evaluate the treatment outcomes of patients who received high-dose-rate intracavitary brachytherapy (HDR-BT) using Iridium-192 with or without external beam radiotherapy as definitive treatment for recurrent cervical cancer after hysterectomy. Thirty-six patients with local recurrence after hysterectomy received radiotherapy including HDR-BT from 2005 to 2013. Overall survival, local control rate, and progression-free survival were estimated retrospectively via the Kaplan-Meier method. Late adverse events were also scored using the Common Terminology Criteria for Adverse Events (version 3.0). Median follow-up time was 38 (range, 7.4–101.3) months. The 3-year estimates of overall survival, local control rate, and progression-free survival were 100.0%, 82.8%, and 76.8%, respectively. Two patients (5.6%) had grade 2 lymphedema, but no other adverse events greater than grade 2 were reported. In conclusion, HDR-BT was an effective treatment modality for patients with cervical cancer recurrence in the vaginal stump.

Keywords: cervical uterine cancer, hysterectomy, vaginal stump recurrence, radiotherapy, brachytherapy

INTRODUCTION

Cervical cancer is one of the most common cancers among women worldwide.[1] It is estimated that 20,000 women are newly diagnosed with cervical cancer (including carcinoma in situ), and 3,000 women die from this disease every year in Japan.[2,3]

For early-stage cervical cancer, some potential useful treatment strategies exist. Radical hysterectomy, a radical treatment for early-stage cervical cancer, achieves excellent clinical outcomes. However, in 15%–20% of patients with early-stage disease, the disease spreads to lymph nodes, and there is involvement of the parametrium and/or positive surgical margins at the time of radical hysterectomy.[4,5] The treatment options for the recurrent cervical cancer depend on the previous treatment. Irradiation or concurrent chemo radiotherapy is an option for recur-

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rent cervical cancer after hysterectomy alone, and data from the literature report 5-year overall survival ranging from 33–74%[6] for those settings. The major concern in terms of safety of this method is that previous operation may increase the radiation dose to the bowel that may increase toxicity. If radiotherapy was already performed as previous treatment and recurrence occurred inside the irradiated field, the treatment option will be limited. Patients with recurrent cervical cancer who are not a candidate for salvage surgery nor salvage radiotherapy are known to have dismal prognosis, reported to have 1-year survival rate between 15–20%. Pelvic exenteration has the potential for long-term survival in in-field recurrent cervical cancer after irradiation. However, it is also associated with multiple complications including operative mortality ranged from 2 to 14%.[6,7] High-dose-rate intracavitary brachytherapy (HDR-BT) is an option for localized recurrent cervical cancer, but with very limited reports, its application in terms of safety and efficacy is not very well known.

In our hospital, many patients who experience cervical cancer recurrence after hysterectomy receive high-dose-rate intracavitary brachytherapy (HDR-BT) and the number of patients receiving this intervention has been increasing. Therefore, in this study, we retrospectively investigated treatment outcomes in patients who received HDR-BT using Iridium-192 with or without external beam radiation therapy (EBRT) for treatment of local recurrence following hysterectomy.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the Nagoya University Hospital (#2016-0102), and all patients provided written informed consent.

Patients

From January 2005 to December 2013, 36 patients who experienced local recurrence after hysterectomy were referred to the Department of Radiology at Nagoya University Hospital. Patients initially underwent both a physical examination and a pelvic examination, along with evaluation of blood counts and x-ray computed tomography and magnetic resonance imaging. No patients had pelvic nodal recurrence and/or distant metastasis before the treatment. Nine patients (25.0%) were from our hospital and 27 (75.0%) were from other medical institutions. The patients from other medical institutions received only HDR-BT in our hospital and underwent other treatments and physical examinations in the respective outside institutions. All patients underwent follow-up for at least 6 months after HDR-BT, which included a review of institutional medical records, letters, and telephone contacts.

Radiotherapy

In the patients with recurrent cervical cancer, EBRT was delivered to local fields, small pelvic fields, or whole pelvic fields on a case-by-case basis. EBRT was performed with an x-ray energy of at least 4 MV photon beams in anterior and posterior parallel fields or box variants. The small pelvic field encompassed the upper half of the vagina, the retrovesical and prerectal regions, and the parametrial stumps including the lateral lymphatic channels. The whole pelvic field encompassed the small pelvic field and the common iliac lymphatic channels. The superior boundary was set at the L4–L5 junction or at the level of the abdominal aortic bifurcation. The external beam daily dose was 1.8–2.0 Gy, and the total dose range was 20–50 Gy.

All patients received HDR-BT using an Iridium-192 source and were treated with cylinder or ovoid applicators. The patients received 5Gy per fraction, once a week with the planned dose evaluated at 5 mm depth from the vaginal stump.

Chemotherapy

In our hospital, chemotherapy was generally administered concurrently with radiation therapy and repeated for three cycles. In principle, each cycle of chemotherapy consisted of cisplatin at a dose of 70 mg/m^2 on day 1 and 5-fluorouracil at a dose of 700 mg/m^2 per day given as a continuous infusion over 96 hours on days 1–4. The second cycle of chemotherapy began on day 22. The third cycle of chemotherapy commenced after completion of radiation therapy on day 43.[4] In the other institutions, other chemotherapy regimens were administered.

Statistical analysis

Overall survival, local control, and progression-free survival rates were estimated using the Kaplan-Meier method. Overall survival and progression free survival were defined as the time from the beginning of the radiotherapy thus for those patients who underwent external irradiation prior to HDR-BT, the first fraction of external irradiation was counted as day1. SPSS software version 23.0 (IBM Corp., Armonk, NY, USA) was used for these analyses.

Late adverse events

Late toxicity was defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (version 3.0).

RESULTS

Thirty-six patients with local recurrence after hysterectomy were referred to the Department of Radiology at Nagoya University Hospital. The pretreatment clinical characteristics of the patients are shown in Table 1. Classification of primary tumors on the basis of histology demonstrated that five patients had adenocarcinoma (n = 4) or adenosquamous cell carcinoma (n = 1). The histology of the primary tumor was unknown in one patient because the time to recurrence was more than 10 years, which created difficulty in reviewing the case. Four patients with recurrent cervical cancer had a history of radiotherapy to the pelvis and received only HDR-BT for recurrent cervical cancer. Thirty-four patients (out of 36) recurrences were diagnosed based on punch biopsy or cytology results, whereas the others were diagnosed comprehensively using pelvic examinations, cytology, tumor markers, and imaging examinations.

All 36 patients underwent radiation therapy including HDR-BT. Half of the patients (n = 18) were treated with HDR-BT alone and the other half were treated with HDR-BT and EBRT. Seven (19%) of the 18 patients treated with EBRT also received concurrent chemotherapy.

Either cylinder or ovoid applicators were used for HDR-BT. The planned doses at 5 mm depth from the vaginal stump were 10–30 Gy in two to six fractions, one fraction a week. The details of HDR-BT are listed in Table 2. The EBRT fields for the 18 patients were local field (n = 7), small pelvic field (n = 5), and whole pelvic field (n = 6).

Seven patients had chemotherapy in other institutions. The precise chemotherapy regimens are listed in Table 3.

Table 1 Pretreatment patient characteristics

Characteristics	Value
Median age (range), years	64.5 (30–89)
Histology, n (%)	
Squamous cell carcinoma	18 (50)
Adenocarcinoma (adenosquamous)	5 (14)
Carcinoma in situ	11 (31)
Severe dysplasia	1 (3)
Unknown	1 (3)
Surgical technique, n (%)	
Total hysterectomy	13 (36)
Modified radical hysterectomy	7 (19)
Radical hysterectomy	13 (36)
Unknown	3 (8)
Pathological T stage of initial surgery, n (%)	
Tis	12 (33)
1a	4 (11)
1b	15 (42)
2a	2 (6)
Unknown	3 (8)
History of radiotherapy, n (%)	
Yes: preoperative	1 (3)
Yes: postoperative	3 (8)
No	32 (89)
History of salvage surgery, n (%)	
Yes	4 (11)
No	32 (89)

Table 2 High-dose-rate intracavitary brachytherapy

	Value
Applicator, n (%)	
Cylinder	21 (58%)
Ovoid	15 (42%)
Radiation dose, Gy	
Total dose (range)	20 (10–30)
One-fraction dose[a)]	4 or 5
Fraction times	2–6

[a)] Evaluation point dose: 5 mm depth from the vaginal stump.

Table 3 Chemotherapy regimen

Adenocarcinoma (n = 3)	Non-adenocarcinoma (n = 4)
CDDP weekly	CDDP weekly
CDDP+5-FU	CDDP weekly
CBCDA+PTX	CDDP+5-FU
	NDP+5-FU

CDDP: cisplatin
CDDP+5-FU: cisplatin plus 5-fluorouracil
CBCDA+PTX: carboplatin plus paclitaxel
NDP+5-FU: nedaplatin plus 5-fluorouracil.

Table 4 Patterns of failure by histologic type

Re-recurrent site	Adenocarcinoma (adenosquamous) (n = 5)	Non-adenocarcinoma (n = 31)	All (n = 36)
None	1 (20)	26 (84)	27 (75)
Stump only	1 (20)	5 (16)	6 (17)
Lymph node in pelvis + distant metastasis	2 (40)	0	2 (6)
Distant metastasis	1 (20)	0	1 (3)

Results are presented as n (%).

Treatment outcomes of recurrent cervical cancer

The median follow-up time for patients with recurrent cervical cancer was 38.0 (range, 7.4–101.3) months. The median time to re-recurrence was 12.7 (2.5–38.9) months. Table 4 shows the re-recurrence rates. According to the histology of the primary tumor, patients were divided into the following two groups: patients with adenocarcinoma and patients with tumors of another histological type (non-adenocarcinoma group). Two patients were included in the non-adenocarcinoma group based on the histology of the recurrent tumor. Among the 36 patients with recurrence, nine patients (25%) experienced re-recurrence: six patients with stump re-recurrence, two with pelvic lymph node metastasis with distant metastasis, and one with distant metastasis only. Of the six cases of stump re-recurrences, the histology of the primary tumor was non-adenocarcinoma in five. The tumor type was adenocarcinoma in all cases of metastatic recurrence. Two patients had pelvic lymph node metastasis as regional metastasis. The sites of distant metastases were peritoneal dissemination in two patients and lung in one patient. Of 36 patients with recurrent cervical cancer, 32 remained alive at the last follow-up examination. Although there were no treatment-related deaths, four patients died, three from disease recurrence and one from lung cancer with no re-recurrence of cervical cancer.

The 1- and 3-year overall survival, local control, and progression-free survival rates were 100%, 91.7%, and 88.8% and 100.0%, 82.8%, and 76.8%, respectively (Table 5).

Late adverse events

Evaluation of adverse events was performed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). No treatment-related deaths were observed in any patients. Details of late adverse events after radiotherapy are listed in Table 6. Late adverse events occurred in three patients (8.3%), and two had grade 2 lymphedema. Two of the patients received radiation therapy including EBRT, and the other had a history of postoperative radiotherapy to the pelvis. There were no reported adverse events greater than grade 2.

Table 5 Overall survival, local control, and progression-free survival rates of 36 patients with recurrent cervical cancer

	OS	LC	PFS
1-year	100%	91.7%	88.8%
3-year	100%	82.8%	76.8%

OS: overall survival
LC: local control rate
PFS: progression-free survival

Table 6 Late adverse events[a)]

	Grade 1	Grade 2	Grade ≥3
Small intestinal disorder	0	0	0
Rectal hemorrhage	1 (2.8%)	0	0
Bladder disorder	0	0	0
Lymphedema	0	2 (5.6%)	0

[a)] National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

DISCUSSION

Past studies have reported ranges of 33%–74% for 5-year overall survival after radiotherapy for recurrent cervical cancer with or without brachytherapy.[8-11] Although the present study is limited by the very small number of patients, it is notable that the histological type in all distant metastases was adenocarcinoma. This result is consistent with the findings of Eifel et al that patients with adenocarcinoma had a greater risk of distant metastases than patients with squamous cell carcinoma,[12] an observation that may lead to the consideration of concurrent chemoradiation therapy to reduce the risk of metastases in patients with the former tumor type. Several trials have suggested the efficacy of concurrent chemoradiation therapy in patients with recurrent cervical cancer.[13,14] However, in the present study, two of the three patients with adenocarcinoma who received concurrent chemoradiation therapy experienced re-recurrence, and distant metastases were not prevented. Concurrent chemoradiation therapy may have had a poor effect in these patients. There is no clear chemotherapy regimen for cervical adenocarcinoma. However, the results of some studies suggest that taxane-containing regimens (paclitaxel-carboplatin or docetaxel-carboplatin or paclitaxel-cisplatin or taxane-anthracycline-platinum) have been effective in cervical adenocarcinoma.[15-19] In specific, Tang et al have reported that additional adjuvant chemotherapy with paclitaxel and cisplatin into concomitant chemoradiation in advanced

cervical adenocarcinoma will improve locoregional control and progression-free survival by more than 10% in randomized control study with more than 400 patients in each group.[17] Kimura et al has described that salvage chemotherapy to recurrent non-squamous carcinoma of cervix treated by taxane, anthracycline and platinum showed overall response rate of 42%. Although this report is consisted of very small number with only 19 patients, it is noteworthy that 79% of patients already had received radiation or chemotherapy prior to the study thus combination chemotherapy containing taxane seems effective for non-squamous cancer that is resistant to the first-line treatment.[19] In our hospital, the combination of cisplatin-5-fluorouracil is the most common chemotherapy regimen for cervical cancer of any histological type. It might be necessary to reconsider the chemotherapy regimen for cervical adenocarcinoma to prevent metastases.

Some studies have found that brachytherapy with EBRT increases intestinal[8] or urinary[9] complications. In the present study, four patients experienced late adverse events, and all of them had received EBRT to the pelvis. Although no adverse events greater than grade 2 occurred, the total dose to the pelvis must be considered. Five of six patients who experienced local re-recurrence were treated with HDR-BT alone. In cases in which complications permit such interventions, it is suggested that other treatments should be provided or that the dose of HDR-BT should be increased.

We acknowledge several limitations in the present study. First, this was a retrospective analysis of the experience of a single institution. Second, chemotherapy regimens differ according to institution. Third, the sample size was small. Fourth, the follow up time is not long enough. However, regarding the dismal outcome of the recurrent cervical cancer patients, and the fact that there have not been many studies of radiotherapy for recurrent cervical cancer, we believe our report is informative. Because existing reports contain small sample sizes as well, further study is required to reach definitive conclusions.

HDR-BT with or without EBRT for cancer recurrence in the vaginal stump after hysterectomy was a safe and effective treatment, and HDR-BT was a good treatment option for local recurrent cervical cancer without distant metastasis. However, the disease-free status of patients with adenocarcinoma was worse because of lymph node and/or distant metastasis, and this subject should receive further analysis.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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