

High-dose-rate intracavitary brachytherapy for non-palpable and non-visible recurrent vaginal stump tumors after hysterectomy

M. Sakaguchi¹, T. Maebayashi¹, T. Aizawa¹, N. Ishibashi¹, T. Saito²

¹Department of Radiology, Nihon University School of Medicine, Itabashi-ku, Tokyo

²Sonodakai Radiation Oncology Clinic, Adachi-ku, Tokyo (Japan)

Summary

Purpose: The purpose of this study was to evaluate patients who were treated with high-dose-rate (HDR) intracavitary brachytherapy for non-palpable and non-visible recurrent vaginal stump that occurred after hysterectomy. **Materials and Methods:** This retrospective study included 11 patients aged 52–81 (median, 61) years. The HDR brachytherapy was performed using a remote after-loading system (RALS). The dose per fraction was planned at mainly 4 Gy/fraction, twice per week, for a total of 32 Gy. **Results:** CR and PR were diagnosed on cytology or visual examination in nine (82%) patients and in one (9%) patient, respectively. SD was noted in one (9%) patient. Isolated stump recurrence developed in five patients and the three-year LC rate was 53%. There was no severe acute and late toxicity. **Conclusion:** Local salvage is possible with a three-year LC rate of 53% with regard to non-palpable and non-visible limited vaginal recurrence of gynecological cancer that responds to HDR brachytherapy (4 Gy/fraction, total 32 Gy).

Key words: High-dose-rate intracavitary brachytherapy; Recurrent vaginal stump; Hysterectomy; Remote after-loading system; Gynecological cancer.

Introduction

Intra-pelvic recurrence of gynecological cancer after radical hysterectomy remains unclear and therapeutically challenging. The recurrence rate of cervical cancer after radical hysterectomy has been reported to be 10–20% for International Federation of Gynecology and Obstetrics (FIGO) Stages IB–IIA and 50–70% for locally advanced disease [1]. Endometrial cancer is successfully treated with abdominal total hysterectomy (ATH) and bilateral salpingo-oophorectomy (BSO) in 80% of patients, and 10–15% of patients show tumor recurrence. About 50% of recurrences are intra-pelvic, and about 50% of intra-pelvic recurrences are limited to the vaginal stump [2]. The effect of postoperative radiotherapy with regards to overall survival (OS) is unclear [3]. In general, recurrent tumors were difficult to control and the prognosis was poor [4], as many of these patients treated by postoperative radiotherapy and more radioresistant than not received radiotherapy. The best treatment method (chemotherapy, radiotherapy, or chemoradiotherapy) for recurrent gynecological cancer remains unclear, as the small number of patients with confined vaginal recurrence, who have not received postoperative radiotherapy previously, makes it difficult to conduct randomized trials [5]. Furthermore, radiotherapy was divided into external irradiation, high-dose-rate (HDR)

brachytherapy, or both when tumor recurrence was noted at the vaginal stump. For intra-pelvic recurrence, whole/part pelvic external irradiation with intra-cavitary irradiation has been considered [6, 7]. However, in previous reports, the stage, recurrence form, and treatment strategy were not consistent, and thus, comparison was difficult. Most previous reports involved a combination of external irradiation and HDR brachytherapy. There have been especially a few reports on treatment methods for non-palpable and non-visible on MRI, and were treated with HDR brachytherapy only. However, the results were difficult to interpret because of the use of different doses and the presence of short follow-up periods [8, 9]. The present authors excluded patients who had combination external beam irradiation and HDR brachytherapy from this analysis and focused on HDR brachytherapy only. The present study aimed to assess local control and survival in patients with vaginal stump recurrences that were non-palpable and non-visible on MRI, and were treated with HDR brachytherapy.

Materials and Methods

This retrospective study included 11 patients aged 52–81 (median, 61) years, who were treated with HDR brachytherapy for vaginal stump recurrences that were non-palpable and non-visible on MRI following hysterectomy. The study was performed be-

Table 1. — *Patients characteristics and treatment features.*

Number	Age	Primary disease	FIGO/TNM ^c	Recurrent lesion	Applicator	Dose per fraction	Total dose	Previous treatment	Distant metastasis	Concurrent or after brachytherapy	Acute side effect	Late side effect
1	62	Endometrial ^a	IA/IA	Lateral wall	Cylinder	4	32	-	-	-	Colpitis	-
2	56	Endometrial	IB/IB	Apex	Ovoid	4	32	TC ^e	-	-	Colpitis	-
3	55	Endometrial	IA/IA	Apex	Ovoid	4	32	-	-	-	Colpitis	-
4	58	Endometrial	II/II	Apex	Ovoid	4	32	TC, DOC ^f	-	PI ^h , ADM ⁱ	Colpitis	-
5	71	Endometrial	IA/IA	Lateral wall	Cylinder	4	32	TC	-	TC, CDDP ^j , ADM, DOC	Colpitis	-
6	69	Cervix ^b	IB1/IB1	Apex	Ovoid	4	32	TC	-	-	-	-
7	61	Endometrial	IIIC1/IIIC	Apex	Ovoid	4	32	TC	-	DC, RTx ^k for recurrence	Colpitis, rectal cystitis	bleeding
8	59	Cervix	-/0	Lateral/apex ^d	Cylinder/ovoid ^d	5/4 ^d	30/16 ^d	TC	-	CDDP·ETP ^l	-	-
9	81	Cervix	IA1/IA1	Lateral wall	Cylinder	4	32	-	-	-	Colpitis	-
10	73	Endometrial	IVB/IVB	Lateral wall	Cylinder	4	32	-	Lung	-	-	-
11	52	Endometrial	IIIC2/IIIC	Apex/lateral ^d	Ovoid/cylinder ^d	5/5 ^d	30/30 ^d	TC	PALN ^g	RTx for PALN	Colpitis, Rectal cystitis	breeding

a: adeno carcinoma b: squamous cell carcinoma c: FIGO (International Federation of Gynecology and Obstetrics)/TNM classification 7th edition d: first treatment/second treatment e: carboplatin+paclitaxel f: docetaxel g: para aortic lymph node h: cisplatin+ifosfamide i: adriamycin j: cisplatin k: extra beam radiotherapy l: etoposide.

tween January 2005 and August 2017. All patients had not received postoperative adjuvant radiotherapy. The staging was decided after surgery according to the FIGO classification and TNM classification 7th edition. All patient information was obtained from institutional records. In all patients, recurrence was confirmed by colposcopy and colposcopic-directed punch biopsy or cytology before treatment initiation. All patients underwent CT to evaluate distant metastasis, and recent patients underwent positron emission tomography as well. All patients had non-palpable recurrence on bimanual recto-vaginal examination, and the recurrence was not visible on MRI [mainly T1-weighted imaging (axial), T2-weighted imaging (axial, sagittal), and diffusion-weighted imaging with or without enhanced T1-weighted imaging]. The authors did not include patients who had a palpable recurrent tumor or a tumor visible on MRI and who received HDR brachytherapy plus external irradiation for the tumor. Additionally, they did not include patients who underwent surgery for recurrence previously.

All patients underwent hysterectomy before HDR brachytherapy. ATH, BSO, and omentectomy were performed according to staging. The stump margins of all patients were negative after surgery. HDR brachytherapy was performed using a remote after-loading system (RALS). The RALS method was determined according to the tumor location at the vaginal stump or vaginal wall. If the disease was limited to the vaginal stump (vault/apex), an ovoid applicator was inserted into the vagina and then packed with gauze to reduce the dose around the organ. If the disease was present at the vaginal wall distal to the stump, a cylinder applicator was inserted. The dose was prescribed at a 0.5-cm depth to the surface of the vaginal mucosa. The dose per fraction was planned at 4, 5, or 6 Gy/fraction (mainly 4 Gy/fraction, twice per week, total 32 Gy). No interstitial brachytherapy was performed.

There was no strict chemotherapy protocol. The decision to administer chemotherapy was based on physician preference according to tumor spread, postoperative staging, risk factors, and institutional treatment protocols available at the time of the patient's diagnosis. Carboplatin plus paclitaxel (TC) was mainly selected after hysterectomy for endometrial cancer. Cisplatin plus ifosfamide or adriamycin, cisplatin alone, or docetaxel alone was

administered after HDR brachytherapy. Cisplatin was used basically for recurrent cervical cancer.

All patients were closely observed twice per week during HDR brachytherapy. The subsequent follow-up period included clinical and cytological assessments and blood examinations, including assessment of tumor markers, at three months and annually thereafter. Additionally, CT was performed to assess distant metastasis every 3–6 months. The clinical response was determined through visual examination and cytology. Complete response (CR) was defined as no visible tumor and cytology of class I, II, or III. Partial response (PR) was defined as a reduction in the visible tumor size but cytology of class IV or V. Progressive disease (PD) was defined as an increase in the visible tumor size. Stable disease (SD) was defined as the absence of a change in the visible tumor size and cytology grade. Responses were scored when the treatment was most effective. Local recurrence was defined as changes similar to those of PD or worsening of the cytology grade to class IV or V. The date of recurrence was determined as the first day when the PD was identified. Adverse events were recorded twice per week during radiotherapy and four weeks after treatment according to the common terminology criteria (CTC) for adverse events, version 4.0 [10].

The OS after HDR brachytherapy was calculated according to the Kaplan–Meier method and was based on the interval between the last day of treatment and the date of death or the most recent follow-up as of August 2017. Data from patients who reached the end of the follow-up period without an event were censored. Local control (LC) was calculated on the basis of the interval from the last day of the treatment until local recurrence. Data from patients who died with no evidence of recurrence were censored.

This retrospective study analyzed data on diagnosis and treatment. Written informed consent was obtained from all patients at the start of HDR brachytherapy for inclusion of their data in this study. All procedures performed were in accordance with the ethical standards of the institutional and national research committees and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

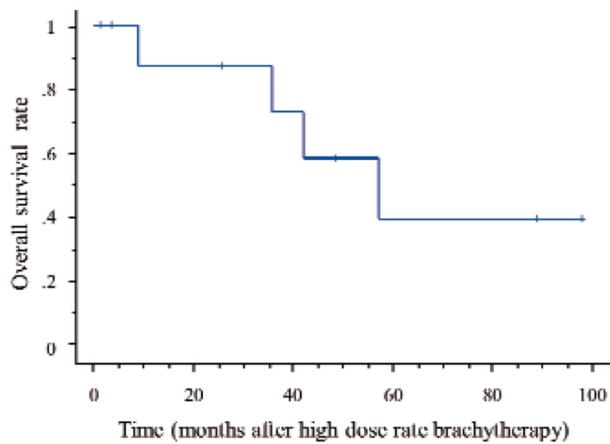


Figure 1. — The three-year OS rate was 72.9%, and the five-year OS rate was 38.9%.

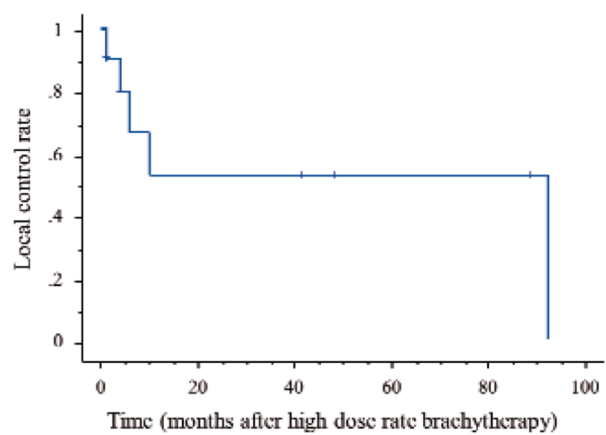


Figure 2. — The overall response rate was 85%. Isolated stump recurrence developed in five patients and the three-year LC rate was 53%.

Results

Baseline patient characteristics and treatment features are listed in Table 1. The median interval to recurrence calculated from the date of hysterectomy to stump recurrence was 16 (range, 8–192) months. Five endometrial cancer patients received chemotherapy after hysterectomy, which was based on TC, according to tumor staging; however, there was no strict protocol. Four patients received chemotherapy after HDR brachytherapy because of adjuvant chemotherapy or recurrence or metastasis, but the type of chemotherapy and course were not maintained. One patient who had para-aortic lymph node (PALN) metastasis received external irradiation after HDR brachytherapy. Concurrent local recurrence and distant metastasis were noted in two patients. The sites of distant metastasis were the PALN and lung.

The median duration of follow-up was 36 (range, 2–98) months. Four patients died during the follow-up. The causes of death were the primary disease or conditions related to the primary disease in two patients and distant metastasis in two patients. The three-year OS rate was 72.9%, and the five-year OS rate was 38.9% (Figure 1).

CR and PR were diagnosed on cytology or visual examination in nine (82%) patients and in one (9%) patient, respectively. SD was noted in one (9%) patient, and PD was not noted. Two patients received HDR brachytherapy again because of recurrence. One patient had CR again and the other patient had SD. One patient received external radiotherapy with the box technique after HDR brachytherapy because of a palpable recurrent tumor. The overall response rate was 85%. Isolated stump recurrence developed in five patients and the three-year LC rate was 53% (Figure 2).

The treatment was well-tolerated. Acute toxicity of grade 1 colpitis and cystitis of the bladder without symptoms were observed in eight (73%) and in two (18%) patients,

respectively. One patient had minor self-limiting symptoms of mild lower abdominal pain, but it was not clear if this was a side effect. One patient had vaginal bleeding as late toxicity, but it was unclear if this was related to toxicity or a recurrent tumor. One patient had grade 1 rectal bleeding as late toxicity, but treatment was not required. This patient received external irradiation after HDR brachytherapy because of recurrence. There was no late toxicity in patients who received HDR brachytherapy twice, but it should be noted that the follow-up period was short. Three patients had mild vaginal atrophy, fibrosis, and telangiectasia as late toxicity. There was no perforation of the small intestine, ileus, or rectovaginal/bladder-vaginal fistula.

Discussion

Intra-pelvic recurrence of gynecological cancer without synchronous systemic progression after radical hysterectomy has been reported in about 50% of patients [11]. The most frequent location of intra-pelvic recurrence after endometrial cancer treatment is the vagina and salvage radiotherapy shows an effect [12]. Patients with cervical cancer often show vaginal recurrence and have good results with radiotherapy. Evans *et al.* [13] reported that no patient who received treatment for a recurrent tumor of the cervix uteri died within 15 months. Recently, the OS rate for recurrent cervical cancer patients has improved and has been reported to be about 30–40% with radiotherapy [14, 15]. Several studies have reported a five-year OS rate of stump recurrence only of around 50–60% [16, 17]. LC and OS following radical radiotherapy for intra-pelvic recurrence of endometrial carcinoma have been reported to be about 50–80% and 40–80%, respectively [18, 19]. A previous report mentioned that there was no difference between recurrent cervical and endometrial cancers, with regards to

either LC or survival [20, 21]. Therefore, in this study, the authors conducted radiotherapy when pelvic recurrence was noted, and they did not divide stump recurrence into cervical and endometrial cancers. In the present study, the five-year OS rate following HDR brachytherapy for vaginal recurrence was lower than that in previous reports [16–19, 22]. In this study, two patients had distant metastasis at HDR brachytherapy, and two patients died because of distant metastasis. On the other hand, LC was comparable to that reported in a previous study.

Several prognostic factors have been identified. At first, when treatment for intra-pelvic recurrence is considered, the location of recurrence is important [23, 24]. Recurrence of gynecological cancer can occur in the peripheral pelvic wall, vaginal stump, and vaginal stump with extension to the pelvic cavity. Deutsch and Parsons [7] reported that the best results were obtained when recurrent cervical cancer was confined to the vagina. Curran *et al.* [25] found that apical recurrence of endometrial cancer had a better response to treatment than more distant metastasis. A recurrent intra-pelvic tumor spreading to the pelvic wall is a significant negative prognostic factor for survival. Jain *et al.* [16] reported five-year OS rates of 42% and 20% after radiotherapy for stump and pelvic wall recurrences of cervical cancer, respectively. Another study reported a five-year survival rate of as low as 0% for patients with recurrences extending to the pelvic wall and a rate of 87% for highly selected patients with small central tumors [6]. Ijaz *et al.* [26] reported that the five-year survival rate was 69% for stump recurrence compared to 18% for recurrence with spread to the pelvic wall. The reasons for the poor outcomes of pelvic wall recurrences include difficulty to increase the radiation dose with HDR brachytherapy and difficulty to exclude the small intestine from the external irradiation field. The presence of many rich lymphatic vessels at the pelvic wall increases the rate of regional and systemic metastasis. When the degree of the spread of recurrence is considered, limited vaginal stump recurrence may show a good outcome. In patients with intra-pelvic disease spread, the combination of HDR brachytherapy and external irradiation has been considered. The size of the recurrent tumor has been also shown to be an important factor [27, 28]. Ito *et al.* [6] analyzed vaginal stump recurrences of cervical cancer and divided the tumors according to size (< 3 and \geq 3 cm). They found that the five- and ten-year survival rates of patients with smaller tumors were 87% and 72%, respectively. Wylie *et al.* [28] reported on recurrent endometrial cancer and mentioned that the five-year LC rate was 80% in patients with tumors < 2 cm compared with 54% in patients with larger tumors ($p = 0.04$). Therefore, if radiotherapy is to be applied in patients with large recurrent tumors, the combination of external/interstitial irradiation is recommended [29]. On the other hand, Ito *et al.* [6] reported that there was no significant difference between HDR brachytherapy alone and HDR

brachytherapy plus external irradiation for small and medium tumors. They also reported that the combination of external irradiation and brachytherapy increased the incidence of late toxicity. Based on these reports, the present study considered that HDR brachytherapy alone might be adequate for patients with non-spreading tumors [non-palpable and non-visible (on MRI)]. Patients with tumor spread of several centimeters, which was not detected on MRI, may have been included in this study. Considering this fact, the present LC rate was comparable with that in previous reports.

The radiation dose of HDR brachytherapy only for a recurrent non-palpable tumor has remained unclear. A previous report mentioned that an important treatment factor was a total dose [30]. A large dose per fraction might lead to an increased risk of late toxicity. The radiation dose should be decided for achieving a balance between tumor control and toxicity prevention. MacLeod *et al.* [9] reported the results of 12 patients with vaginal intraepithelial neoplasia (VAIN) after radical hysterectomy that was treated with HDR brachytherapy (mainly total dose of 42.5 with 8.5 Gy/fraction). The HDR brachytherapy has been used in treatment. Ogino *et al.* [31] reported the results of VAIN after hysterectomy that was treated with HDR brachytherapy (total dose of 30 or 25 Gy with 6 or 5 Gy/fractions). The treatment was well-tolerated with no severe toxicity. Teruya *et al.* [32] suggested that patients with carcinoma *in situ* of the vagina after hysterectomy should receive a total dose of 30–40 Gy with 4 or 6 Gy/fraction prescribed at a 0.5-cm depth from the vaginal surface to control recurrence without severe toxicity. In this series, 4 Gy/fraction was a slightly lower dose compared with that in the previous study prescribed at a 0.5-cm depth from the vaginal surface, without severe side effects. The authors did not distinguish VAIN; thus, the results of LC involving treatment with 4 Gy/fraction (total 32 Gy) were comparable with that in the previous report.

In the present study, acute toxicity affected group 1 colpitis and cystitis, and these findings were better compared to those in previous studies [6, 17]. All patients underwent hysterectomy for the primary tumor, with accompanying complications, such as adhesion and lymphedema, associated with the hysterectomy. Thus study confirmed that HDR brachytherapy, even with chemotherapy for curative intent, is feasible in these patients, with a very low risk of late severe toxicity. The influence of the dose prescription at 0.5-cm depth from the vaginal surface is considered rather than the radiation dose. In a previous report, some patients were treated with a dose prescription at 1.0-cm depth from the vaginal surface or had additional external radiotherapy. Although the effect was better with this approach, the toxicity could increase. In this study, late toxicity involving grade 1 vaginal mucosal radiation reactions, such as atrophy, stenosis, and telangiectasia were noted. Patients who received HDR brachytherapy or external radio-

therapy again after original HDR brachytherapy had vaginal bleeding, but the authors could not determine whether this was associated with tumor recurrence or late toxicity. One patient who received external irradiation again had grade 1 late toxicity of rectal bleeding but no other severe late toxicity.

The present study has some limitations. This was a retrospective study with a small number of patients in a single center. The present follow-up period was short; therefore, late toxicity was unclear. Furthermore the authors could not estimate irradiate volume and dose of rectum. Because of the small number of patients, this data did not allow univariate and multivariate analyses, and it was difficult to determine whether the addition of systemic chemotherapy or other factors improved OS and LC. Studies in the literature describe the feasibility of combined chemoradiotherapy for recurrent cervical cancer [5, 33]. There are many reports about cisplatin for cervical cancer, and it is used as the primary drug because of an effective rate of 20–30% [34]. Chemoradiotherapy, including cisplatin plus ifosfamide or paclitaxel, has been used [5, 35]. For endometrial cancer, TC and adriamycin plus cisplatin therapies are generally considered. However, the combination of HDR brachytherapy and chemotherapy was not considered in this clinical experience and the drug used in this study was not maintained. Systemic progression may result in death after successful local radiotherapy, and thus, an addition of chemotherapy should be considered. The LC rate was also affected by chemotherapy. Furthermore, the histological grade has been reported to be a predictive factor [25, 28]. However, in this study, only five patients had data on histological grade (grade 1), and the data of other patients were missing. These limitations may be addressed in the future by performing studies involving multiple centers in multiple countries.

Conclusion

The results suggested that local salvage is possible with a three-year LC rate of 53% with regard to non-palpable and non-visible limited vaginal recurrence of gynecological cancer that responds to HDR brachytherapy (4 Gy/fraction, total 32 Gy).

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Corresponding Author:
M. SAKAGUCHI, M.D.
Department of Radiology
Nihon University School of Medicine
30-1, Oyaguchi Kami-cho, Itabashi-ku
Tokyo, 173-8610 (Japan)
e-mail: sakaguchi.masakuni@nihon-u.ac.jp