
Ultrasonic scalpel ablation for vaginal intraepithelial neoplasia occurring after hysterectomy

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Summary

Purpose of investigation: This pilot study aimed to assess the feasibility and efficacy of ultrasonic scalpel ablation for vaginal intraepithelial neoplasia (VAIN) Grade 3 lesions occurring after hysterectomy for cervical malignancies. *Materials and Methods:* A total of 11 cases of VAIN 3 that occurred after hysterectomy for cervical in-situ and invasive carcinoma were treated using ultrasonic scalpel ablation. The clinical courses and treatment outcomes of the cases were retrospectively analyzed along with four cases that were treated using conventional CO₂ laser vaporization. A review of related articles was conducted to compare the therapeutic efficacy and indications for various treatments. *Results:* In all of the cases, the procedure was conducted safely with no significant complications. After treatment, the cytology of the vaginal stump was normalized in 14 cases (93.3%). One patient's cytology was not normalized; she was treated with a partial vaginectomy. Re-recurrence occurred in three of the four (75%) patients treated with CO₂ laser vaporization and three of the 11 (27.3%) patients treated with ultrasonic ablation. All but one patient remained free of disease after the second treatment for VAIN. *Conclusion:* Ultrasonic ablation may be feasible and convenient and as effective as CO₂ laser vaporization for the treatment of VAIN after hysterectomy.

Key words: Vaginal intraepithelial neoplasia (VAIN); Ultrasonic scalpel; Ablation; Hysterectomy; CO₂ laser vaporization.

Introduction

Vaginal intraepithelial neoplasia (VAIN) is relatively rare compared with cervical intraepithelial neoplasia (CIN) [1, 2]. However, VAIN sometimes progresses to vaginal carcinoma, so it must be treated carefully [3-7]. Unlike CIN, which affects a specific area of the uterine cervix, VAIN can occur in any part of vagina, and it is difficult to correctly define the extent of the lesion. Accordingly, the treatment strategy and modality for VAIN differ significantly from those for CIN. CIN is treated primarily with surgical resection (conization or hysterectomy), which is not applicable to VAIN. Although various treatment modalities, such as local ointment application, laser vaporization, surgical resection, and irradiation have been used, there is no standardized treatment for VAIN, partly because of its rarity [3, 5, 8-12]. The recurrence rate of VAIN after treatment is relatively high [10, 13].

VAIN occasionally occurs in patients after they undergo a hysterectomy for uterine cervical cancer and CIN or for benign disease [14, 15]. According to previous reports, VAIN occurs after the treatment of CIN or cervical malignancies in approximately 50-90% of cases [4, 10, 11, 13]. Some reports suggest that the likelihood of developing VAIN varies according to the stage of the primary disease [16, 17]. When VAIN is found after hysterectomy, it is difficult to select a treatment method because of a lack of evi-

dence. While the present authors found some published reports describing treatments for such cases, most of them included a small number of cases. Because these events are likely to involve relatively older patients and those with complications after aggressive treatment for primary disease [5, 7, 18, 19], the treatment for recurrent VAIN should be less invasive but effective.

In this study, the authors conducted a pilot study using an ultrasonic scalpel for vaginal epithelium ablation to treat VAIN after simple or radical hysterectomy for cervical malignancies, including CIN3 and invasive carcinoma. A total of 11 cases were analyzed for the outcome along with four cases that were treated using conventional CO₂ laser vaporization. This is the first report on the use of ultrasonic ablation to treat VAIN in the vaginal stump after hysterectomy. Ultrasonic scalpels are more widely available and more familiar than CO₂ laser to gynecological surgeons; therefore, ultrasonic scalpel ablation could serve as an additional modality for treating VAIN if it is found to be as effective as other treatments. The present authors reviewed previous studies that reported the outcomes of treatments for VAIN that developed after hysterectomy for cervical malignancies.

Materials and Methods

The authors retrospectively reviewed the medical records of patients who underwent hysterectomy (either simple or radical) for CIN3 and invasive cervical cancer at Kinki University Hospital between January 2005 and April 2013. Four cases were treated with CO₂ laser vaporization and 11 cases were treated with ablation using an ultrasonic scalpel. For follow-up screening, the cytology of the vaginal stump was examined one month after the operation, and subsequent cytology checks were repeated every three to six months. If abnormal cytology was reported, biopsies of the vaginal stump were conducted under colposcopy. Recurrence was defined when a pathological diagnosis of VAIN3 or higher was made; in each case, the patient was treated using the most appropriate method. Approval for the current study was obtained from the Institutional Review Board of our institute. The authors received patient informed consent before conducting the procedure.

CO₂ laser vaporization was performed using a procedure similar to one that was reported previously [20]. All of the procedures were performed under intravenous anesthesia in the treatment room on the ward. First, the authors applied 3% acetic acid and observed the vaginal stump via colposcopy to identify the abnormal area. Then, Lugol's solution was applied to the vaginal stump, and a CO₂ laser was applied to vaporize the suspicious area. Ablation using an ultrasonic scalpel was performed in a similar setting under intravenous anesthesia. Using a sono surg flat hand-piece, the entire surface of the suspicious area that was unstained by Lugol's solution was ablated in coagulation mode (70% output power). The surgical procedure took approximately ten minutes with minimal blood loss. The average length of hospital stay was two days.

All of the statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R. More precisely, it is a modified version of the R commander designed to add statistical functions that are frequently used in biostatistics [21].

The authors searched PubMed and reviewed all of the reports that included cases with VAIN3 after hysterectomy.

Results

The mean age of the patients at the time of vaporization or ablation was 63 ± 15 (range 35-85) years. The median follow-up time after vaporization or ablation was 27 (range 1-70) months. Regarding the histology of cervical cancer, all 15 cases were squamous cell carcinoma that included CIN3. The stages of the primary cervical cancer were CIN3 (n=4), IA1 (n=1), IA2 (n=1), IB1 (n=4), and IIB (n=5; Table 1). The initial method used to treat the cervical cancer was chosen according to the stage of the cancer: five cases underwent simple hysterectomy and ten cases underwent radical hysterectomy (including radical trachelectomy for one case). Table 2 shows the time to progressions the patients' progress after hysterectomy, the methods of treatment, the cytology after treatment, and recurrence during the follow-up period. The interval from hysterectomy to the VAIN3 diagnosis and treatment was < six months in three cases, six to 12 months in four cases, 13-60 months in three cases, and > 61 months in five cases, and the median interval was 19 (3-254) months. Four cases were treated with

Table 1. — Characteristics of patients.

Patient characteristics	Subjects (n=15)
Age (years)	63±15 (35-85)
History of cervical neoplasia	
Carcinoma in situ	4
Cervical cancer	
1A1	1
1A2	1
1B1	4
2B	5
Type of hysterectomy	
Total abdominal hysterectomy	2
Total vaginal hysterectomy	2
Laparoscopy-assisted vaginal hysterectomy	1
Radical hysterectomy	9
Radical trachelectomy	1

Table 2. — Progresses after hysterectomy, methods of treatment, cytology after treatment, and recurrence during follow up

Patient		15
Time to disease (months)	-6	3
	7-12	4
	13-60	3
	61+	5
Method of treatment	CO ₂ laser vaporization	4
	Ultrasonic ablation	11
Cytology after treatment	Returned to normal	14
	Persistent abnormal	1
Recurrence during follow up	No recurrence	9
	Recurrence	6

CO₂ laser vaporization and 11 cases were treated using ablation with an ultrasonic scalpel. The cytology of the vaginal stump was normalized in 14 cases (93.3%) following the treatment. In one case, the cytology was not normalized, and the patient underwent a partial vaginectomy. There were no surgical complications resulting from vaporization or ablation.

During the follow-up period after the first vaporization or ablation, six cases (40%) were diagnosed with a recurrence of VAIN3. The original disease stages in these cases were CIS in one case, IA1 in one case, IA2 in one case, IB1 in two cases, and IIB in one case. The mean interval from the first VAIN3 treatment to re-recurrence was 29 ± 15 (1-52) months. The cumulative rate of recurrence was 6.7% at one year, 24.6% at three years, and 69.8% at five years (Figure 1). Re-recurrence occurred in three out of four (75%) cases treated with CO₂ laser vaporization and three out of 11 (27.3%) cases treated with ultrasonic ablation. Whole-pelvic radiation was performed in two of these cases, tumorectomy via laparotomy in one case, vaginectomy in one case, and repeat ablation in two cases (Table 3). All but one of these cases remained disease-free

Table 3. — Summary of recurrent cases.

	Primary lesion	Treatment	Interval to re-recurrence (months)	Treatment for recurrence	Subsequent course
1	1B1	Laser vaporization	45	Concurrent chemo-radiotherapy	NED
2	1A1	Laser vaporization	52	Radiotherapy→ surgery + chemotherapy	DOD
3	CIN3	Laser vaporization	17	Ultrasonic ablation	NED
4	1A2	Ultrasonic ablation	36	Ultrasonic ablation	NED
5	1B1	Ultrasonic ablation	23	Radiotherapy	NED
6	2B	Ultrasonic ablation	Persistent	Surgery	NED

Primary lesion are all cervical cancer except for case 3. NED: no evidence of disease, DOD: dead of disease.

Table 4. — Review of the literature including cases with VAIN3 after hysterectomy.

Author	Method	Disease	n	Recurrence or persistent rate	95% CI	FU month
Rome <i>et al.</i> , 2000 [5]	CO ₂ laser	VAIN1-3	8	2/8 (25%)	0.032 - 0.651	60
Dodge <i>et al.</i> , 2001 [6]	CO ₂ laser	VAIN1-3	16	8/16 (50%)	0.247 - 0.753	NA
Yalcin <i>et al.</i> , 2003 [20]	CO ₂ laser	VAIN2-3	16	5/16 (31%)	0.11 - 0.587	27
Kim <i>et al.</i> , 2009 [16]	CO ₂ laser	VAIN1-3	68	18/68 (27%)	0.165 - 0.386	33
Wang <i>et al.</i> , 2014 [17]	CO ₂ laser	VAIN1-3	39	21/39 (54%)	0.372 - 0.699	27
Robinson <i>et al.</i> , 2000 [22]	CUSA	VAIN1-3	29	10/29 (34%) *	0.179 - 0.543	53
Present study	CO ₂ laser	VAIN3	4	3/4 (75%)	0.194 - 0.994	27
Present study	Ultrasonic ablation	VAIN3	11	3/11 (27%)	0.060 - 0.610	27
Rome <i>et al.</i> , 2000 [5]	Local excision	VAIN1-3	7	4/7 (57%)	0.184 - 0.901	60
Rome <i>et al.</i> , 2000 [5]	Upper vaginectomy	VAIN1-3	35	7/35 (20%)	0.084 - 0.369	60
Indermaur <i>et al.</i> , 2005 [7]	Upper vaginectomy	VAIN2-3	104	6/52 (12%)	0.044 - 0.234	25
Murta <i>et al.</i> , 2005 [23]	Surgery	VAIN1-3	7	1/7 (14%) *	0.004 - 0.579	NA
Rome <i>et al.</i> , 2000 [5]	5-FU	VAIN1-3	4	1/4 (25%)	0.006 - 0.806	60
Dodge <i>et al.</i> , 2001 [6]	5-FU	VAIN1-3	5	3/5 (60%)	0.147 - 0.947	NA
Murta <i>et al.</i> , 2005 [23]	5-FU	VAIN1-3	16	6/16 (38%) *	0.152 - 0.646	NA
Lin <i>et al.</i> , 2012 [24]	Imiquimod	VAIN2-3	6	2/6 (33%) *	0.043 - 0.777	34
Graham <i>et al.</i> , 2007 [18]	brachytherapy	VAIN3	22	5/22 (23%)	0.078 - 0.454	77
Blanchard <i>et al.</i> , 2011 [25]	brachytherapy	VAIN3	28	2/28 (7%) *	0.009 - 0.235	41
Song <i>et al.</i> , 2014 [19]	brachytherapy	VAIN1-3	34	4/34 (11%)	0.033 - 0.275	48

* The data of post-hysterectomy were not available. FU: follow up; NA: not available.

after the second treatment for VAIN3.

One patient whose primary disease was Stage IA1 cervical carcinoma underwent vaginal hysterectomy as the primary surgery. Fourteen years after the primary surgery, a VAIN3 lesion was found, and the patient underwent CO₂ laser vaporization. Four years later, invasive squamous cell carcinoma accompanied by an intraperitoneal lesion was found. Whole pelvic radiation was applied and resulted in a complete response. However, the patient suffered from yet another recurrence, and despite two additional surgeries and six courses of paclitaxel/carboplatin chemotherapy, she died of the disease.

The authors searched PubMed and found 12 reports on the results of treatments for VAIN that occurred after hysterectomy (Table 4) [5-7, 16-20, 22-25]. CO₂ laser vaporization is the most commonly reported treatment. The recurrence rate after treatment ranges from 25% to 54%. Various lesion resection methods are reported and recurrence occurred in 12% to 57% of patients. Although the number of cases is small, upper vaginectomy had a lower recurrence rate (12-21%) than local resection did (57%).

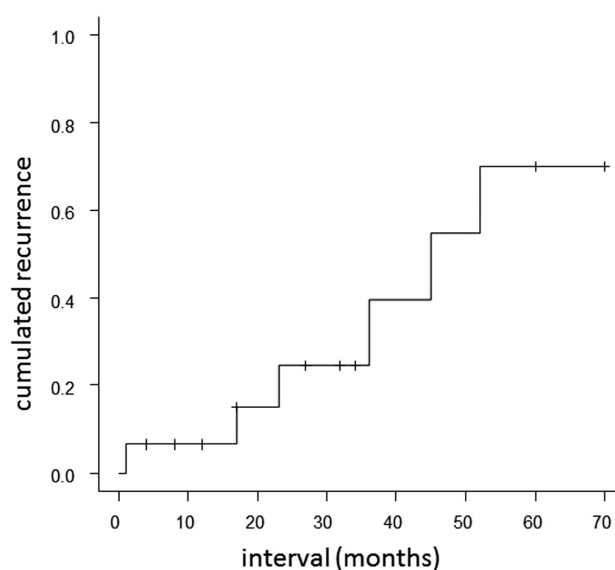


Figure 1. — Cumulative curve of recurrence after hysterectomy for cervical malignancies.

The local application of ointments such as 5-FU and imiquimod had recurrence rates of 25% to 60%. Brachytherapy is employed mostly for VAIN3 cases and shows a relatively high efficacy, with a recurrence rate of 7-23%.

Discussion

This study indicated that the authors' treatment procedure is efficient, especially for the initial control of the disease. Fourteen out of 15 (93%) patients with VAIN3 demonstrated normalized intravaginal cytology after the treatment. Zeligs *et al.* reported the treatment results for 53 cases of VAIN and showed that 49 (92%) patients demonstrated normalization [26]. Roughly, the regression rate of VAIN in response to treatment ranges from 70% to 95%, and regression may be influenced by the grade of the disease and the treatment method used. However, despite favorable initial disease control, the present study also demonstrated that the recurrence rate increased over time; in this study, the cumulative recurrence rate during the observation period was 40% (6/15) for a median follow-up duration of 27 months, and the average interval from treatment to recurrence in these cases was 29 ± 15 (1-52) months. Specifically regarding VAIN after hysterectomy, there are few reports regarding the efficacy of treatment, and these have an insufficient number of cases because VAIN after hysterectomy is relatively rare. Kim *et al.* reviewed 68 cases of VAIN after hysterectomy that were treated with laser vaporization in their institute [16]. Re-recurrence after laser treatment occurred in 18 (26.5%) cases during a median follow-up period of 33 months. The risk factors for failure of the first vaporization are the patient's age (≤ 48 years) and grade (VAIN3) prior to the treatment. When the analysis was restricted to VAIN3 cases, 13 out of 26 (50%) cases had recurrence during the follow-up period, which is highly consistent with the present report. Wang *et al.* reported 39 cases of post-hysterectomy VAIN that were treated with laser vaporization [17]. None of those VAIN3 patients achieved disease remission following their first treatment, although all of the patients showed remission after the second vaporization. The authors reported that VAIN3 before treatment was the only risk factor for the failure of the first treatment, suggesting that VAIN3 lesions require more thorough treatment irrespective of the primary disease (CIN3 or invasive cancer) and hysterectomy procedure (simple or radical). Because the present series included only VAIN3 cases, the efficacy of the authors' procedure is likely no lower than that found in other reports.

Generally, VAIN treatment includes laser vaporization, local application of ointments, vaginectomy, and brachytherapy. Dodge *et al.* conducted a retrospective review of 121 VAIN cases in their institution [6]. The VAIN patients were treated either with CO₂ laser, 5-FU, vaginectomy, or observation with no treatment, and recurrence or

progression occurred in 33% of the cases. Importantly, in their report, the risk of recurrence appeared to vary according to the treatment. The patients who were treated with partial vaginectomy had the lowest recurrence rate (0%), followed by those treated with laser vaporization (38%) and 5-FU (59%, $p = 0.001$). Yalcin *et al.* reported 24 VAIN cases in which 70.8% were successfully treated with a single CO₂ vaporization treatment [20]. Of the post-hysterectomy VAIN cases, nine of 16 (69%) showed remission. Murta *et al.* analyzed 33 cases of VAIN in which ten of 16 (63%) patients achieved remission after 5-FU treatment, while six of seven (86%) patients treated with surgery showed remission [23]. Lin *et al.* reported the efficacy of imiquimod application for six patients with VAIN2-3 patients (with/without CIN) in which complete regression was noted in four (67%) patients, while one (16.7%) patient showed stable disease, and one patient showed progression [24]. Although the number of reported cases in some of the treatments is too small for comparison, it appears that surgery and brachytherapy are the most effective modalities, laser vaporization has intermediate efficacy, and topical ointment application is the least effective treatment; notably, Table 4 lists the treatments from most to least invasive. When only the VAIN cases after hysterectomy are considered, several reports show the efficacy of laser vaporization, as cited above, but no published report compares vaporization with other modalities.

In the present series, 11 of 15 cases were treated with ablation using an ultrasonic scalpel. The only report on the use of an ultrasonic scalpel for VAIN treatment is by Robinson *et al.*, who reported the efficacy of cavitation ultrasonic surgical aspiration (CUSA) for VAIN treatment [22]. Among 46 VAIN patients, 29 patients were treated with CUSA, and the others were treated using other modalities, including laser vaporization, 5-FU, and vaginectomy. The authors demonstrated that although the CUSA group had a higher percentage of VAIN3 cases, a significantly greater proportion of the patients in this group showed complete remission. In the present study, which included only VAIN3 patients, three of the 11 (27%) cases treated with ultrasonic scalpel ablation showed recurrence, while three of the four (75%) cases treated with laser vaporization showed recurrence. It is inappropriate to compare efficacy in a small number of cases with different backgrounds, especially when the studies include different observation periods. However, the results shown here suggest that for the local treatment of VAIN following hysterectomy, ultrasonic scalpel ablation might be an alternative method that is at least as effective as laser vaporization. Ultrasonic scalpels offer the following advantages over CO₂ lasers: they are more readily available to gynecologists in typical facilities because they are widely used in gynecologic surgery, and gynecologists are more familiar with them than with laser apparatuses, considering that CO₂ laser is only used for VAIN that is rela-

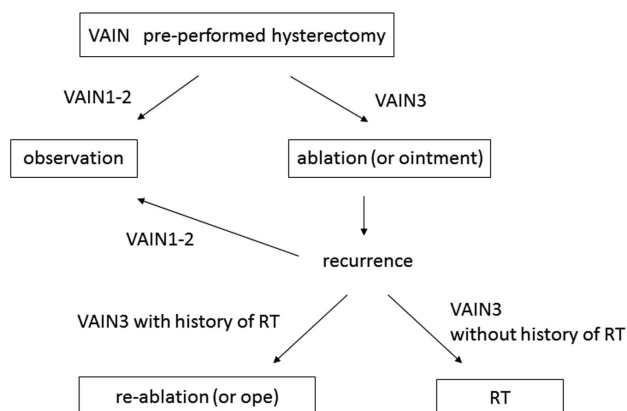


Figure 2. — The present authors’ recommended therapeutic scheme for VAIN after hysterectomy. VAIN3 after hysterectomy will be treated with ultrasonic ablation, and VAIN1-2 cases will be placed under observation. If VAIN3 recurs, VAIN3 cases with a history of radiation therapy will be treated with re-ablation or surgery, and VAIN3 cases without a history of radiation therapy will be treated with radiation (brachytherapy).

tively rare.

VAIN sometimes occurs long after a previous hysterectomy for CIN or cervical cancer [27]. In the present series, more than half of the cases recurred more than a year after the hysterectomy, and five out of 15 cases occurred five years after the hysterectomy. In such cases, it is difficult to distinguish whether the recurrent lesion is a true recurrence of the previous disease or a de novo development of VAIN, considering that VAIN occasionally occurs after hysterectomy even in cases of benign disease [5, 23]. In such cases, it is possible that VAIN is associated with a persistent HPV infection [28]. Frega *et al.* reported that HPV DNA testing and cytology during the follow-up period may be useful for predicting the persistence and progression of VAIN in vaginal carcinoma cases [29]. In particular, positivity for high-risk types of HPV (type 16 or 18) was significantly higher in patients with recurrent VAIN. Vinokurova *et al.* reported that some high-grade types of VAIN may emerge from monoclonal lesions derived from high-grade CIN or cervical cancer caused by high-risk HPV types [30]. These data suggest that HPV testing at the time of VAIN recurrence after hysterectomy may serve as a risk indicator for re-recurrence, although further study is needed.

In conclusion, the present study indicates that VAIN after hysterectomy for cervical cancer, including CIN, is effectively treated with local vaporization/ablation. In particular, the authors provided the first report of the use of ablation using an ultrasonic scalpel, a modality that appears to be safe, effective, and convenient, although the small number of patients included in this study is a limitation. Long term follow-up results indicated that late recurrence may occur

over time, and continuous follow-up is warranted. A review of the literature pertaining to treatments for VAIN after hysterectomy indicates that various types of treatment, including vaporization, ointment application, surgery, and radiotherapy, are all effective to differing degrees. Figure 2 shows the present authors’ recommended therapeutic scheme for VAIN after hysterectomy.

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