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Risk Factor and Treatment of Vaginal Intraepithelial Neoplasia After Hysterectomy for Cervical Intraepithelial Neoplasia

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Objectives: The aim of the study were to identify the risk factors for recurrent vaginal intraepithelial neoplasia (VaIN)1+ and to evaluate the efficacy of laser vaporization in patients who underwent hysterectomy for the treatment of cervical intraepithelial neoplasia (CIN).

Methods: Medical records of 374 women who underwent hysterectomy for the treatment of CIN were retrospectively reviewed. Recurrence was defined as VaIN1+ diagnosis by colposcopy-directed biopsy.

Results: Among 374 patients, 36 (9.6%) had VaIN1+ during a median follow-up of 32 (0–193) months: 13 (3.5%) had VaIN1, 6 (1.6%) VaIN2, 15 (4.0%) VaIN3, and 2 (0.5%) invasive cancer. Multivariate analysis showed that age of greater than 50 years was the only independent risk factor for VaIN1+ recurrence (odds ratio, 3.359; 95% CI, 1.60–7.07; $p = .001$). Among the 34 patients with VaIN, 21 (61.8%) were treated with laser vaporization and 11 (32.3%) were observed without treatment. Time to second recurrence was longer in the VaIN treated by laser vaporization group than that in the observation group (mean time to subsequent recurrence, 128.7 [95% CI, 101.4–156.0] vs. 41.8 [15.7–67.9] months; $p = .003$). Moreover, laser vaporization (hazard ratio, 0.125; 95% CI, 0.03–0.59; $p = .009$) was the only independent good prognostic factor for the second VaIN1+ recurrence.

Conclusions: Patients older than 50 years who underwent hysterectomy for the treatment of CIN might be highly at risk of VaIN1+. Laser vaporization is the only independent prognostic factor that might prevent the second VaIN1+ recurrence.

Key Words: vaginal intraepithelial neoplasia, cervical intraepithelial neoplasia, laser vaporization, hysterectomy, recurrence, prognosis

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Vaginal intraepithelial neoplasia (VaIN) is a rare precancerous lesion occurring in a woman's lower reproductive organs. Vaginal intraepithelial neoplasia diagnosis has been steadily increasing over the past few decades because of increased disease awareness and expanded cytologic screening and colposcopy.[1,2] However, its exact incidence rate remains unknown, although it is reported to be approximately 0.2–0.3 per 100,000 women in the United States.[3]

Vaginal intraepithelial neoplasia occurring several months or years postoperatively are reported in 1%–7% of patients who underwent hysterectomy for cervical intraepithelial neoplasia (CIN) treatment.[4–7] Other studies reported that hysterectomy for the treatment of CIN itself was identified as the risk factor of VaIN occurrence.[8–10] Vaginal intraepithelial neoplasia after hysterectomy is a frustrating situation for doctors and patients who considered hysterectomy as a definitive treatment for CIN. Although VaIN shares almost similar risk factors with CIN, including human papillomavirus (HPV) 16 and 18 infections, immunosuppression, smoking, and multiple sexual partners.[11,12] Some patients who have undergone hysterectomy for CIN relapse with VaIN, but others do not.

Vaginal intraepithelial neoplasia is managed in various ways including follow-up without treatment, topical agent administration, laser treatments, radiation, lesion excision, and vaginal resection. However, there is no established standard treatment for VaIN to date.[13] Some studies reported that regardless of the management, patients diagnosed with high-grade VaIN are reported to have an increased risk of recurrence or progress to invasive cancer.[14,15] Another study of 127 patients with VaIN reported that VaIN grade was not associated with the presence of treatment.[16] Furthermore, risk factors for VaIN recurrence or persistence after hysterectomy for CIN and how to reduce them remain to be elucidated. The need for low-grade VaIN treatment also remains unclear.

This study aimed to identify risk factors of VaIN in patients who underwent hysterectomy for the treatment of CINs and explore the best possible treatment options to minimize the risk of further recurrence.

METHODS

This retrospective cohort study was conducted using medical records of patients who underwent total hysterectomy for CIN treatment from January 2001 to August 2019 at the Seoul National University Bundang Hospital. The institutional review board of our institution approved this study (B-2005-612-104).

A total of 374 patients histologically diagnosed with CIN 1, 2, 3, carcinoma in situ, and adenocarcinoma in situ who underwent total hysterectomy were included in this study. Patients diagnosed with cervical cancer or VaIN history preoperatively or concurrently diagnosed with VaIN were excluded. Patients who underwent radiation therapy on the pelvis preoperatively and those in immunosuppressed status were also excluded. Patients who underwent subtotal hysterectomy were also excluded. Hysterectomy was performed via laparotomy or minimal invasive surgery (MIS), including robotic and laparoscopic surgery. Resection margin after hysterectomy was considered to be involved when high-grade CINs were reported.

During the follow-up period after hysterectomy, PAP smear was performed at 3–6 months after hysterectomy. For the PAP smear, conventional cytology was used until 2003 and liquid-based cytology

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TABLE 1. Demographic and Clinicopathologic Characteristics of the Patients ($N = 374$)

Characteristics	*n* (%)
Age at hysterectomy, y	
Mean ± SD	54.37 ± 35.35
≤50	214 (57.2)
>50	160 (42.8)
Parity	
0	12 (3.2)
≥1	351 (93.9)
Unknown	11 (2.9)
Initial histology	
CIN 1	17 (4.6)
CIN 2	12 (3.2)
CIN 3/CIS	294 (78.6)
AIS	51 (13.6)
HPV infection	
HPV 16 or HPV 18	63 (16.8)
Neither HPV 16 nor 18	311 (83.2)
Surgical approach of hysterectomy	
MIS	342 (91.4)
Open	32 (8.6)
Resection margin involvement[a] after hysterectomy	
Yes	9 (2.4)
No	354 (94.7)
Unknown	11 (2.9)
VaIN1+ after hysterectomy	36 (9.6)
VaIN1	13 (3.5)
VaIN2	6 (1.6)
VaIN3	15 (4.0)
Carcinoma	2 (0.5)[b]
Primary treatment modality of VaIN	
Observation	11 (2.9)
Laser vaporization	21 (5.6)
Vaginal resection	2 (0.5)
Second recurrence of VaIN	
Yes	14 (41.2)
No	20 (58.8)
Follow-up period, median (range), mo	32 (0–193)

AIS, adenocarcinoma in situ; CIS, carcinoma in situ.

[a]Involvement with high-grade lesions.

[b]Two with cancer recurrence were transferred to other hospitals and lost to follow-up.

afterward. Colposcopy-directed biopsy was performed in case of abnormal cytology.

For VaIN treatment, laser ablation was applied for lesions at vaginal vault suture line and extending into dog ear according to the institutional protocol using a CO_2 laser (AcuPulse Model; Lumenis Lasers, Inc). Before laser vaporization, we applied 3% acetic acid and Lugol solution to demarcate the lesion.

Recurrence of VaIN 1, 2, 3, or vaginal cancer (1+) was defined as histological confirmation of VaIN 1, 2, 3, or vaginal cancer by colposcopy-directed biopsy during the follow-up period after the total hysterectomy. The second VaIN1+ recurrence was defined as a histological confirmation of VaIN 1, 2, 3, and vaginal cancer by punch biopsy during the follow-up observation after the VaIN1+ treatment. Recurrence-free survival (RFS) was defined as the period from the time of negative PAP result after the VaIN1+ treatment after hysterectomy to the second VaIN1+ recurrence.

To analyze the correlation between the VaIN1+ recurrence after a total hysterectomy and clinicopathologic factors, Pearson χ^2 test and Fisher exact test were used for categorical variables and Student *t* test for continuous variables. Fisher exact test was used to identify the relationship between adjuvant treatments and second VaIN recurrence. Multiple logistic regression analysis was used to analyze risk factors of VaIN1+ recurrence. Cox proportional hazard regression model was used to determine covariates significantly associated with second VaIN1+ recurrence. Kaplan-Meier survival curve and log-rank test were used to compare RFS according to treatment modality. SPSS software (version 21.0; SPSS, Inc, Chicago, IL) was used for all statistical data analyses.

RESULTS

In this study, a total of 374 patients who underwent total hysterectomy due to CIN were included. The median follow-up period was 32 (0–193) months. Patient demographic and clinicopathologic characteristics are listed in Table 1.

The mean age of patients at the time of hysterectomy due to CIN was 54.37 ± 35.35 (mean ± SD) years. For initial histology, 17 patients (4.5%) were diagnosed with CIN 1 with benign diseases, such as myoma, adenomyosis, endometrial hyperplasia with abnormal uterine bleeding, or cervical obliteration making punch biopsy or cervical excision difficult. Thirty-six patients (9.6%) had VaIN1+ recurrence after hysterectomy. Among them, 2 with cancer recurrence were transferred to other hospitals and lost to follow-up. For VaIN treatment of the 34 patients, laser vaporization was performed in 21 patients (61.8%), vaginal resection in 2 (5.9%), and observation in 11 (32.3%). Thereafter, 14 patients (41.2%) had second VaIN1+ recurrence. No patient had vaginal cancer at the second recurrence.

The clinicopathologic characteristics of the group with VaIN1+ recurrence after hysterectomy are listed in Table 2.

The age of the recurrence group was 57.42 ± 11.74 (mean ± SD), which was significantly higher than that of the nonrecurrence group, that is, 50.77 ± 11.43 ($p = .001$). In addition, a significant relationship was observed between the recurrence and positive resection

TABLE 2. The Association Between Clinicopathologic Factors and VaIN1+ After Hysterectomy

	Recurrent VaIN1+		
Factors	No (*n* = 338)	Yes (*n* = 36)	*p*
Age at hysterectomy, y	50.77 ± 11.43	57.42 ± 11.74	.001
Parity	2.11 ± 1.06	2.10 ± 1.27	.967
Initial histology			.673
LSIL	15 (4.4)	2 (5.6)	
HSIL	323 (95.6)	34 (94.4)	
HPV infection			.097
HPV 16 or 18	53 (15.7)	10 (27.8)	
Neither HPV 16 nor 18	285 (84.3)	26 (72.2)	
Surgical approach of hysterectomy			.216
MIS	311 (92.0)	31 (86.1)	
Open	27 (8.0)	5 (13.9)	
Resection margin involvement[a]			<.001
No	327 (96.7)	27 (75)	
Yes	0 (0.0)	9 (25)	

Values are presented as *n* (%) or mean ± SD.

[a]Involvement with high-grade lesions.

TABLE 3. Logistic Regression Analysis of Risk Factors for VaIN1+ After Hysterectomy

	Univariate			Multivariate		
Variables	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Age, ≤50 (ref) vs. >50, y	3.418	1.63–7.18	.001	3.359	1.60–7.07	.001
Parity	0.993	0.70–1.41	.967			
Initial histology, LSIL (ref) vs. HSIL	0.789	0.17–3.60	.760			
HPV 16 or 18, none (ref) vs. either	2.068	0.94–4.54	.070	1.979	0.89–4.41	.095
Resection margin involvement,[a] no (ref) vs. yes	1.957E+10	—	.999			
Surgical approach of hysterectomy, MIS (ref) vs. open	0.538	0.19–1.50	.235			

HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; OR, odd ratio.

[a]Involvement with high-grade lesions.

margin involvement ($p < .001$). Parity, initial histology, positive or negative for HPV 16 or 18, and MIS operation were not associated with recurrence.

Results of univariate and multivariate logistic regression analyses, performed to identify risk factors of VaIN1+ recurrence after hysterectomy, are shown in Table 3. The analysis revealed that age of greater than 50 years (odds ratio, 3.359; 95% CI, 1.598–7.071; $p = .001$) was the only statistically significant independent risk factor for the recurrence.

Table 4 depicts the results of univariate and multivariate Cox regression analyses on risk factors of the second VaIN1+ recurrence. Laser vaporization (hazard ratio, 0.125; 95% CI, 0.03–0.59; $p = .009$) was the only significant independent good prognostic factor for the second recurrence. Among the 13 patients with VaIN1, 4 who underwent laser vaporization had no recurrence, and 3 of 9 patients (33.3%) without further treatment had relapses. The significant difference of recurrence was statistically significant ($p = .026$).

Figure 1 illustrates the Kaplan-Meier curves for RFS of patients with VaIN1+ after hysterectomy treated by laser vaporization or observation. The patient treated by laser vaporization had longer time to second recurrence than those under observation (mean time to subsequent recurrence, 128.7 [95% CI, 101.4–156.0] vs. 41.8 [95% CI, 15.7–67.9] months; $p = .003$).

One of the 2 patients who underwent vaginal resection relapsed, with the mean time to subsequent recurrence of 49.5 (95% CI, 48.8–50.2) months.

DISCUSSION

In our study, the recurrence rate of VaIN1+ after hysterectomy for CIN was 9.6% and was relevant to age ($p = .001$) and resection margin involvement of hysterectomy specimen ($p < .001$). Age of greater than 50 years was the independent risk factor for VaIN1+ ($p = .001$). Rate of the second VaIN1+ occurrence was 41.2%. In addition, the laser vaporization procedure for the VaIN1+ treatment was identified as the independent good prognostic factor of the second recurrence ($p = .009$).

Patients with all grades of VaIN were included in this study. Because no optimal treatment guideline was available for each VaIN grade to date, the need for VaIN1 treatment remains unknown.[17] In clinical management, deciding whether to treat VaIN1 is often difficult, especially when it persists. In a previous study of 163 patients with VaIN, grade was not a risk factor for recurrence.[18] Vaginal intraepithelial neoplasia persisted and recurred regardless of the grade, and the median time to progression was not statistically different according to the grade.[18] In another study of 127 patients with VaIN, the persistence or recurrence rate of VaIN during the 34-month average follow-up period was 11%, indicating no significant association with grade or treatment.[16] Therefore, not only high-grade VaIN but also low-grade VaIN was considered as recurrence in our study.

Vaginal intraepithelial neoplasia incidence rate of 9.1% in our study after total hysterectomy for CIN treatment is similar to

TABLE 4. Cox Regression Analysis of RFS for the Second Recurrence of VaIN1+

	Univariate			Multivariate		
Variables	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age, ≤50 (ref) vs. >50, y	4.912	0.64–37.60	.125	3.640	0.45–29.34	.225
Parity	1.165	0.78–1.73	.450			
HPV 16 or 18, no (ref) vs. yes	0.396	0.09–1.77	.226			
Initial histology, LSIL (ref) vs. HSIL	0.675	0.09–5.19	.706			
Resection margin involvement,[a] no (ref) vs. yes	0.155	0.02–1.19	.073	0.189	0.02–1.50	.115
Surgical approach of hysterectomy, MIS (ref) vs. open	0.875	0.20–3.92	.862			
Treatment of VaIN1+ after hysterectomy						
Observation (ref)						
Laser vaporization	0.224	0.07–0.69	.009	0.125	0.03–0.59	.009
Vaginal resection	0.369	0.05–2.97	.347			
Histology at recurrence, LSIL (ref) vs. HSIL	0.531	0.18–1.54	.243	2.696	0.60–12.19	.198

[a]Involvement with high-grade lesions.

HR, hazard ratio; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

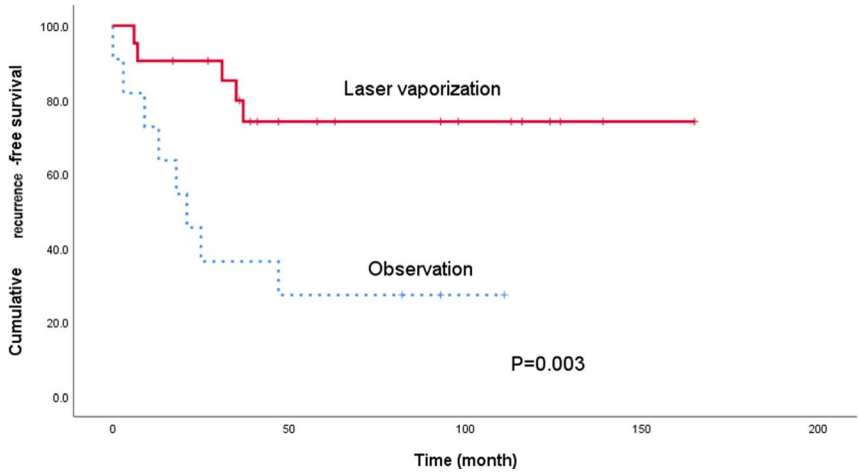

FIGURE 1. Kaplan-Meier survival curves for recurrence 1 free survival of VaIN1+ according to management. Laser vaporization (n = 21); observation (n = 11).

or slightly higher than that in the previous studies that reported between 1% and 7%.[12–15] Although this could be due to the smaller sample size in this study, this could also be due to the increased detection rate after the expansion of cytologic screening and colposcopy as compared with the time when the previous studies were conducted.[1,2,4–7] In addition, in our study, old age was identified as an independent VaIN1+ risk factor for patients who underwent hysterectomy due to CIN. A previous study also demonstrated that patients who developed VaIN 2 or 3 or vaginal cancer after hysterectomy for CIN were significantly older than those who did not.[7] Moreover, in univariate analysis, the resection margin status of hysterectomy specimens was associated with VaIN1+ occurrence afterward ($p < .001$). Another study explained that insufficient vaginal cuff excision might be related to the early recurrence. Hence, they recommended that at least 1 cm of the vaginal wall should be removed when performing hysterectomy for CIN III.[19] Furthermore, another study advised that patients scheduled hysterectomy for CIN would undergo more careful and thorough colposcopic assessment to determine vaginal involvement.[10]

Human papillomavirus infection is a well-known risk factor of VaIN and vaginal cancer.[20] The infection of high-risk HPV (either 16 or 18) was significantly related to VaIN relapse in the study with previously hysterectomized patients.[21] In our study, although the positivity of HPV 16 or 18 was not related to VaIN1+ recurrence (p = .097), its positive rates were higher in the group with VaIN1+ recurrence (27.8% vs. 15.7%). The statistical insignificance might be due to the small number of patients in our study.

The initial VaIN grade was not an independent risk factor for both the first and second VaIN1+ recurrence. Furthermore, in subgroup analysis of VaIN 1, laser vaporization was significantly associated with lower second recurrence (p = .009). In treating VaIN1, laser vaporization could be more beneficial than observation. Vaginal intraepithelial neoplasia itself is reportedly at high risk of recurrence.[22] In this study, the rate of the second VaIN1+ recurrence after the first recurrence was 41.2%. Moreover, the laser vaporization procedure was a statistically significant good prognostic factor based on multivariate analysis (p = .009), and the duration until the second recurrence was significantly longer (p = .003). Laser vaporization might be the safe and efficient treatment for VaIN for CIN after hysterectomy. Research on laser treatment has been prevalent and recommended in previous studies.[21] A study of 28 VaIN patients who underwent hysterectomy for CIN or cervical cancer found that laser vaporization was beneficial for the treatment of VaIN.[19] In this study, the severity of VaIN was an independent risk factor for VaIN recurrence or persistence, which is contrary to our results.

Currently, there is no standard treatment for VaIN recurrence at posthysterectomy for CIN. The main advantage of our study is that it provides useful information in managing these patients. Furthermore, our results indicate that careful and regular follow-up should be considered in patients who underwent hysterectomy for CIN especially those older than 50 years.

This study has limitations in that it is conducted retrospectively with a small size of sample from a single center. Furthermore, treatment option was determined by each physician's discretion, which may induce bias possibly affecting the results of the study because of the retrospective design of the study. There could also be a limitation in that the intervals between follow-up observation during the surveillance period after a total hysterectomy for CIN were uneven. Moreover, the confounding effects of the immunosuppressive conditions of each subject were not controlled because of their heterogeneity.

In conclusion, patients older than 50 years who underwent hysterectomy for the treatment of CIN seem to have significantly increased risk of VaIN recurrence. Laser vaporization could more effectively reduce the second VaIN recurrence than vaginal resection or observation.

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