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Follow-Up of HPV Clearance after LEEP Conization and Vaporization for CIN2+, and Vaporization for VaIN2

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Abstract

LEEP conization with vaporization was performed for 86 CIN2+ cases. Our data suggest that combining LEEP conization and vaporization results in a higher estimated cumulative HPV clearance rate than LEEP alone. The clearance rate tended to be better in younger patients. Vaporization could provide a promising therapeutic option for VaIN2 associated with high-risk HPV infection. Treatment of CIN2+ and VaIN2 using ball electrode vaporization and LEEP conization appears feasible and effective, even in settings lacking specialized surgical devices. After conservative treatment of CINs or VaIN, HR-HPV persists in some cases even in the NILM state without dysplasia, and long-term follow-up is needed.

Keywords

HPV, CINs, LEEP Conization, Vaporization, VaIN

1. Introduction

Persistent infection with high-risk human papillomavirus (HPV) is well-established as the leading cause of both cervical cancer [1] and vaginal stump cancer [2]. The progression risk from cervical intraepithelial neoplasia (CIN) to cervical cancer is closely linked to the specific genotype of HR-HPV present [3]. Conse-

quently, HPV genotyping serves as an essential tool in monitoring CIN1/2 patients during follow-up [4]. In contrast to many Western countries where HPV vaccination has been systematically implemented, Japan initiated its national vaccination program in 2013. However, due to safety concerns raised by reported adverse events [5], the government suspended proactive recommendations until 2023. As a result, a substantial proportion of women in Japan have remained unvaccinated. While there are no direct data on the prevalence of CINs and VaINs in Japan, we have cited the annual incidence of cervical cancer: the prevalence of cervical cancer in Japan is about 10,000 cases per year [6]. The prevalence of CIN3 may be two to three times higher, as 30% to 50% of untreated CIN3 cases progress to invasive cervical cancer [7]. The prevalence of VaINs is reported to be 100 times lower than CINs [8]. Our previous research addressed HPV genotype distribution at a single Japanese institution with low vaccination coverage, while also evaluating short-term clearance outcomes following loop electrosurgical excision procedure (LEEP) conization combined with vaporization for CIN2$^+$ lesions [9]. The addition of peripheral tissue vaporization appeared to enhance lesion removal and HPV clearance, producing outcomes comparable to LLETZ or LEEP combined with CO_2 vaporization [9]. LLETZ, and LEEP and CO_2 laser vaporization achieve better HPV reduction rates than LEEP alone, but LLETZ may be associated with subsequent obstetric complications [10], and LEEP and CO_2 laser vaporization require special equipment, so in the present study, we investigated the effectiveness of LEEP and vaporization therapy. Although LEEP conization is recognized as a standard treatment for CIN2$^+$, recurrence has been linked to both residual disease and persistent HPV infection [11]-[15]. Negative surgical margins combined with HPV clearance are strong predictors of favorable outcomes, whereas persistent HPV infection substantially raises the likelihood of recurrence, even when excision margins are clear [16]. This underscores the importance of structured long-term monitoring, including HPV testing, cytology, and colposcopy after LEEP conization [9]. In the present study, follow-up was systematically conducted at 1.5, 6-, 12-, 24-, and 36-months post-treatment, including HPV testing, cytological evaluation, and colposcopic inspection.

Separately, vaginal intraepithelial neoplasia (VaIN) can be detected in the vaginal stump during cytological screening, irrespective of prior cervical pathology or hysterectomy status [8]. VaIN is classified as a precancerous lesion that may progress to invasive cancer if untreated [2] [17]. For VaIN2/3, clinical intervention is generally warranted [17], although the optimal management strategy for VaIN2 associated with HR-HPV remains uncertain. Existing approaches—including surgical excision, laser vaporization, photodynamic therapy (PDT), and topical treatments—may risk damaging healthy surrounding tissue [17]. Within this study, patients diagnosed with VaIN2 were offered electro-vaporization, and subsequent follow-up included serial HPV genotyping, cytology, and colposcopy to assess treatment response.

2. Materials and Methods

Patient Selection

The present study design is illustrated in Figure 1. This study was conducted at Gujo City Hospital, where patients exhibiting abnormal cervical cytology between January 2021 and December 2024 underwent colposcopic evaluation using the DZ-C100 system (CASIO Co., Ltd., Japan). Biopsy samples were histologically classified following the World Health Organization (WHO) criteria, encompassing LSIL/CIN1, HSIL/CIN2, HSIL/CIN3, and carcinoma in situ (CIS) [18]. Vaginal lesions were also categorized as LSIL/VaIN1, HSIL/VaIN2, or HSIL/VaIN3 [19]. Patients diagnosed with CIN2$^+$ or VaIN2 were enrolled in follow-up between January 2013 and December 2023.

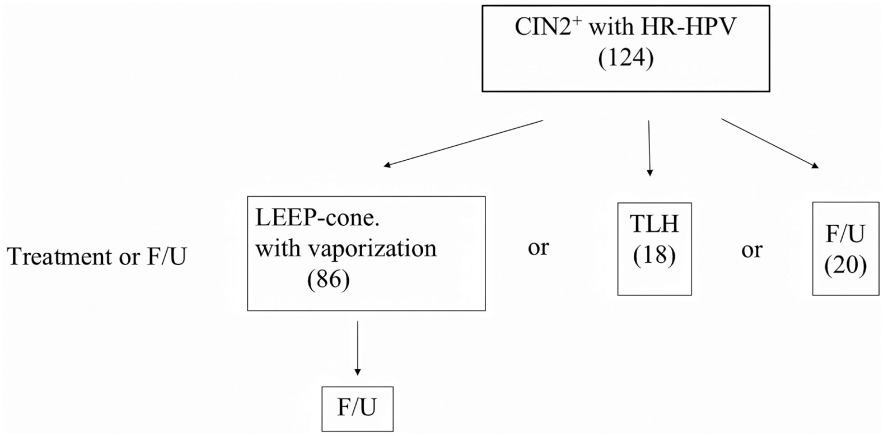

Figure 1. Study the flowchart. A total of 86 cases were submitted to the LEEP conization with vaporization.

HPV Detection

Genotyping of HPV was performed on all patients with histologically confirmed CIN2-3, CIS, or VaIN2-3 following colposcopy-guided biopsy. Typing was outsourced to SRL Inc. (Tokyo) and executed via the Luminex × MAP platform [20]. A threshold of ≥1000 viral DNA copies defined a positive result. This method targeted high-risk genotypes including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Postoperative HPV testing was conducted at approximately 1.5 months after LEEP conization and vaporization, once wound healing was complete. For patients remaining HPV-positive, further testing was performed at 6-month intervals until HPV clearance was confirmed. Cytology and colposcopic examinations were carried out alongside HPV testing; if HPV had cleared, subsequent follow-up was limited to cytology and colposcopy annually.

LEEP Conization and Vaporization

Prior to excision, colposcopy was used to delineate lesion margins. Under intravenous anesthesia (pentazocine and thiamylal sodium) combined with local administration of 1% lidocaine, LEEP conization was performed using a high-frequency electrosurgical generator. The loop size (Megadyne Medical Products Inc.,

Draper, UT, USA) was selected based on the extent of cervical involvement. Lesion margins were pre-marked with a 3-mm diameter ball electrode, ensuring at least a 5 mm safety distance before excision at 60 W continuous wave output. The LEEP conization technique consisted of a cone-shaped cut using a 40W continuous wave (ERBE Elektromedizin GmbH, Germany), and hemostasis was achieved using the same 3-mm diameter ball electrode set at 60 W. Vaporization was performed using 60 W coagulation mode (ERBE Elektromedizin GmbH) [21] with the same ball electrode to ensure there were no gaps for vaporization. The same area was vaporized for about 0.1 seconds, and this was the target of the cervix, but even with VaIN3, the thickness was less than 0.5 mm [22], so vaporization was about 1mm. To reduce the risk of recurrence, the peripheral tissue surrounding the excised area was vaporized extensively (**Figure 2(a)**). "Peripheral tissue" refers to the area surrounding the resection site. Vaporization was performed broadly near the vaginal fornix, ensuring that adjacent areas were not affected. Resected specimens were oriented, fixed on corkboards, and preserved in 10% buffered formalin. Final diagnoses followed WHO standards, and all surgical margins were reviewed. Immunohistochemical p16 staining (clone E6H4, Roche Diagnostics, Basel, Switzerland) was performed according to manufacturer instructions [23] to validate CIN diagnosis. Postoperatively, patients not seeking future pregnancies were advised to use condoms to minimize reinfection risks.

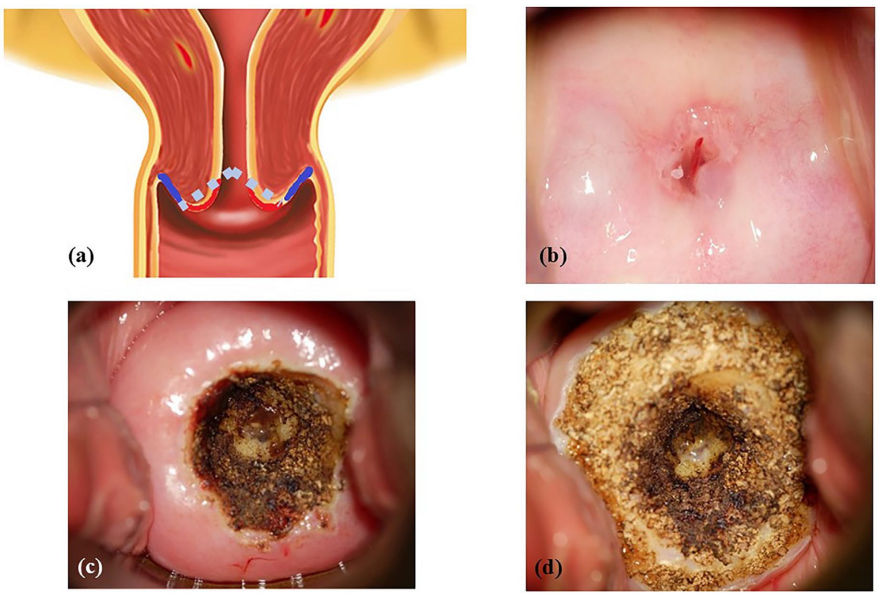

Figure 2. A characteristic case. (a) Shema of LEEP conization and vaporization. CIN lesion showed a red line, a light blue line revealed a cut-line by LEEP conization, and dark blue lines showed the vaporized area. (b) Before the LEEP conization, colposcopy findings showed thickened white epithelium with coarse punctation. (c) Findings after hemostasis with LEEP conization. (d) The area around the excised lesion was vaporized with the ball electrode as widely as possible.

Management of VaIN2 with HR-HPV

Patients with VaIN2 associated with HR-HPV were primarily monitored conservatively. However, for those opting for immediate intervention, electro-vaporization was offered. Procedures were carried out using a 3 mm diameter ball electrode at 60 W continuous wave (ERBE Elektromedizin GmbH) under intravenous anesthesia. Since VaIN lesions typically extend no deeper than 0.5 mm [22], vaporization was performed in a broad but superficial fashion (about 1 mm) to minimize unnecessary injury to healthy mucosal tissues.

3. Results

LEEP Conization and Vaporization for CIN2$^+$

124 cases of CIN2$^+$ associated with HR-HPV were identified during the study period (**Figure 1**). Of these, 86 patients underwent LEEP conization combined with vaporization. Notably, only one of these patients had a history of quadrivalent HPV vaccination, yet progression to CIN3 occurred due to HPV type 52, which is not targeted by the vaccine. The remainder of the cohort had no prior HPV vaccination history. Catch-up vaccination, when administered post-treatment, was only offered after confirming HR-HPV negativity.

Figure 2 and **Figure 3** illustrate representative cases, including a patient with HPV52-associated CIN3 confirmed by colposcopic biopsy. The clinical process is depicted from preoperative colposcopic findings (**Figure 2(b)**) to immediate post-procedural hemostasis (**Figure 2(c)**) and peripheral vaporization (**Figure 2(d)**).

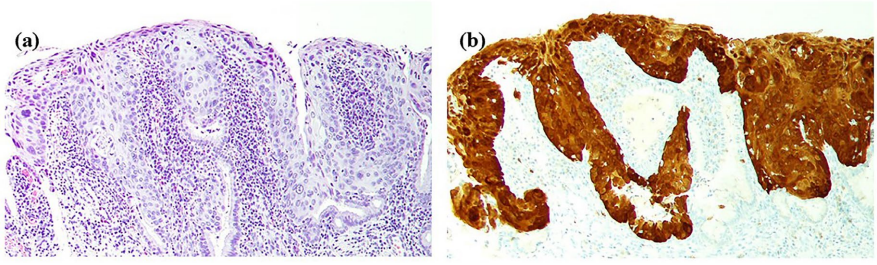

Figure 3. A characteristic case. (a) A colposcope-targeted biopsy revealed CIN3 with hyperchromatic nuclei in all layers (Hematoxylin & Eosin staining, × 50). (b) The nuclei were positive for p16, suggesting HPV infection (sABC staining, × 50).

The HPV genotypes in the CIN treatment group are shown in **Table 1**.

Final histopathological assessments for the 86 cases revealed:

- CIS: 5 cases;
- CIN3: 23 cases;
- CIN2: 58 cases.

The mean age of the treatment group was 45.8 ± 16.3 years.

Although two cases demonstrated positive surgical margins on histopathological review, subsequent colposcopic and cytological examinations post-healing showed no evidence of residual or recurrent disease.

One exemplary case (**Figure 3(a)**) involved CIN3 with strong p16 immunoreactivity (**Figure 3(b)**) and HPV52 infection.

Table 1. HPV genotypes in 86 patients of the LEEP conization and vapolization group.

HPV genotypes	No. of cases	Coexistence with other genotypes (%)
16	16 (18.6%)	4 (25%)
18	3 (3.5%)	1 (33.3%)
31	5 (5.9%)	3 (60%)
33	3 (3.5%)	0 (0%)
35	1 (1.2%)	0 (0%)
39	8 (9.3%)	3 (37.5%)
45	3 (3.5%)	1 (33.3%)
51	9 (10.5%)	2 (22.2%)
52	25 (29.1%)	2 (8%)
56	6 (7.0%)	1 (16.7%)
58	4 (4.7%)	0 (0%)
59	3 (3.5%)	0 (0%)

Analysis of HPV clearance trends suggested that patients aged ≥ 45 years exhibited higher early negative conversion rates, particularly for HPV16/18, although sample size limitations prevent firm conclusions. Estimated cumulative HPV clearance rates were calculated based on the proportion of HPV-negative cases at each follow-up time point, since the observation periods varied among participants, patients were discontinued from follow-up in this analysis. After 3 years, the cumulative clearance for HPV16/18-associated CIN2$^+$ was estimated at 83% (**Table 2**). Interestingly, for non-16/18 HR-HPV, younger patients (<45 years) displayed better clearance rates beyond the first year (**Table 3**).

Table 2. HPV estimated cumulative clearance rate in CIN2+ with HPV16/18.

	Pre-treatment (mean age) observation period	1.5 M	6 M	1Y	2Y	3Y
Total	18 (38.3 ± 12.9) 4.3 ± 2.4	13 (72%)	14 (78%)	15 (83%)	15 (83%)	15 (83%)
<45 years	15 (32.8 ± 6.0) 4.0 ± 2.2	10 (67%)	11 (73%)	12 (80%)	12 (80%)	12 (80%)
≥45 years	3 (60.0 ± 9.7) 5.3 ± 2.6	3 (100%)	3 (100%)	3 (100%)	3 (100%)	3 (100%)

Table 3. HPV estimated cumulative clearance rate in CIN2+ without HPV16/18.

	Pre-treatment (mean age) observation period (years)	1.5 M	6 M	1Y	2Y	3Y
Total	68 (46.0 ± 15.0) 3.2 ± 1.8	40 (57%)	45 (64%)	48 (69%)	52 (74%)	54 (77%)
<45 years	38 (34.2 ± 6.7) 3.1 ± 2.1	20 (53%)	24 (63%)	26 (68%)	29 (76%)	30 (79%)
≥45 years	30 (58.9 ± 10.1) 3.3 ± 1.5	20 (63%)	21 (66%)	22 (69%)	23 (72%)	24 (75%)

A summary of HPV clearance dynamics is illustrated in Figure 4. Kaplan-Meier curves of HPV clearance rates are also shown in Figure 5.

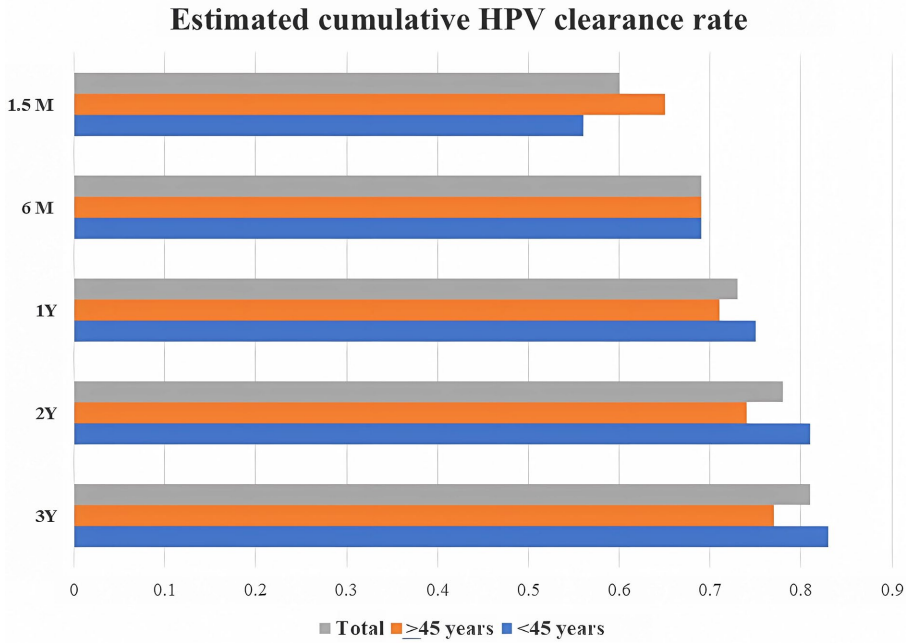

Figure 4. Estimated cumulative HPV clearance rates after LEEP conization and vaporization in 86 cases of CIN2$^+$ with high-risk HPV infection. Initially, patients aged ≥ 45 years showed a higher estimated cumulative clearance rate. However, after one year, the clearance rate tended to be higher among patients aged < 45 years.

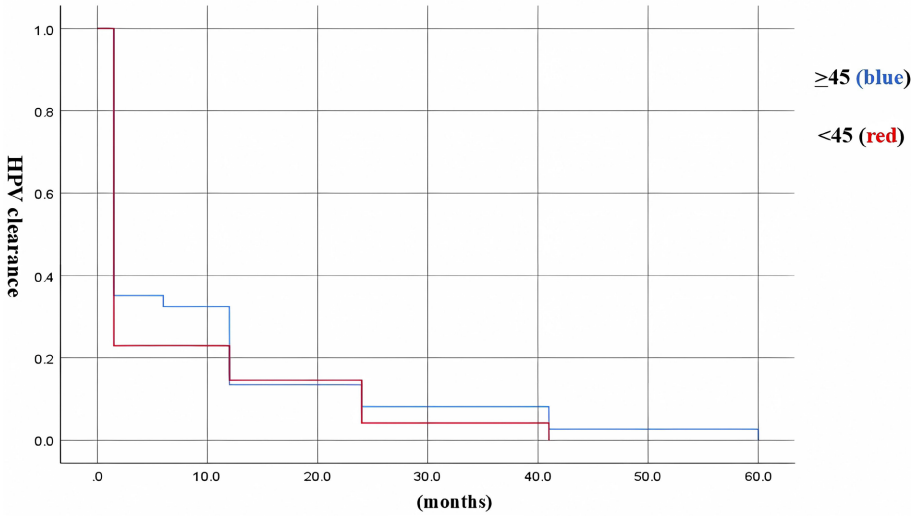

Figure 5. Kaplan-Meier curves of HPV clearance rates, divided into those aged 45 years (blue line) and under (red line). The log-rank (Mantel-Cox) method revealed no significant difference with a significance probability of 0.418.

Observational Follow-Up of Untreated CIN2$^+$ Cases

Among 20 patients electing surveillance over immediate treatment, five were infected with HPV16 or HPV18 (Table 4). One patient experienced spontaneous

clearance within one year, while two remained persistently infected for 2 - 5 years. Nevertheless, no lesion progression was observed. For the remaining 15 cases (non-16/18 HR-HPV), one achieved spontaneous clearance, and eight had persistent infection over extended follow-up (3 - 11 years). No cases showed lesion advancement. Eight patients discontinued follow-up.

Table 4. HPV status in untreated CIN2+ cases with HR-HPV.

Mean age [observation period[a)]]	Cases	Untreated	Disappeared	Drop-out[b)]
CIN2$^+$ with HPV16/18	5	2	1	2
38.4 ± 7.5 (3.4 ± 3.0)		worsening (−) (2 - 5 yrs)	1 yr	
CIN2$^+$ without HPV16/18	15	8	1	6
40.9 ± 16.1 (5.4 ± 3.4)		worsening (−) (3 - 11 yrs)	5 yrs	

[a)]Drop-out cases were countted until the time of consultation. [b)]moved or stopped to the hospital.

Total Laparoscopic Hysterectomy (TLH) Subgroup

Eighteen patients with concurrent gynecological pathology, including fibroids, opted for TLH as primary management for CIN2$^+$.

VaIN2 with HR-HPV

Among cases of VaIN2 diagnosed at the vaginal stump, 11 were confirmed HR-HPV positive. Three patients selected electro-vaporization using a ball electrode at 40 W continuous output. A representative example (**Figure 6**) involves a patient with prior TLH for CIN3 and subsequent diagnosis of VaIN2 associated with HPV68. Post-treatment assessments at 1.5 months demonstrated complete lesion clearance with negative HPV status.

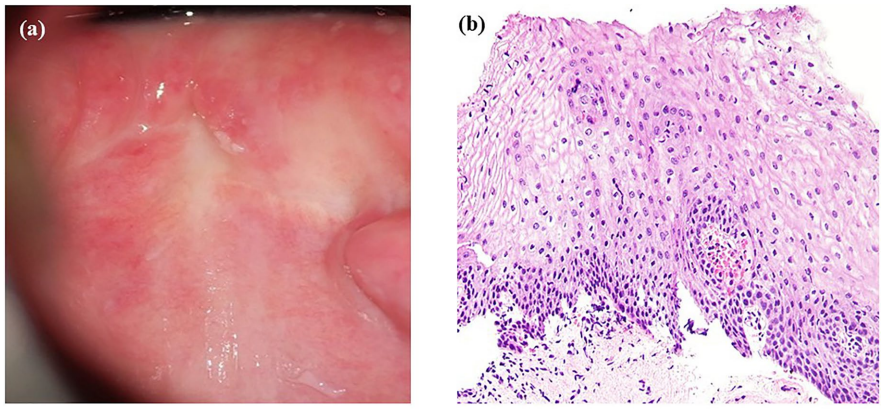

Figure 6. Representative case of VaIN2. (a) Following application of acetic acid, a slightly thickened acetowhite epithelium was observed at the vaginal stump. (b) Biopsy of this area confirmed the diagnosis of VaIN2.

In another treated case, HPV persisted despite cytological and colposcopic normalcy. A third case achieved long-term clearance for 2 years post-treatment before

recurrence was identified at 2.5 years, raising the possibility of reinfection or lesion relapse. Five VaIN2 cases managed conservatively were monitored for 5 - 13 years. Four exhibited persistent HPV infection without lesion progression, while one case showed spontaneous clearance within one year (Table 5).

Table 5. HPV status after vaporization, and untreated for VaINs cases with HPV-positive.

VaIN2 (mean age)	After vaporization status, at six months.			
Observation period[a] (yr)	cases	NILM[b] & HPV(−)	NILM but HPV(+)[c]	NILM & HPV(-) →VaIN2 & HPV(+)[d]
Vaporization (56.7 ± 4.5)	3	1	1	1
7.7 ± 4.5	(HPV genotype)	HPV68(+)	HPV52, 58(+)	HPV56(+)
		VaIN2(+) with HPV-positive.		
Untreated follow-up (54.3 ± 10.3)	5	4	worsening(−) (5 - 13 yrs)	
5.4 ± 4.1		1	disappeared (1 yr)	
	3	drop-out[e] (2 - 5 yrs)		

[a]Drop-out cases were counted until the time of consultation. [b]NILM, negative for Intraepithelial lesion or malignancy. but HPV(+). [c]NILM & no colposcopic abnormality but HPV(+). [d]NILM & HPV(−), until 2 yrs, but VaIN2(+) & HPV(+) after then, worsening (−) for 10 years. [e]moved or stopped to the hospital.

4. Discussion

Several previous investigations have established persistent HR-HPV infection and positive surgical margins as the primary predictors of CIN recurrence following conization [9] [11]-[15] [24]. In this study, although two cases exhibited positive margin status post-LEEP, no evidence of residual disease was detected during early postoperative surveillance, which included HPV testing, cytology, and colposcopic assessment. The additional peripheral tissue vaporization performed in conjunction with LEEP may have played a role in eliminating microscopic residual lesions.

CIN recurrence is known to increase over time when managed conservatively [14] [15]. Interestingly, throughout the follow-up period of up to three years, no recurrence was identified in this cohort, even among patients who exhibited persistent HPV positivity. These observations suggest that LEEP combined with adjunctive vaporization could lower the risk of early lesion recurrence, even in the presence of conventional risk factors.

While spontaneous clearance of HPV has been documented in the literature [24], a meta-analysis has shown that post-treatment clearance rates typically improve over time, with reported medians of 73% at 3 months, 79% at 6 months, 85% at 12 months, and 90% at 24 months [13]. In contrast, our observed clearance rates were slightly lower at each time point, reaching 82% at 3 years post-treatment.

Reports comparing treatment strategies suggest that the likelihood of HPV clearance is lower following LEEP alone when compared to cases treated with LEEP combined with CO_2 vaporization or LLETZ [13]. Similarly, the integration

of cold coagulation has been shown to improve clearance relative to LEEP monotherapy [25] [26]. However, unlike cold coagulation, which primarily serves a hemostatic function, our vaporization technique was designed to ablate adjacent tissues to eradicate any remaining subclinical disease. Although there is no histological evidence that vaporization therapy can remove remaining latent HPV infection, even VaIN3 is only 0.5 mm, and vaporization to a depth of about 1 mm, as we have done, is thought to be sufficient to vaporize the epithelium where HPV may be present. Electric vaporization involves increasing the temperature (burn) of the surrounding tissue by using high-frequency current, and depending on the depth, wound healing is said to be slower than with laser vaporization [21]. At the same depth, wound healing time is longer with electric vaporization [21]. The therapeutic effect is said to be the same regardless of the vaporization method, and vaporization has been reported to be more effective for HPV-positive CIN lesions than for the spontaneous regression of HPV [25]. Additionally, we agree that host factors such as immune response and wound healing may influence viral clearance. It has been reported that HPV recurrence is more frequent in immunosuppressed states [27], thus, a good immune response during tissue repair may be involved in preventing HPV recurrence.

Laser vaporization as monotherapy has also been reported as a successful treatment for CIN1 linked to HPV infection [27]. In the current study, although no colposcopic abnormalities were detected postoperatively, it is conceivable that residual subclinical HPV infection was present and eliminated through electro-vaporization. Our combination of LEEP conization and targeted vaporization minimized cervical tissue loss while avoiding the need for laser systems, presenting a cost-effective and practical alternative.

Previous systematic reviews have also reported that younger people have better clearance rates [16], and the spontaneous HPV clearance rates were higher in younger women [24]. It has also been reported that younger people have better outcomes in cases of persistent HPV infection associated with CINs [27]. In the present report, the estimated cumulative HPV clearance rate tended to be higher in patients under 45 years of age after one year or more than in patients over 45. This phenomenon would be difficult to explain but may be due to immunological differences between young and elderly patients [27]. Although spontaneous elimination has been reported [27], our findings suggest that the addition of vaporization to LEEP could improve the HPV elimination rate, as suggested by our findings. Compared with the findings of Hoffman *et al.* [13], our results indicate that LEEP conization combined with electric vaporization yields comparable cure rates and HPV clearance to more invasive procedures such as LLETZ and LEEP with CO_2 vaporization, which require specialized and more costly equipment.

Concerning VaIN2, persistent HR-HPV infection was common in our cases, yet lesion progression was not observed. For patients preferring active intervention, electro-vaporization was offered as a treatment option. Considering the limited depth of VaIN lesions (<0.5 mm) [23], this minimally invasive approach

seems appropriate. Notably, although all treated lesions regressed visually, HPV persistence was identified in two cases over prolonged follow-up, underlining the importance of continued surveillance even after apparent clinical remission.

In conclusion, after conservative treatment of CINs or VaINs, HR-HPV persists in some cases even in the NILM state without dysplasia, and long-term follow-up is needed.

5. Conclusion

This study suggests that LEEP conization combined with peripheral tissue vaporization represents a viable strategy for the management of $CIN2^+$ lesions. Throughout the follow-up period, HPV clearance rates observed in this cohort appeared comparable to those reported for LLETZ or LEEP performed with CO_2 vaporization. Additionally, the application of vaporization in VaIN2 cases linked to persistent HR-HPV infection showed promising outcomes, highlighting its potential as a therapeutic alternative. Given the straightforward technical requirements of this approach, relying on ball electrode vaporization rather than laser-based systems, it offers a practical and cost-effective option for healthcare settings lacking access to advanced surgical equipment. After conservative treatment of CINs or VaIN, HR-HPV persists in some cases even in the NILM state without dysplasia, and long-term follow-up is needed.

Consent

Consent was obtained from all patients before participation in this study. Written consent for publication was obtained for cases that included photographs and pathological specimens.

Ethical Approval

Ethical approval for this clinical study was granted by the Ethics Committee of Gujo City Hospital (Approval No. 24022902).

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Conflicts of Interest

All authors declare that they have no competing interests.

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Abbreviations

CIN, cervical intra-epithelial neoplasia; VaINs, vaginal intra-epithelial neoplasia; HC, hybrid capture; HPV, human papillomavirus; HR, high-risk; LEEP, loop electrosurgical procedure; LLETZ, large loop excision of the transformation zone; PCR, polymerase chain reaction; PDT, photodynamic therapy; TLH, total laparoscopic hysterectomy; NILM, negative for intraepithelial lesion or malignancy.