



ORIGINAL ARTICLE

Risk factors for recurrence of cervical intraepithelial neoplasia after loop electrosurgical excisional procedure in patients with positive margins

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Abstract

Aim: Loop electrosurgical excisional procedure (LEEP) is a major treatment method for cervical precancerous lesions. However, recurrence rates were estimated to be 15%, and the risk is increased if a surgical margin is involved by dysplastic cells. This study aimed to identify the risk factors for recurrence of cervical precancerous lesions in patients with positive margins.

Methods: We retrospectively reviewed medical records of patients who underwent LEEP between 2012 and 2014 and had a positive surgical margin. Clinicopathologic factors were collected, including age, parity, menopausal status, smoking, human papilloma virus infection, results of cytology/biopsy/LEEP, and specimen size and volume.

Results: A total of 117 patients with positive margins were included, and 26 (22.2%) patients had recurrence. According to a multivariate analysis, the recurrence rates were significantly higher in parous women (adjusted hazard ratio [HR], 2.92; 95% confidence interval [CI], 1.00–8.49), but positive margins at the exocervix (adjusted HR, 0.39; 95% CI, 0.17–0.91) and volume $\geq 4000 \text{ mm}^3$ (adjusted HR, 0.36; 95% CI, 0.16–0.82) showed negative correlation.

Conclusions: The risk of recurrence for cervical precancerous lesions increased in patients with a history of previous delivery, positive margin at the endocervix, and specimen volume of LEEP $< 4000 \text{ mm}^3$. These results could help gynecologists determine optimal treatment options for patients with positive margins.

KEYWORDS

cervical intraepithelial neoplasia, conization, LEEP, positive surgical margins, recurrence

INTRODUCTION

Cervical intraepithelial neoplasia (CIN) refers to the presence of dysplastic cells limited to the cervical epithelium, which can progress to cervical cancer without treatment.¹ In 2014, the incidence rates of CIN1-2 were estimated to be 425.4 per 100 000 and CIN3 was 39.8 per 100 000 in Korea.² The annual incidence is estimated to be 2.7 per 1000 women of all ages in the United States.³ The loop electrosurgical excisional procedure (LEEP) has been widely used as a standard treatment for cervical precancerous lesions; it plays a major role in the diagnosis and treatment of by removing and defining the extent of cervical lesion.⁴

Despite the satisfactory treatment efficacy of LEEP, recurrence rates are still high and reported to be 15%.⁵

Factors associated with recurrence of CIN are margin involvement, histologic grade, glandular involvement, persistent human papillomavirus (HPV) infection, age, and immunosuppression.^{6–8} A meta-analysis showed that relative risk was 5.47 in patients with positive margins for recurrent CIN.⁹ Nevertheless, management for these patients varies, including follow-up, repeated excision, or hysterectomy. However, an optimal treatment strategy remains controversial. Additionally, the sensitivity of the positive margin was low in predicting residual or recurrent CIN2-3.¹⁰ To determine which patients can benefit from treatment such as, repeated LEEP or hysterectomy, we performed this study to identify the predictive factors in patients who underwent LEEP for CIN and had margin involvement.

METHODS

We included patients who underwent LEEP for CIN between January 2012 and December 2014 at a tertiary institution, the Gachon University Gil Medical Center. Cervical intraepithelial neoplasia was diagnosed by colposcopy-directed biopsy (CDB) in whom abnormal cervical cytology was found. A positive margin was diagnosed if dysplastic cells were found at either the exocervical or endocervical resection margins. When surgical margin was not evaluable due to thermal artifact, pathologist reviewed the specimen and decided the margin status depending on cellularity, cell thickness, nucleus-to-cytoplasmic ratio, maturation, glandular involvement. After an initial LEEP, the patients revisited the clinic within 3–6 months and received liquid-based cytology, HPV test, colposcopy, and, if necessary, CDB. HPV genotyping was performed with Roche Cobas HPV test based on real-time polymerase chain reaction. Recurrence was identified if the cytology result was a high-grade squamous intraepithelial lesion (HSIL) or CIN2-3 was found on biopsy. This study was approved by the Institutional Review Board (GCIRB2019-282). All procedures involving human participants performed in this study complied with the Declaration of Helsinki (revised in 2013). The requirement for informed consent was waived because of the retrospective nature of the study.

Demographic findings, such as age, menopausal status, parity, results of cervical cytology and CDB, and status of HPV infection were retrieved from the medical records. We also collected the following pathological findings: severity of CIN, margin status, location of positive margin, presence of glandular involvement. The length and width of the LEEP specimen were determined by measuring the major and minor axes of specimen base and the depth was defined as the distance between distal margin and proximal margin of the specimen. The length, width, and depth of the specimens were obtained from the gross descriptions in the pathology reports. The volume of each specimen was determined by multiplying its length, width, and depth (Figure 1). In case of additional endocervical sweep or multiple sweeps due to

relatively large size of lesion, the sum of the specimen depths and volume were defined as the final depth and volume. For example, if the length, width, and depth

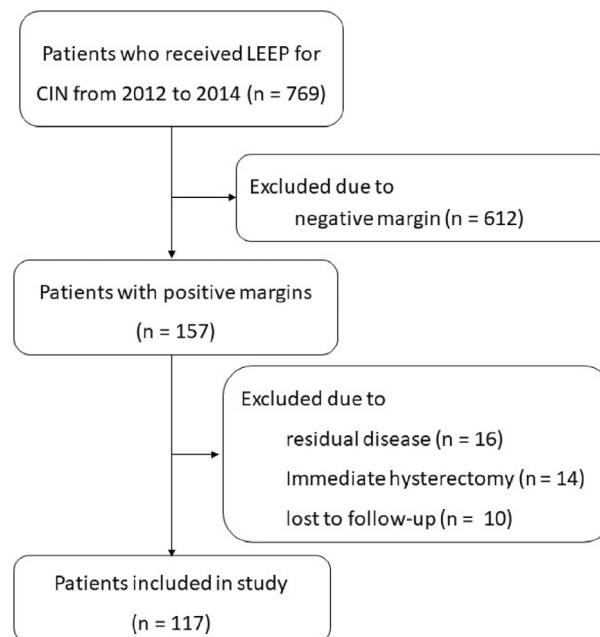


FIGURE 2 Study flow chart. LEEP, loop electrosurgical excisional procedure; CIN, cervical intraepithelial neoplasia.

TABLE 1 Baseline characteristics.

	Sample size (n = 117)
Age	41.65 ± 12.97
Menopause state	23 (19.7)
Nullipara	36 (30.8)
Smoking	24 (20.5)
Initial cytology	
LSIL	21 (17.9)
HSIL	96 (82.1)
HPV infection	
No	12 (10.3)
16/18	41 (35.0)
Other high-risk type	64 (54.7)
Degrees of CIN	
CIN1-2	21 (17.9)
CIN3-CIS	96 (82.1)
Depth (mm)	7.15 ± 3.20
Volume (mm ³) ^a	5650.36 ± 5070.70
Recurrence	26 (22.2)

Note: Data are expressed as mean (standard deviation) or number (%).

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

^aThe volume of specimen was determined by multiplication of length, width, and depth.

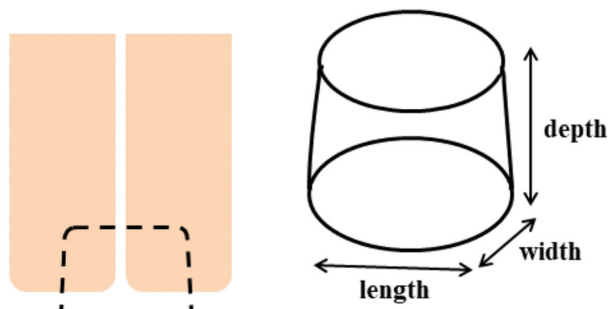


FIGURE 1 Histological measurements and definitions.

were identified as 15, 13, and 5 mm, respectively in pathologic report, the volume of specimen would be 975 mm³.

We compared patients with recurrence to those without recurrence to identify risk factors for recurrence. Additionally, we calculated the recurrence rates of patients with positive margins. Continuous data are expressed as mean $\pm$ standard deviation, and categorical data are presented as number of cases. Patient characteristics were compared using Student's *t* test and chi-square test. Cox proportional hazard regression analysis was used to determine the risk factors. All variables with a *p*-value ≤ 0.25 in the univariate analysis were included as explanatory variables. Disease-free survival (DFS) was defined as the interval between the

date of LEEP and recurrence date. Survival analysis was performed using the Kaplan–Meier method. Statistical analysis was performed using SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). The results were considered statistically significant if *p*-value was < 0.05 .

RESULTS

We identified 769 patients, of which 612 were excluded because of negative margins. An additional 40 patients were excluded because they had undergone immediate hysterectomy or were lost to follow-up (Figure 2). A total of 117 patients with positive resection margins were

TABLE 2 Comparison between patients with and without recurrence.

	No recurrence (<i>n</i> = 91)	Recurrence (<i>n</i> = 26)	<i>p</i> -Value
Age	40.5 $\pm$ 12.48	45.6 $\pm$ 14.13	0.08
Menopause			0.29
No	75 (82.4)	19 (73.1)	
Yes	16 (17.6)	7 (26.9)	
Parity			0.05
Nullipara	32 (35.2)	4 (15.4)	
≥ 1	59 (64.8)	22 (84.6)	
Smoking			0.46
No	71 (78.0)	22 (84.6)	
Yes	20 (22.0)	4 (15.4)	
Initial cytology			1.00
LSIL	17 (18.7)	4 (15.4)	
HSIL	74 (81.3)	22 (84.6)	
HPV infection			0.40
No	9 (9.9)	3 (11.5)	
16/18	30 (33.0)	11 (42.3)	
Other high-risk type	52 (57.1)	12 (46.2)	
Degrees of CIN			
CIN1	6 (6.6)	2 (7.7)	
CIN2	11 (12.1)	2 (7.7)	
CIN3	28 (30.8)	5 (19.2)	
CIS	46 (50.5)	17 (65.4)	
Number of specimens			0.18
1	57 (62.6)	20 (76.9)	
≥ 2	34 (37.4)	6 (23.1)	
Glandular involvement			0.56
No	16 (17.6)	3 (11.5)	
Yes	75 (82.4)	23 (88.5)	
Depth (mm)	7.05 $\pm$ 2.84	6.85 $\pm$ 3.17	0.76
Volume (mm ³) ^a	6013.33 $\pm$ 5431.68	3793.58 $\pm$ 2617.27	0.01

Note: Data are expressed as mean (standard deviation) or number (%).

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

^aThe volume of specimen was determined by multiplication of length, width, and depth.

analyzed, and their baseline characteristics are depicted in Table 1. The mean depth and volume of specimens were 7.15 mm and 5650.36 mm³. During median follow-up period of 23 months (range, 3–76 months), 26 patients (22.2%) experienced recurrence. Among patients with recurrent disease, 12 patients (46.2%) received LEEP again, 8 patients (36.8%) underwent hysterectomy, and others were lost to follow-up. The patients were compared between those with and without recurrence (Table 2). Among patients with recurrence, more patients were significantly parous ($p = 0.05$), and the volume of the specimen was smaller ($p = 0.01$). In contrast, no significant differences were detected in age, initial cytology, prevalence of HPV infection, and pathological findings of LEEP.

Table 3 presents the univariate analysis of risk factors for recurrence. We determined age ($p = 0.07$), parity ($p = 0.10$), specimen volume ≥ 4000 mm³ ($p = 0.03$), and location of the positive margin ($p = 0.03$) to be included in the multivariate analysis. However, degree of CIN, depth, persistent high-risk HPV infection after LEEP were not candidates for explanatory variables. Multivariate analysis showed that parous women were at higher risk of recurrence (adjusted hazard ratio [HR], 2.92; 95% confidence interval [CI], 1.00–8.49), while positive margins at the exocervix (adjusted HR, 0.39; 95% CI,

0.17–0.91) and volume ≥ 4000 mm³ (adjusted HR, 0.36; 95% CI, 0.16–0.82) lowered recurrence rates. However, age was not associated significantly with DFS (Table 4).

Mean duration of DFS was 48.60 ± 5.48 months in patients with specimen volume < 4000 mm³ and 57.95 ± 2.82 months in patient with volume ≥ 4000 mm³

TABLE 4 Multivariate analysis of factors associated with recurrence in patients with positive margin.

Characteristics	Adjusted HR	95% CI	<i>p</i> -Value
Age	1.00	0.97–1.03	0.93
Parity			
Nullipara	1		
≥ 1	2.92	1.00–8.49	0.05
Location ^a			
Endocervix	1		
Exocervix	0.39	0.17–0.91	0.03
Volume ^b			
< 4000 mm ³	1		
≥ 4000 mm ³	0.36	0.16–0.82	0.02

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aLocation of positive margin.

^bThe volume of specimen was determined by multiplication of length, width, and depth.

TABLE 3 Univariate analysis of factors associated with recurrence in patients with positive margin.

	No recurrence (<i>n</i> = 91)	Recurrence (<i>n</i> = 26)	HR (95% CI)	<i>p</i> -Value
Age	40.5 $\pm$ 12.48	45.6 $\pm$ 14.13	1.03 (0.99–1.06)	0.07
Parity				
Nullipara	32 (35.2)	4 (15.4)	1	
≥ 1	59 (64.8)	22 (84.6)	2.42 (0.83–7.03)	0.10
Degrees of CIN				
CIN1/2	17 (18.7)	4 (15.4)	1	
CIN3/CIS	74 (81.3)	22 (84.6)	1.15 (0.39–3.34)	0.80
HPV infection				
No	9 (9.9)	3 (11.5)	1	
Yes	82 (90.1)	23 (88.5)	0.81 (0.24–2.72)	0.74
Depth	7.05 $\pm$ 2.84	6.85 $\pm$ 3.17	1.05 (0.95–1.18)	0.36
Volume ^a				
< 4000 mm ³	37 (40.7)	17 (65.4)	1	
≥ 4000 mm ³	54 (59.3)	9 (34.6)	0.36 (0.16–0.82)	0.02
Location ^b				
Endocervix	41 (45.1)	18 (69.2)	1	
Exocervix	50 (54.9)	8 (30.8)	0.39 (0.17–0.91)	0.03
High-risk HPV after LEEP				
Negative/not checked	58 (63.7)	13 (50.0)	1	
Positive	33 (36.3)	13 (50.0)	1.42 (0.66–3.07)	0.37

Note: Data are expressed as number (%).

Abbreviations: CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; HPV, human papilloma virus; HR, hazard ratio; LEEP, loop electrosurgical excision.

^aThe volume of specimen was determined by multiplication of length, width, and depth.

^bLocation of positive margin.

($p = 0.01$). When DFS was analyzed according to the positive margin location, the mean duration was 47.15 ± 4.19 months in the group with positive margins at the endocervix and 64.56 ± 3.73 months in the group with positive margins at the exocervix ($p = 0.02$) (Figure 3).

DISCUSSION

Margin involvement has been reported to be a risk factor for CIN recurrence.⁹ Previous literatures found that cone depth was associated with margin involvement and a minimum of 9 mm depth should be removed to achieve free margin. However, there is no clear definition of adequate cone volume.^{11,12} Furthermore, it is still challenging for gynecologists to choose the optimal treatment for patients with positive margins. In this study, we performed a retrospective analysis to identify the risk factors for recurrence in patients with positive margins. The recurrence rate was 22.2% in our patients, and parous women were at higher risk than nullipara. However, women with positive margins at the exocervix or specimen volume $\geq 4000 \text{ mm}^3$ had a lower risk than their counterparts.

In this study, the patients visited our outpatient clinic 3–6 months after the LEEP, and recurrence was defined when the cytology or biopsy results were HSIL or CIN2-3. Similar criteria were used in other studies, except for follow-up intervals. A retrospective study identified recurrence if CDB and endocervical curettage found CIN and cancer, irrespective of severity at 3, 6, 12, 18, and 24 months of examination.¹³ Recurrence was determined as CIN2-3 lesions 1 year after LEEP in another study.¹⁴

HPV test or cervical cytology in 6 months was recommended by the American Society for Colposcopy and Cervical Pathology guidelines and Korean Society of Gynecologic Oncology, respectively.^{15,16}

Parity was significantly associated with recurrent CIN. A study conducted by Japan Society of Obstetrics and Gynecology also documented that high parity was one of the independent predictors of recurrence in patients with positive margins.¹⁷ However, gravidity was not related to increased risk of CIN.¹⁸ Eversion of transformation zone in multiparous women is susceptible to direct exposure to HPV infection and other contributing factors.¹⁹ Cervical trauma and cellular oxidative stress during delivery may facilitate damage to DNA, leading to HPV integration.²⁰

A positive endocervical margin was a predictive factor for recurrence in this analysis. Similarly, a retrospective study of 270 patients revealed that positive endocervical margins were associated with a higher risk of HSIL during follow-up than negative margins. Risk was even higher when positive margins were at both endocervical and deep resection margins.²¹ Additionally, a meta-analysis found that residual or recurrent CIN was more frequently diagnosed if the endocervical margin was positive than when only the exocervical margin was involved (16.3% and 7.2%, respectively).¹⁰

The length, width, and depth were multiplied to calculate the specimen volume. Other studies investigated the optimal size of the specimen to avoid positive margins or recurrence and determined the volume of specimens using the semi-ellipsoid volume formula ($\frac{2}{3} \times \pi \times A \times B \times C$), where A , B , and C refer to the length of three semi-axes of the ellipsoid.^{22–24} However, these studies

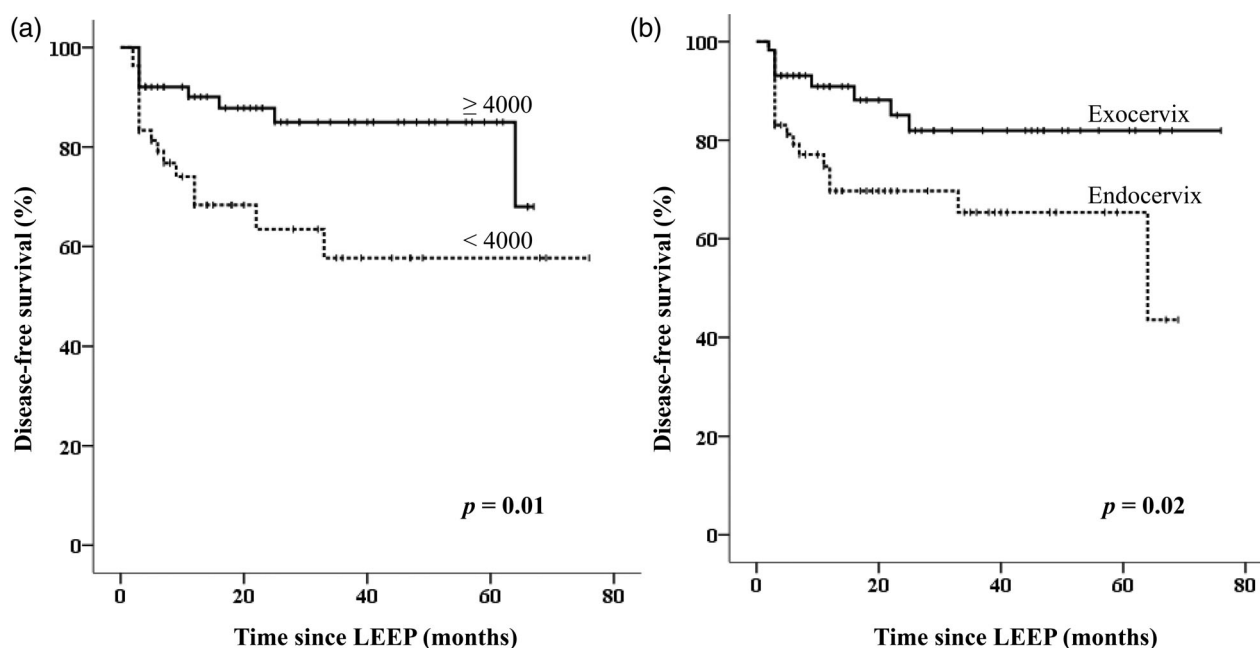


FIGURE 3 Disease-free survival stratified by (a) volume of specimen (mm^3) and (b) location of positive margins. The volume of specimen was determined by multiplication of length, width, and depth. LEEP, loop electrosurgical excisional procedure.

failed to find significant associations between the volume of the specimen and recurrence. However, we used a straightforward formula and found that the volume was related to recurrence.

A LEEP specimen volume of $<4000 \text{ mm}^3$ was an independent risk factor for recurrence compared to a larger volume. We found the median volume of specimens was 4277 mm^3 (interquartile range, 2125–7524). To identify the lowest volume associated with recurrence of CIN, we examined every 100 mm^3 around 4000 mm^3 . One study analyzed patients with positive margins who underwent hysterectomy after LEEP. It was found that disease volume of $\geq 50\%$ of the total specimen was associated with residual disease.²⁵ Additionally, the risk of residual disease was increased if >2 quadrants were involved by the disease.²⁶ To remove CIN effectively, one should perform LEEP for a sufficient volume of the cervix. Meanwhile, several studies reported inconsistent results regarding whether cone depth was an important risk factor.^{27–29} In our study, depth was not a significant factor. Therefore, further studies are required to define the predictive role of cone depth.

It is necessary to find optimal volume of LEEP specimens to avoid disease recurrence, however, previous literatures failed to correlate volume of specimens and recurrence of CIN.^{22–24} Furthermore, gynecologists frequently encounter difficulty in measuring volume of specimens when multiple fragments are removed. Our results identified a simple method to calculate volume of LEEP and cutoff value of 4000 mm^3 which predicts recurrence.

This study has certain limitations owing to its retrospective nature. LEEP procedure could not be standardized, and sample size could not be calculated before conducting study. Thus, the external validity of this study reduced and further studies with adequate sample size and standardization of the procedure are needed to confirm our data.

In conclusion, recurrence was significantly associated with parous women, positive margin at the endocervix, and specimen volume of LEEP $<4000 \text{ mm}^3$. Treatment, including repeated LEEP and hysterectomy, should be considered in patients with positive margins, especially, who have risk factors for recurrence.

AUTHOR CONTRIBUTIONS

Soo Hyun Oh analyzed and interpreted the data and drafted the manuscript. Kwang Beom Lee and Jin Woo Shin designed and conceptualized the study, analyzed, and interpreted the data, and revised the manuscript. Seungho Lee designed and conceptualized the study, revised, and supervised the manuscript for important intellectual content. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

The authors thank Yoojin Cho, MD and Kyungjoo Cho, MD for their great support for this study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests for this article.

DATA AVAILABILITY STATEMENT

The Institution Review Board and the privacy policy of our institution do not allow patient data collected for research purposes to be made publicly available. The data that support the findings of this study will be available on reasonable request and the authorization from the Institution Review Board and our institution is needed a priori.

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How to cite this article: Oh SH, Lee KB, Shin JW, Lee SH. Risk factors for recurrence of cervical intraepithelial neoplasia after loop electrosurgical excisional procedure in patients with positive margins. *J Obstet Gynaecol Res*. 2023;49(8): 2102–8. <https://doi.org/10.1111/jog.15704>