



Predictive Factors for Residual High-Grade Cervical Intraepithelial Lesions or Carcinoma on Final Pathology in Patients with Positive Surgical Margins After Cervical Conization and Endocervical Curettage

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ABSTRACT

Objective: To evaluate the presence of residual preinvasive or invasive cervical disease after re-conization or hysterectomy in women with positive surgical margins following excisional treatment for high-grade squamous intraepithelial lesions (HSIL), and to identify pathological factors that may be related to residual disease.

Material and Methods: This retrospective cohort included 48 women with positive ectocervical margins, endocervical margins, or endocervical curettage (ECC) margins after initial excisional procedures (cold-knife conization, loop electrosurgical excision procedure, or needle excision of the transformation zone). All patients underwent either re-conization or hysterectomy. Cone volume was calculated using the semi-ellipsoid formula ($\pi/6 \times \text{anteroposterior} \times \text{transverse} \times \text{length}$). Categorical variables, including margin type, ECC results, human papillomavirus status, and excisional technique, were compared using the chi-square test or Fisher's exact test.

Results: Residual HSIL or carcinoma was identified in 45.9% of patients undergoing repeat excision, whereas 54.1% had only low-grade intraepithelial lesions or no preinvasive lesion. Ectocervical margin positivity showed limited predictive value for residual high-grade pathology. Endocervical margin positivity and ECC positivity demonstrated similar distributions, with residual HSIL or carcinoma present in approximately half of these patients. Residual pathology occurred following both cold-knife conization and electrosurgical excisional techniques. Residual disease occurred more frequently after cold-knife conization than after electrosurgical techniques; however, this difference was not statistically significant ($p=0.051$).

Conclusion: Residual high-grade disease was detected in nearly half of the patients undergoing repeat surgery after a margin-positive conization. Although certain variables such as excisional technique and endocervical margin involvement showed numerical differences, none reached statistical significance. These findings suggest that no single clinical or pathological factor reliably predicts residual disease, and margin status alone may be insufficient to guide management decisions.

Keywords: Cervical intraepithelial neoplasia; conization; margin; HSIL; LEEP; NETZ

INTRODUCTION

Cervical high-grade squamous intraepithelial lesions (HSIL) represent a clinically significant stage within the spectrum of human papillomavirus (HPV)-associated cervical disease. These lesions constitute the primary target of excisional

treatment, aimed at preventing progression to invasive cervical cancer while providing definitive histopathological diagnosis.¹ HSIL can be effectively treated with excisional procedures such as cold knife conization (CKC), loop electrosurgical excision procedure (LEEP), and needle excision

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of the transformation zone (NETZ). However, surgical margins may be positive, creating significant clinical uncertainty for subsequent treatment.²

Excisional treatment is the standard of care for histologically confirmed cervical intraepithelial neoplasia (CIN) 2 and CIN 3 according to American Society for Colposcopy and Cervical Pathology (ASCCP) and European Society of Gynaecological Oncology (ESGO) guidelines, which emphasize achieving clear margins to minimize residual or recurrent disease.^{3,4} Positive surgical margins are reported in approximately 12-44% of excisional procedures. Higher rates (23-44%) have been reported after LEEP, while lower rates (12-29%) have been reported after CKC.^{5,6} Despite this, surgical margin status alone does not reliably predict persistent or residual HSIL. Many women with positive surgical margins do not demonstrate residual disease at follow-up or on repeat excision. In a large systematic review including 29 studies, residual CIN2+ was detected in 32.3% of margin-positive patients.⁷ Similarly, residual CIN2+ has been reported in approximately 34.3% of women with positive margins.⁸ These findings indicate that positive margins may be associated with a persistently high-risk of disease, but they also show that most patients have no residual lesions. Therefore, the margin status should be interpreted as a risk factor rather than a definitive indicator, and careful patient selection is important when considering re-excision. Several clinical and pathological features have been reported as potential predictors of residual disease after conization, including endocervical margin involvement, endocervical curettage (ECC) positivity, higher CIN grade, HPV 16/18 infection, and insufficient cone depth or volume. However, the predictive performance of these factors remains inconsistent across studies, and none has shown adequate accuracy to guide management in isolation.^{9,10}

The present study aims to investigate residual disease in women who underwent a repeat excision or hysterectomy following a margin-positive conization. Additionally, the clinical and pathological parameters that predict residual HSIL or cancer were evaluated.

MATERIAL AND METHODS

This retrospective cohort study included 48 women who had positive surgical margins for HSIL in the ectocervix, the endocervix, or both, and/or a positive ECC following an initial excisional procedure performed in patients with preinvasive cervical disease. All patients were managed at a single tertiary referral center between September 2019 and November 2024, and complete clinical and pathological records were available for review. Women who did not undergo a second surgical

procedure, who had incomplete pathology reports, or who were followed outside the institution were excluded. Initial excisional techniques consisted of CKC, LEEP conization, or NETZ, selected according to surgeon preference. Excisional procedures (CKC, NETZ, or LEEP) were performed in the operating room under general or regional anesthesia. As part of the standard surgical protocol to minimize bleeding and facilitate manipulation, a No. 0 polyglactin suture was placed at the 3- and 9-o'clock positions of the cervix. CKC was then carried out using a scalpel to remove the entire transformation zone. NETZ was performed with a 10.2-cm needle electrode (E-Z Clean Electrosurgical Tips; Megadyne Medical Products™, Draper, UT), whereas LEEP conization was performed with a 15-20-mm loop electrode. For both NETZ and LEEP conization, the electrosurgical generator was typically set to a 40-W pure-cut mode. ECC was routinely performed immediately after excision. Following tissue removal, hemostasis was achieved using a ball electrode with a ≥ 40 -W coagulation. For proper specimen orientation, a suture was placed at the 12 o'clock margin of the cone, and both the conization specimen and the ECC sample were submitted to pathology in separate containers, each containing 10% neutral buffered formalin. Surgical margins were considered positive when the lesion was located at the ectocervical and/or endocervical margins.

Residual disease was defined as the presence of HSIL (CIN 2-3), microinvasive carcinoma, or invasive carcinoma in the repeat conization or hysterectomy specimen. Cone volume was calculated using the semi-ellipsoid formula based on the anteroposterior (AP), transverse (T), and longitudinal (L) dimensions provided in the pathology report of the initial conization: $\text{Volume} = (\pi/6) \times \text{AP} \times \text{T} \times \text{L}$.

Following the initial procedure, each patient underwent either repeat conization or hysterectomy based on a clinical evaluation that considered age, reproductive period, availability of sufficient cervical tissue, and comorbidities. Pathological outcomes from the second surgical procedure were categorized into two clinical groups. The low-risk group consisted of women with no preinvasive lesions or low-grade intraepithelial lesions (LSIL), whereas the high-risk group comprised women with HSIL (CIN 2 or CIN 3), microinvasive carcinoma, or invasive squamous cell carcinoma. All clinical variables, operative details, and pathological findings were extracted from electronic medical records using a standardized data collection form to ensure accuracy and internal consistency. The study was approved by the Ankara Bilkent City Hospital Institutional Ethics Committee (approval number: TABED 1-25-1885, date: 19.11.2025), and all procedures were conducted in accordance with Declaration of Helsinki and with strict adherence to patient confidentiality.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26. Associations between categorical variables, including margin characteristics, ECC results, HPV type, conization technique, and final pathological outcome, were evaluated using the chi-square test; Fisher's exact test was used when expected cell counts were insufficient. Continuous variables such as age, cone volume, and the interval between the initial conization and the final surgical procedure were categorized based on their median values. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 46.6 ± 11.53 years (range, 24-72 years). The median cone volume was 2.64 cm^3 (range, $0.31\text{-}18.90 \text{ cm}^3$). The median interval between the initial conization and the subsequent surgical procedure was 84 days (range 25-387 days). When surgical margin patterns were examined, endocervical margin positivity, ECC positivity, or both were

notably frequent. Thirty-six (75%) patients had a positive endocervical margin and/or a positive ECC, with or without a positive ectocervical margin. However, 16 (33.3%) patients had positive ectocervical margins, with or without positive endocervical margins or positive ECC. Isolated endocervical margin positivity was present in 29.2% of patients, isolated ECC positivity in 4.2%, and combined endocervical margin positivity with ECC involvement in 33.3%. In contrast, only 25% of patients had isolated ectocervical margin positivity. Electrosurgical methods, such as NETZ and LEEP, constituted the majority of conization techniques. The NETZ applied to 52.1% of patients and LEEP applied to 8.3% of patients, whereas CKC was performed in 39.6% of patients. Most initial conization pathology results demonstrated HSIL, predominantly CIN 3, with 38 patients (79.2%) diagnosed with CIN 3. HPV testing was available for 38 patients, of whom 79.2% were HPV-positive; among these, 66.7% had HPV 16 and/or 18, and 10.4% had other high-risk types. The baseline clinical and pathological characteristics of the cohort are summarized in Table 1.

TABLE 1: General features before final surgical procedure.

Features		Mean \pm SD	Median (range)
Age (years)		46.6 \pm 11.53	46 (24-72)
Conization material's volume (cm ³)		4.2 \pm 3.90	2.64 (0.31-18.90)
Time between conization and final surgical procedure (day)		101.6 \pm 64.87	84 (25-387)
		n	%
Type of positivity after conization and ECC	Only ectocervical margin positivity	12	25
	Only endocervical margin positivity	14	29.2
	Only ECC positivity	2	4.2
	Ectocervical margin and endocervical margin positivity	3	6.3
	Ectocervical margin and ECC positivity	-	-
	Endocervical margin and ECC positivity	16	33.3
	Ectocervical margin and endocervical margin and ECC positivity	1	2.1
Conization procedure	Cold conization	19	39.6
	NETZ	25	52.1
	LEEP conization	4	8.3
Pathologic result of conization and ECC	HSIL (CIN 2)	9	18.8
	HSIL (CIN 3)	38	79.2
	HSIL (undetermined)	1	2.1
Cervical smear	Normal cytology	6	12.5
	ASCUS	16	33.3
	LSIL	6	12.5
	ASC-H	5	10.4
	HSIL	12	25
	Not reported	3	6.3

Features		Mean ± SD	Median (range)
HPV result	Negative	2	4.2
	Positive	38	79.2
	Unknown	8	16.7
HPV type ¹	16 and/or 18	32	66.7
	Others	5	10.4
	Unknown	1	2.1
Colposcopy	Performed	43	89.6
	Not performed	5	10.4
Colposcopic biopsy result ²	No preinvasive lesion	4	9.3
	LSIL	4	9.3
	HSIL (CIN 2)	8	18.6
	HSIL (CIN 3)	21	48.8
	HSIL (undetermined)	6	14

ECC: Endocervical curettage; LEEP: Loop electrosurgical excision procedure; NETZ: Needle excision of the transformation zone; CIN: Cervical intraepithelial neoplasia; ASCUS: Atypical squamous cell of undetermined significance; ASC-H: Atypical squamous cell cannot rule out high grade intraepithelial lesion; LSIL: Low grade intraepithelial lesion; HSIL: High grade intraepithelial lesion; SD: Standard deviation; HPV: Human papillomavirus; ¹: n=38 patients with HPV positivity; ²: n=43 patients who underwent colposcopic procedure.

Management strategies were distributed relatively evenly: conization was performed in 52.1% of cases and hysterectomy in 47.9%. Twenty-two patients (45.9%) had residual high-grade disease (HSIL, microinvasive carcinoma, or cancer), while the remaining 26 patients (54.1%) had only LSIL or no preinvasive lesions. The final pathology revealed CIN 3 in 15 patients (31.2%), CIN 2 in 2 patients (4.2%), microinvasive carcinoma in 1 patient (2.1%), and squamous cell carcinoma in 1 patient (2.1%). The pathological outcomes following the second surgical procedure are summarized in Table 2.

Of the two patients diagnosed with carcinoma, one had microinvasive squamous cell carcinoma, and the other had invasive squamous cell carcinoma. The patient diagnosed with microinvasive carcinoma was 72 years old. HPV testing

was negative, cervical cytology showed HSIL, and colposcopic biopsy revealed HSIL. CKC was performed. Pathological examination showed HSIL, with positive endocervical surgical margins and positive ECC samples. The cone volume was 3.67 cm³. Due to insufficient remaining cervical tissue, a hysterectomy was performed, and microinvasive squamous cell carcinoma was diagnosed in the hysterectomy specimen. The second patient was 61 years old. Cervical cytology revealed Atypical squamous cell of undetermined significance with HPV-16 positivity. Colposcopic biopsy demonstrated HSIL. The NETZ procedure was performed. The conization specimen showed HSIL with positive ectocervical margins. Due to insufficient remaining cervical tissue, a hysterectomy was performed, and invasive squamous cell carcinoma was diagnosed.

Features		n	%
Surgical procedure after conization and ECC	Re-conization	25	52.1
	Hysterectomy	23	47.9
Final pathologic result	No preinvasive lesion	19	39.5
	LSIL	7	14.6
	HSIL (CIN 2)	2	4.2
	HSIL (CIN 3)	15	31.2
	HSIL (undetermined)	3	6.3
	Microinvasive SCC	1	2.1
	SCC	1	2.1

ECC: Endocervical curettage; LSIL: Low grade intraepithelial lesion; HSIL: High grade intraepithelial lesion; CIN: Cervical intraepithelial neoplasia; SCC: Cervical squamous cell carcinoma.

When the relationship between residual high-grade disease and clinicopathological variables was examined, no statistically significant differences were identified. However, several variables demonstrated numerical differences without reaching statistical significance. The most notable numerical difference was observed in the association between conization technique and residual disease. Residual HSIL or carcinoma was identified in 63.2% of women who underwent cold-knife conization (n=12/19), compared with 34.5% (n=10/29) among those treated with NETZ or LEEP, but this difference did not reach statistical significance (p=0.051). Similarly, when evaluating the interval between conization and the final surgical procedure, the residual disease rate was 59.1% (n=13/22) in women who underwent the second surgery more than 84 days later, compared with 34.8% (n=8/23) in those with a shorter interval (p=0.102). The relationship between clinical and pathological factors and residual disease was presented in Table 3.

DISCUSSION

In our cohort, 45.9% of women undergoing repeat surgery were found to have residual HSIL or cancer. This result is consistent with previous reports showing that approximately half of margin-positive women harbor clinically significant residual disease at re-excision.¹¹ However, in our study, none of the evaluated clinical or pathological variables demonstrated a statistically significant association with residual high-grade disease. A numerical difference was observed across types of initial excisional procedure, although it did not reach statistical significance. Residual high-grade disease was numerically less frequent after electrosurgical excision than after cold-knife conization. Previous studies have reported clinically significant residual disease following repeat surgery in a substantial proportion of women with positive surgical margins after conization.^{12,13} In addition, several studies have suggested an association between the type of initial excisional

TABLE 3: Factors affecting residual lesions (HSIL or cancer) in final surgical procedure in patient with margin positivity after conization and endocervical curettage.

Factors		Residue lesion in final surgical procedure after conization and endocervical curettage		p-value
		No preinvasive lesion or LSIL	HSIL or cancer	
		n (%)	n (%)	
Age ¹	≤46 years	14 (58.3)	10 (41.7)	0.562
	>46 years	12 (50)	12 (50)	
Conization material's volume ^{1,2}	≤2.64 cm ³	11 (50)	11 (50)	0.763
	>2.64 cm ³	12 (54.5)	10 (45.5)	
Time between conization and final surgical procedure ^{1,3}	≤84 days	15 (65.2)	8 (34.8)	0.102
	>84 days	9 (40.9)	13 (59.1)	
Conization procedure	Cold conization	7 (36.8)	12 (63.2)	0.051
	NETZ or LEEP conization	19 (65.5)	10 (34.5)	
Ectocervical margin	Negative	16 (50)	16 (50)	0.413
	Positive	10 (62.5)	6 (37.5)	
Endocervical margin and/or ECC	Negative	8 (66.7)	4 (33.3)	0.316
	Positive	18 (50)	18 (50)	
Surgical procedure after conization and ECC	Re-conization	16 (64)	9 (36)	0.154
	Hysterectomy	10 (43.5)	13 (56.5)	
HPV type ⁴	16 and/or 18	19 (59.4)	13 (40.6)	0.377
	Others	4 (80)	1 (20)	
Colposcopic biopsy result ⁵	No preinvasive lesion or LSIL	5 (62.5)	3 (37.5)	0.477
	HSIL or cancer	17 (48.6)	18 (51.4)	
Colposcopic biopsy and conization and ECC result ⁶	HSIL (CIN 2)	5 (71.4)	2 (28.6)	0.353
	HSIL (CIN 3)	21 (52.5)	19 (47.5)	

¹: Median value; ²: n=44 patients, four patients excluded because of the diameter of the conization specimen was not reported; ³: n=45 patients, Time between conization and final surgical procedure wasn't known in three patients; ⁴: n=37 patients, HPV genotype was unknown in 11 patients; ⁵: n=43 patients, who underwent colposcopic procedure; ⁶: n=47 patients, the grade of CIN couldn't be determined in one patient; HPV: Human papillomavirus; ECC: Endocervical curettage; CIN: Cervical intraepithelial neoplasia; LSIL: Low grade intraepithelial lesion; HSIL: High grade intraepithelial lesion; LEEP: Loop electrosurgical excision procedure; NETZ: Needle excision of the transformation zone

procedure and the risk of residual high-grade lesions, with electrosurgical techniques generally associated with lower residual disease rates compared with cold knife conization.¹⁴ This difference has been attributed to variations in excision geometry, thermal effects, and the ability to achieve adequate lateral margins.^{15,16} Our findings are consistent with these observations, as residual high-grade lesions were observed less frequently after electrosurgical procedures than after cold knife conization, although the association reached only borderline statistical significance.

The literature consistently identifies endocervical margin involvement as a stronger predictor of residual CIN 2+ than ectocervical margin involvement. Across multiple series evaluating repeat surgical specimens following conization, residual high-grade disease has been reported in approximately 30-50% of patients with endocervical margin positivity, whereas the corresponding rate for isolated ectocervical margin involvement is substantially lower and generally remains below 10%.^{5,17,18} Residual high-grade lesions have been reported in approximately 30-55% of patients with positive surgical margins after LEEP, in 20-40% after cold-knife conization, and in 15-30% after larger excisional procedures such as NETZ. Nevertheless, across all these techniques, endocervical margin involvement remains the most consistent predictor of residual disease.^{5,11,12,17} This pattern is thought to reflect the anatomical trajectory of high-risk HPV-associated neoplasia, which frequently extends proximally into the endocervical canal. Our findings are consistent with this distinction. Isolated ectocervical margin positivity was rarely associated with high-grade residual pathology, whereas endocervical margin involvement and ECC positivity showed nearly equal proportions of high- and low-risk pathological outcomes. Despite this association, the predictive value of these markers remained insufficient for guiding clinical management in isolation echoing the conclusions of ASCCP and ESGO recommendations, which caution against reliance on margin status alone.^{3,19}

ECC positivity has been proposed as an additional risk factor for residual CIN 2+, with some studies reporting strong associations, particularly among women with concomitant endocervical margin involvement.²⁰ However, its sensitivity varies widely, especially after LEEP, where thermal artifact and tissue fragmentation may obscure histological interpretation.²¹ The results of our cohort reflect this variability. While ECC positivity was more common among women with high-risk outcomes, nearly half of ECC positive patients did not harbor clinically relevant pathology at repeat excision.^{17,20}

Cone volume has recently been investigated as a potential parameter reflecting excision depth and lesion burden.^{19,22}

In our cohort, cone volume did not demonstrate a statistically significant association with residual disease. Therefore, cone volume alone may have limited value as a predictive marker for residual high-grade pathology. Similar findings have been reported in external studies, where cone volume demonstrated statistical correlation but lacked sufficient discriminatory performance for clinical application.²³

The distribution of residual disease across excisional techniques in our study mirrors prior comparative analyses.²⁴ While CKC generally achieves clearer margins and deeper tissue sampling, our data did not reveal an advantage for CKC over LEEP/NETZ in preventing residual high-grade pathology. This observation aligns with multiple studies showing that procedural choice alone does not adequately stratify the risk of persistence or recurrence and must be interpreted alongside lesion characteristics and margin location.^{25,26}

The clinical management of margin-positive HSIL remains a complex balancing act between avoiding overtreatment and preventing undertreatment. Repeat excision may expose patients, particularly those of reproductive age, to adverse outcomes such as cervical stenosis, infertility, cervical insufficiency, and preterm birth. Large meta-analyses have confirmed increased preterm birth risk following deeper or repeated cervical excisions.²⁷ Conversely, under-treatment risks missing persistent HSIL or microinvasion, especially in cases where initial sampling may have been incomplete or affected by fragmentation.¹⁶ The identification of reliable predictors for residual disease thus remains a pressing clinical need.

Our findings support a multifactorial approach integrating endocervical margin status, ECC results, cone volume, and index pathology, rather than relying on any single parameter. Such approaches align with evolving risk-based models that incorporate virologic, cytological, and pathological features to refine prediction of CIN 2+ persistence.²⁸ While HPV genotype and viral load could further enhance prediction accuracy, these data were not available for all patients in our cohort and represent an important area for future study.

Study Limitations

This study underscores the limitations of relying solely on surgical margin assessment and emphasizes the value of composite clinical and pathological evaluation. Given that nearly half of women with positive margins did not have residual high-grade disease, individualized management strategies, particularly for women desiring fertility preservation, are warranted. Conversely, the substantial proportion of women with residual HSIL or carcinoma underscores the need for continued vigilance and risk-stratified indications for secondary excision.

CONCLUSION

Residual HSIL or carcinoma was detected in nearly half of the women undergoing repeat excision after a margin-positive conization. Residual disease was numerically lower among patients treated with electrosurgical techniques than among those who underwent cold-knife conization; however, this difference did not reach statistical significance. Overall, no single clinical or pathological parameter reliably predicted residual disease. This study is limited by its retrospective single-center design and modest sample size, which may affect generalizability. Therefore, larger prospective studies are needed to validate these observations.

Ethics

Ethics Committee Approval: The study was approved by the Ankara Bilkent City Hospital Institutional Ethics Committee (approval number: TABED 1-25-1885, date: 19.11.2025), and all procedures were conducted in accordance with Declaration of Helsinki and with strict adherence to patient confidentiality.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.Ö.U., Concept: Y.Ö.U., Design: Y.Ö.U., O.A., M.Ü., F.K., Data Collection or Processing: Y.Ö.U., O.A., M.Ü., F.K., Analysis or Interpretation: A.E.K., A.B., M.Ş., Z.Ö.B., Literature Search: Y.Ö.U., A.E.K., M.Ş., Writing: Y.Ö.U., A.B., Z.Ö.B.

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