

Factors Predicting Recurrence of Cervical Intraepithelial Neoplasia after Excisional Procedure-A 10-year Experience from A Tertiary Care Center

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ABSTRACT

Aim: Cervical intraepithelial neoplasia (CIN) is a precancerous condition of the uterine cervix commonly encountered in clinical practice. Treatment of CIN is excisional or ablative. This study aims to elucidate and evaluate the possible risk factors commonly associated with the recurrence of CIN following an excisional procedure.

Materials and methods: This was a retrospective study conducted between 2010 and 2019. Patients who underwent excisional procedures for CIN2/3 were included. The information was collected from the hospital database. Clinical and sociodemographic data, recurrence characteristics, and follow-up data were analyzed.

Results: Recurrent lesions were noted in 26 (15.4%) patients. The pattern of recurrence was CIN in 13 patients (50%), vaginal intraepithelial neoplasia (VAIN) in 11 (42.3%), and cervical cancer in 2 (7.7%) patients. The median follow-up time was 8 (1–117 months). Univariate analysis showed HIV-positive women were at greater risk of recurrence (HR = 2.8, 95% CI = 0.93–8.5; $p = 0.009$) but advanced age, presence of involved margins, endocervical gland or crypt involvement, and high-risk HPV status post-procedure were not ($p > 0.1$) associated with recurrence in our study.

Conclusion: Excisional procedures are successful and patients with risk factors like HIV seropositivity and positive margins should be targeted for close surveillance or offered a hysterectomy.

Clinical significance: Following excisional procedures, patients with risk factors for recurrence should be advised of close surveillance or offered a hysterectomy.

Keywords: Cervical intraepithelial neoplasia, Excisional procedure, Follow-up, hysterectomy, Recurrence.

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INTRODUCTION

Cervical intraepithelial neoplasia (CIN) is a precancerous condition of the cervix which is commonly encountered in clinical practice.^{1,2} It is classified into low-grade CIN1 or high-grade CIN2/3 which are also known as a low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL), respectively. According to several studies, it has been shown that persistent infection with human papillomavirus leads to a high risk of developing CIN. The histopathological examination of cervical punch biopsy or excision specimen clinches the diagnosis of CIN. Progression of premalignant lesions to cancer cervix is up to 50% for CIN3.³ The gold standard for diagnosing precancerous cervical lesions is colposcopy-directed biopsy. Using a reference scoring system like Reid's or Swede's score may help in colposcopic interpretation and diagnosis.⁴ Treatment for CIN 2/3 is excisional or ablative. The recent WHO guidelines advocate the use of the loop electrosurgical excision procedure (LEEP) technique as a see and treat method of treatment for patients with high-grade lesions to reduce the number of hospital visits.

Involvement of the surgical margins, endocervical involvement, high-risk human papillomavirus (HPV) persistence, human immunodeficiency virus (HIV) infection are the probable risk factors for residual/recurrent HSIL.⁵ A positive margin after the excision procedure for CIN regardless of the grade of CIN is a well-defined

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predictor of persistent disease.⁶ Some investigators have suggested that these patients can be followed up, however, many clinicians opt for re-excision or hysterectomy.

Overall, 5–17% of patients who undergo excisional or ablative procedures will have recurrent or persistent CIN.⁷ We analyzed the data of patients who underwent excisional procedures and assessed the risk factors associated with recurrence as the data on this group of patients is scarce.

MATERIALS AND METHODS

This was a retrospective study of a cohort of women diagnosed with HSIL of the cervix and treated by LEEP/conization in the Department of Gynecologic Oncology in a tertiary care center between January 2010 and December 2019. The records were retrieved from the electronic database. Ethical clearance was obtained from the institutional review board (IRB no.13023/24/06/20) which waived the need for patient consent as the study was retrospective.

The aims and objectives were to study the clinicopathologic profile, demographic profile, and to analyze the colposcopic findings and to determine the rate of recurrence after treatment of CIN2/3 lesions, and to find out the factors predicting recurrence.

The data collected included age, body mass index (BMI), menopausal status, parity, pap smear report, cervical biopsy and colposcopy details, type of excisional procedure, final histopathology report of the excision specimen, the thickness of cone specimen, margin involvement including location, endocervix and endocervical crypt involvement, HR (high risk) HPV status pretreatment and posttreatment, HIV positivity, follow-up smear and HPV status, recurrence and time interval of recurrence, and treatment done for recurrence. Inclusion criteria were women with a histological diagnosis of CIN2/3 in the excision specimen or those who underwent hysterectomy post-excision given the margin positivity or crypt involvement and patients with at least one follow-up visit after the excisional procedure. Exclusion criteria were women with other histologic diagnoses, women who did not come for follow-up, and those who underwent hysterectomy for some other reasons and were found to have CIN.

Follow-up was done at 6 months after excisional procedures with a pap smear performed at each visit. If a repeat pap smear showed atypical squamous cells indicating high-grade lesion (ASC-H) and/or HPV positivity, a colposcopy-guided punch biopsy was recommended.

After the women had two or more consecutive biopsies which were negative, they were considered as free of residual lesions, regardless of the HPV or cytology results in our study. HSIL lesions found in the resection margins, whether the ectocervical margin, endocervical margin, or both, was regarded as the positive margin. HSIL lesion diagnosed in patients who underwent repeat procedures within 3 months was considered as residual lesion and if diagnosed more than 3 months after surgery, it was considered recurrent or persistent lesion, which needed to be proved by the colposcopy-directed punch biopsy or post-operation pathology.⁸ CIN1 was also considered a recurrent/persistent lesion in this study.

Statistical Analysis

A total of 168 patients were identified. Quantitative variables were summarized using counts and percentages. The association between margin positivity and recurrent or persistent disease with the various factors was assessed using Pearson’s Chi-square test. A *p*-value of < 0.05 was considered to be significant. Cox-regression analysis was done and the hazard ratio (HR) and its 95% confidence interval were presented. Statistical analysis was performed using IBM SPSS for Windows (version 22.0) and Stata 1C (version1).

RESULTS

Overall, 206 patients were diagnosed to have HSIL during the study period. Out of these, 11 cases were diagnosed as carcinoma cervix after punch biopsy and were excluded from the study. Another

Table 1: Clinico-demographic profile

Variable	N = 168
Age	
<40 years	50 (29.7%)
>40 years	118 (70.3%)
Body mass index (kg/m ²)	
<18	6 (3.5%)
18–25	65 (38.6%)
25–30	77 (45.8%)
>30	20 (11.9%)
Parity	
Nullipara	3 (1.8%)
Multipara	165 (98.2%)
Symptoms	
Asymptomatic	31 (18.4%)
Discharge per vaginum	46 (27.4%)
AUB	91 (54.2%)
HIV status	
Positive	9 (5.4%)
Negative	78 (46.4%)
Not tested	81 (48.2%)
Pre-treatment pap diagnosis	
LSIL	17 (10.1%)
ASCUS	12 (7.2%)
ASC-H	21 (12.5%)
HSIL	118 (70.2%)

Values expressed as *n*(%). AUB, abnormal uterine bleeding; HIV, human Immunodeficiency virus; LSIL, low-grade squamous intra-epithelial lesion; ASCUS, atypical squamous cells of unknown significance; ASC-H, atypical Squamous cell-high-grade; HSIL, high-grade intra-epithelial lesion

27 cases were excluded from the study because of the lack of correlation between cytology, biopsy, and colposcopic findings, incidentally found to have CIN after surgery and no follow-up after the procedure. A total of 168 patients (CIN2, 7.2%, CIN3, 92.8%) were included in the study. The mean age was 46.3 years (range: 24–80 years). **Table 1** summarizes the clinical characteristics of the patients. The histopathological characteristics are summarized in **Table 2**.

In general, excisional procedures were successful, with 84.6% of the cases having no signs of recurrence or persistent CIN 2–3 during follow-up. Recurrent lesions occurred in 26 (15.4%) patients. Two invasive squamous cervical carcinomas and 11 vaginal intraepithelial neoplasia were detected during follow-up. CIN 1 and CIN 3 were diagnosed in four and nine patients, respectively. The median lag time between excisional procedure and persistent or recurrent CIN 2–3 was 8 months (range: 4–66 months). **Table 3** outlines the characteristics of recurrence. Out of the 26 cases of recurrences, CIN 1 in four cases (15.4%), CIN 3 in nine cases (34.6%), VAIN in 11 cases (42.3%) of which VAIN 1 was found in 2 (7.7%) cases and VAIN 3 in 9 (34.6%) cases, and SCC in 2 cases (7.7%). Re-excision for recurrent CIN 3 was done for 2 (7.7%) patients, and vaginectomy for VAIN 3 was done for 7 (34.6%) patients. Hysterectomy was done for 8 (30.7%) patients of which 3 cases were CIN1, four cases were CIN3 and one was squamous cell carcinoma (SCC) cervix. Three (19.2%) patients were kept on follow-up. Five (19.2%) patients were lost to follow-up.

Table 2: Histopathological details

Variable	N = 168
Transformation zone	
Type I	126 (75.0%)
Type II	34 (20.2%)
Type III	5 (3.0%)
Unknown	3 (1.8%)
Swedes score	
≤6	100 (59.5%)
>6	66 (39.2%)
Unknown	2 (1.2%)
Histopathology post-excision	
CIN 1	5 (2.3%)
CIN 2	12 (7.2%)
CIN 3	132 (78.5%)
Cancer	09 (5.4%)
Negative for CIN/cancer	10 (5.6%)
Mode of excision	
LEEP	141 (84.0%)
Conization	16 (9.5%)
Hysterectomy	11 (6.5%)
Margin involvement	
Ectocervical	06 (3.5%)
Endocervical	07 (4.2%)
Deep	07 (4.2%)
>1 margin	11 (6.5%)
Negative	128 (76.1%)
Unknown	09 (5.3%)
ECC	
Positive	18 (10.7%)
Negative	104 (61.9%)
Unknown	46 (27.4%)
Endocervical crypt/glandular involvement	
Positive	38 (22.6%)
Negative	121 (72.2%)
Unknown	09 (5.4%)

Values expressed as n (%). CIN, cervical intraepithelial neoplasia; LEEP, loop electro-surgical excision procedure; ECC, endocervical curettage

Predictors of Recurrence Based on Univariate Analysis

Univariate logistic analysis showed the hazard ratio (HR) related to CIN 2–3 recurrence posttreatment (Table 4). HIV-positive women were found to be at increased risk (HR = 2.8, 95% CI = 0.93–8.5; *p* = 0.009) compared with HIV-negative women. The type of transformation zone was also an important factor related to the recurrence of CIN (*p* = 0.03), with HR 4.5 (95% CI = 1.17–6.6).

The other possible factors such as increased age, Swede’s score, histopathology of the excised specimen, margin positivity, endocervical curettage (ECC) and endocervical gland or crypt involvement, HR HPV status post-procedure was also analyzed but we could not find any significant association since the sample size was small.

Table 3: Univariate analysis for factors predicting recurrence of CIN

Variable	Total N = 168	Recurrence N = 26	No recurrence N = 142	<i>p</i> -value
Age				
<40 years	50	10 (20.0%)	40 (80.0%)	0.34
>40 years	118	16 (13.6%)	102 (86.4%)	
HIV status				
Positive	9	4 (44.4%)	5 (55.6%)	0.01
Negative	78	17 (21.8%)	61 (78.2%)	
Not tested	82	5 (4.5%)	77 (95.5%)	
Margin status				
Ectocervical (+)	6	2 (33.0%)	4 (67.0%)	0.29
Endocervical (+)	7	1 (14.7%)	6 (85.3%)	
Deep margin (+)	7	0 (0.0%)	7 (100%)	
>1 margin (+)	11	0 (0.0%)	11 (100%)	
Margin (–)	128	21 (15.5%)	107 (84.5%)	
Unknown	9	2 (22.2%)	7 (77.8%)	
Crypt/glandular involvement				
Positive	38	3 (7.8%)	35 (92.2%)	0.18
Negative	121	20 (16.5%)	101 (83.5%)	
Unknown	9	3 (33.3%)	6 (66.7%)	
HR-HPV status post procedure				
Positive	9	4 (44.4%)	5 (55.6%)	0.21
Negative	56	9 (16.1%)	47 (83.9%)	
Unknown	103	13 (12.6%)	90 (87.4%)	
Cone specimen thickness (n = 16)				
<10 mm	4	1 (15.0%)	3 (85.0%)	0.71
≥10 mm	12	2 (16.6%)	10 (83.4%)	

Values expressed as n or n (%), HIV, human immunodeficiency virus; HR-HPV, high-risk-human papillomavirus

Table 4: Type of recurrence and its treatment

Type of recurrence	N = 26	Treatment of recurrence	N = 26
CIN 1	4 (15.4%)	Hysterectomy	3
		Follow-up	1
CIN 3	9 (34.6%)	Re-excision	2
		Hysterectomy	4
		Lost to follow-up	3
VAIN 1	2(7.7%)	Follow-up	1
VAIN 3	9(34.6%)	Vaginectomy	7
		Lost to follow-up	2
SCC cervix	2 (7.7%)	Hysterectomy	1
		Radiotherapy	1

Values expressed as n or n (%), CIN, cervical intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia; SCC, squamous cell carcinoma

The median follow-up period was 8 months (range: 1–117 months). Only 30.1% of patients had followed up for at least 2 years. The median recurrence-free interval was 8 months (range:



4–66 months). At 51 months, 63.5% of patients were disease-free. 95% CI (69.49–94.03).

DISCUSSION

The excisional procedures like LEEP and conization are both diagnostic and therapeutic and provide a conservative approach to treat CIN. But cervical lesions show persistence or recurrence in some patients after the excisional procedure.

A meta-analysis by Fernanda VF et al.⁹ had shown that there was a great variability interval of 7–51.7% for the recurrence rates shown in the literature after treatment of CIN through excisional procedures.

Kang et al.¹⁰ reported that after LEEP, the recurrent disease ranged from 5 to 30%, requiring close follow-up or re-treatment once the lesion is identified. These findings are consistent with our study which has shown a recurrence rate of 15.4%.

Many studies have shown that the presence of margin positivity is an important factor for disease persistence/recurrence.^{11–15} The study population in those studies underwent follow-up regularly after excisional procedures for CIN2/3. In our study population, most of the patients underwent definitive treatment like re-excision or hysterectomy after having been diagnosed with a positive margin. Hence, we could not find any significant association between margin positivity and recurrence of CIN. Univariate analysis showed *p*-value of 0.3 (HR = 0.5, 95% CI = 0.1–2.2). Patients with a margin positivity can be followed up, but they generally do not want a close follow-up and request for re-excision. In our follow-up on those patients who underwent repeat treatment, we found out that only two patients with positive margins who underwent hysterectomy had a recurrence in the form of VAIN. Our findings are supported by a meta-analysis by Arbyn et al.¹⁵ which had shown that margin positivity was less sensitive in predicting recurrence or residual CIN. However, we found that 22 patients (15.5%) with a clear margin developed recurrent CIN. This result is supported by the study of Lubrano et al.¹⁶ Our study strongly suggests that previous evidence status of positive resection margins has only limited usefulness in predicting the recurrent/persistent CIN.

A study by Costa S et al.¹⁷ had shown that increasing age is a known predictor of CIN 2–3 treatment failure though it is not always observed, which is consistent with our finding. We could not find any association between increasing age and recurrent CIN. In our study, majority of women who developed recurrence were in the perimenopausal age group.

Increasing age has been identified as one of the possible predictors of persistence/recurrence in many studies.^{18–20}

The incidence of CIN is increased in HIV-infected patients. The increased risk of CIN is related to the greater prevalence of HPV infection in these patients.²¹ Another study by Malapati R et al.²² also said that HIV-positive status is a significant factor associated with recurrent CIN. Our study revealed that 44.4% of patients with HIV infection developed recurrence (*p* = 0.009).

Nam et al.²³ demonstrated that persistent HPV infection can be a risk factor for recurrence. According to a study by Arbyn et al.,¹⁵ the ability of testing HPV to predict persistent/recurrent CIN 2/3 is 91% (95% CI = 82–96%), and it does not differ significantly between patients who have positive vs negative margins. In our study, only 65 (38.6%) patients underwent posttreatment HPV testing, out of

which recurrence developed in 4 patients (*p* = 0.2). We did not find any significant association with HPV status and recurrence which may be due to the less sample size, the poor patient compliance on follow-up, and also related to the cost of the testing.

A study by Alukal et al.²⁴ had shown that 65.8% of the patients with type III transformation zone had recurrent disease. In our study, we got a significant association between the type of transformation zone and recurrence (*p* = 0.016).

According to Papoutsis et al.²⁵ residual disease is reduced if the thickness of conization is more than 10 mm. According to Kliemann et al.²⁶ if the thickness of the cone is 20 mm, then there is 100% chance of complete resection of CIN 2–3. Another study by Beyer et al.²⁷ mentions that if the cone thickness is 20 mm, then the negative margin is almost 100%. In our study, we noticed that the recurrence rate was less in patients with a thickness of the cone specimen more than or equal to 10 mm compared with those with a thickness <10 mm (16.6% vs 25%, respectively).

In our study, we found that 84.6% of the patients who underwent excisional procedure had no signs of recurrence or persistent CIN 2–3 during follow-up. Recurrent lesions occurred in 26 cases (15.4%). The need for repeat excisional procedure/hysterectomy for those with probable risk factors of recurrence can be individualized. In our population, the adherence to follow-up was very poor. Thus, we considered that the presence of margin positivity or endocervical crypt involvement does not always require surgical re-treatment. In young patients, after an initial excisional procedure like LEEP, a close follow-up is acceptable. In patients older than 35 years, it is reasonable to do a re-excision or hysterectomy.

CONCLUSION

Excisional procedures are successful in those patients with probable factors for recurrence like HIV seropositivity, margin positivity, and advanced age should be targeted for close surveillance or offered hysterectomy.

Clinical Significance

Following excisional procedures, patients with risk factors for recurrence of HIV seropositivity, margin positivity, and advanced age should be targeted for close surveillance or offered hysterectomy.

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