



Evaluation of Factors Affecting Margin Positivity and Persistent Disease After Leep for Cervical Intraepithelial Neoplasia

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Abstract

Background Cervical intraepithelial neoplasia (CIN) is the precursor lesion of cervical cancer. Untreated high-grade CIN significantly increases the risk of developing invasive cancer. Conization is the main treatment. Loop electrosurgical excision procedure (LEEP) is the most common conization method used. The study aims to assess the risk factors associated with positive margin and persistent disease after LEEP for CIN.

Materials and Methods A total of 156 patients who underwent LEEP during 2011–2018 included in the study. We analyzed the socio-demographic characteristics, colposcopy details, dimensions of LEEP specimen (thickness, length, volume) and histopathology (margin positivity, grade). Persistent disease was histologically confirmed by repeat LEEP and hysterectomy.

Results Margin positivity was noted in 33.3% (52) patients. Residual disease was noted in 26.2% (41) of the patients who had undergone a repeat LEEP or hysterectomy. There was a significant association between margin positivity and Swede score of 5 or more, a high-grade lesion on IFCPC score, inner margin involvement, LEEP done in a single pass. The cutoff for margin positivity was length of 0.513 cm and thickness of 0.35 cm. A significant association between residual disease and margin positivity, postmenopausal status, Swede score of 5 or more, high-grade lesion on IFCPC score, inner margin involvement was observed. The chance of residual disease was less if the cone specimen had minimum length of 0.775 cm and minimum thickness of 0.65 cm.

Conclusion When in doubt regarding the margins, it is always better to perform multiple passes for lesions with a high Swede score with an initial smear of HSIL. Postmenopausal women with inner margin positivity have a high chance of residual disease and should be either kept on close follow-up or consider a repeat procedure.

Introduction

Loop electrosurgical excision procedure (LEEP) has been widely used both for diagnostic and therapeutic approaches for preinvasive high-grade disease. It helps in avoiding unnecessary further treatment. However, around 10–30% of patients with high-grade squamous intraepithelial lesion (HSIL) who are treated with LEEP have persistent disease. The options for management of a positive margin after LEEP are follow-up with more frequent cytologic assessment and human papillomavirus (HPV) testing, repeat conization or hysterectomy. A positive surgical margin is one of the most important predictors of recurrence [1]. Therefore, we should try to avoid positive surgical margin while performing LEEP and make every effort to avoid incomplete excision [2]. Persistent HSIL, number of involved margin sections, location of involved margin sections, histological grade of the specimen, pathology of the endocervical curettage (ECC), human

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papillomavirus load and human immunodeficiency virus (HIV) infection are the possible predictors of persistent/recurrent HSIL [3]. A positive margin after LEEP is finding of CIN along the specimen margin regardless of the CIN grade is a well-defined predictor of persistent disease [4]. Even though some investigators suggest that this population can be followed up without the need for secondary surgery, most clinicians finally end up doing a repeat LEEP or hysterectomy for these patients [5]. The chances of spontaneous regression for HSIL and LSIL are around 60% and 30%, respectively. Moreover, a positive margin need not always have a residual disease on the cervix as the heat and coagulation effect produced due to LEEP can have some ablative effect on the positive margins (Fig. 1).

We analyzed the data of patients who underwent LEEP and tried to assess the factors which may help us to predict a positive margin. We also assessed the data of patients who underwent a repeat LEEP or hysterectomy following a positive margin to assess for the presence of residual disease and predict the risk factors. Statistical significant association between margin positivity and residual disease and the various factors was assessed using Pearson's Chi-square/Fisher's exact test. A p -value < 0.05 was considered as significant. ROC analysis was done to obtain a cutoff for the mean length and thickness of cone specimen whereby we could predict the chance of margin positivity and residual disease using the Youden index (Fig. 2) [6].

Methodology

This study was approved by the institutional research committee. We reviewed the medical records of 156 patients who underwent LEEP in our department from October 2011 to September 2018. Information was collected regarding patient characteristics like age, parity, menopausal status,

cervical smear, cervical biopsy details, colposcopic details like Swede score, type of transformation zone, IFCPC score. Details regarding the dimensions of the initial LEEP specimens, i.e., thickness, length and mean cone volume, were assessed. The thickness was measured from the surface to stromal margin, and the length was measured from ecto to endocervical margin as defined in 2011 IFCPC nomenclature [7]. In case of multiple passes the mean length and mean thickness were taken. The cone volume was calculated by adding the volume of individual cone specimens. The histology of the first LEEP specimen and ECC specimen, and location of involved margin sections were taken. A histopathological report on CIN 1 and above was taken as margin positivity. The patients with histologically positive margin underwent a repeat LEEP or hysterectomy. The persistence of residual disease was assessed in these patients (Fig. 3).

Results

A total of 156 patients who had undergone LEEP were included. The mean age of patients who had undergone LEEP was 47.8. Around 39.1% ($n = 61$) of the women were postmenopausal and 60.8% were premenopausal. The most common smear report for which the patients had undergone evaluation was HSIL for 71.8% ($n = 112$) followed by smear report of LSIL in 12.2% ($n = 19$). Most of these patients underwent cervical biopsy following an abnormal cervical smear. The most common histology in cervical biopsy was CIN 3 seen in 49.4% ($n = 77$) of the patients (Table 1).

The colposcopic details of the patients were evaluated. Most of the women had a Type 3 transformation zone seen in 49.4% ($n = 77$) of the patients. The Swede score of 0–4 was seen in 9.6% ($n = 15$) of the patients, and a score of 5 and above was observed in 90.4% ($n = 141$) of the patients.



Fig. 1 Colposcopic picture of high-grade lesion

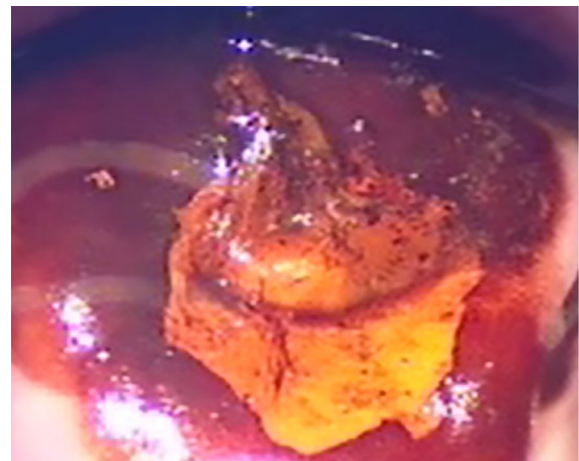


Fig. 2 After iodine application

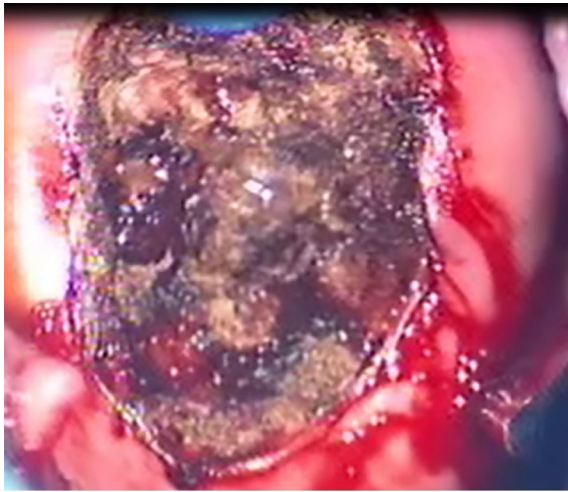


Fig. 3 Post LEEP picture

High-grade lesions according to the IFCPC score were noted in 71.2% ($n = 111$) of the patients. In total, 51.3% ($n = 80$) of the patients underwent LEEP in a single pass. The LEEP specimen was assessed for the mean length of the specimen, thickness of the specimen and mean cone volume. The mean length of the LEEP cone was 0.82 ± 0.25 cm, and the mean thickness of the cone was 0.81 ± 0.35 cm. The mean cone volume was 799 ± 0.7 cm [1]. The most common histology

of the LEEP specimen was CIN 3 in 57.1% ($n = 89$) of the patients (Table 1).

Of these patients, margin positivity was noted in 33.3% ($n = 52$) patients. The mean age of patients with margin positivity was 49.7 years. Inner margin was found to be positive in 26.9% of the patients ($n = 42$). Endocervical curettage was found to be positive in 24.4% ($n = 38$). The margin-positive patients underwent a repeat LEEP or hysterectomy. Residual disease was noted in 26.2% ($n = 41$) of the patients who had undergone a repeat LEEP or hysterectomy (Table 1).

No difference was noted in the patients with and without margin positivity in terms of parity, menopausal status, type of transformation zone. But a significant relationship was noted between margin positivity and smear report of HSIL ($p = 0.001$), positive endocervical curettage ($p = 0.001$), Swede score of 5 and more ($p = 0.018$), high-grade lesion on IFCPC score ($p = 0.001$), LEEP done in a single pass ($p = 0.035$) (Table 2).

No difference was noted among patients with and without residual disease in terms of parity, type of transformation zone and number of passes in which LEEP. But a significant association was noted between residual disease and margin positivity ($p = 0.008$), postmenopausal status ($p = 0.016$) and smear report of HSIL ($p = 0.001$), Swede score of 5 and more ($p = 0.007$), high-grade lesion on IFCPC score ($p = 0.003$), inner margin involvement ($p = 0.008$) (Table 3).

It was observed that using the Youden index, the chance of margin positivity was very high when the mean length of

Table 1 Clinical characteristics of the patients evaluated

Clinical characteristics	Subgroups	No. ($n = 156$)	Percentage (%)
Menopausal Status	Premenopausal	95	60.9
	Postmenopausal	61	39.1
Smear Report	ASCUS	9	5.8
	ASC-H	8	5.1
	LSIL	19	12.2
	HSIL	112	71.8
	SCC	8	5.1
Type of TZ	Type 1	52	33.3
	Type 2	27	17.3
	Type 3	77	49.4
Swede score	0–4	15	9.6
	5 or more	141	90.4
Ifcpc score	Low grade	45	28.8
	High grade	111	71.2
ECC	Positive	38	24.4
	Negative	118	75.6
No of passes of Leep	Single	80	51.3
	Multiple	76	48.7
Histology of LEEP specimen	CIN 1	25	16
	CIN 2	20	12.8
	CIN 3	89	57.1
	SCC	22	14.1
	Margin	Positive	52
	Negative	104	66.7

Table 2 Factors affecting margin positivity

	Margin negative (n = 104)	Margin positive (n = 52)	p value*
Post menopausal Status	39	22	0.562
Cervical smear- HSIL	71	41	0.001**
Type of transformation zone	37	15	0.539
Type 1	19	8	
Type 2	48	29	
Type 3			
Positive endocervical curettage	12	26	0.001**
Swede score 5 or more	29	8	0.018**
IFCPC- high grade	62	49	0.001**
Inner margin positivity	8	34	0.001**
LEEP done in single Pass	47	33	0.035**

*Used Chi-square/ Fisher's exact test

**statistically significant at 5% level

Table 3 Factors affecting residual disease

	No residual disease (n = 11)	Residual disease (n = 41)	p-value
Margin Positivity	4	33	0.008**
PostMenopausal Status	1	21	0.016**
Cervical smear- HSIL	8	33	0.001**
Type of transformation zone	6	10	0.059**
TZ-1	2	4	
TZ-2	3	27	
TZ-3			
Swede score 5 or more	10	40	0.007**
IFCPC- high grade	6	39	0.003**
Inner margin positivity	2	38	0.008**
LEEP done in single Pass	6	23	1.000

*Used Student's t test

**statistically significant at 5% level

the cone was less than 0.513 cm and the mean thickness of cone was less than 0.35 cm. The chance of residual disease was less if the cone specimen had a minimum length of 0.775 cm and a minimum thickness of 0.65 cm.

Discussion

The present study observed that LEEP provides a conservative approach to treat HSIL especially in women who are young or who desire to preserve their fertility. But the pre-invasive lesions persist in a certain portion of patients after

LEEP. Positive margins after excisional procedure have been identified as a predictive factor of disease persistence. Studies have defined margin positivity as the presence of CIN in the involved margin. The studies which included margin positivity with only HSIL have a very less margin positivity rate of around 6–10%. We included all cases with a positive margin with both LSIL and HSIL. Hence the margin positivity rate is high as around 33.3%. Highly variable surgical margin positivity rates, which extend from 2.8 to 59.5%, have been published [8–10]. The margin positivity rate in our study was comparable to a similar study by Yasin et al. which had a positivity of around 30.6% [11]. The aim was to not miss any case which could have a residual disease turning into malignancy even if the patient is lost to follow up at a later stage.

We found that the chance of getting a positive margin was high when the Swede score was high, positive endocervical curettage, LEEP was done in a single pass. Residual disease was found in 41 patients, i.e., around 26.2% of patients. This was slightly higher when compared to similar studies as by Sankasem et al. which had a persistent disease in only 18.9% [12]. The persistence of HPV infection has also been evaluated by various studies for predicting persistent disease. Even though patients with a positive margin can be kept on follow up, most often these patients are unwilling for a close follow-up and straightaway request for a repeat procedure. The risk was higher for residual disease when these margin-positive patients were postmenopausal, with high colposcopic score and inner margin positivity. Several studies determined 'postmenopause' was a risk factor for surgical margin positivity, and our study confirmed this [13].

Papoutsis et al. reported that conization thickness of more than 10 mm led to significantly less residual disease [14]. Kliemann et al. reported that the chances of complete resection of CIN 2–3 are around 100% with a cone thickness of 20 mm [15]. Beyer et al. reported 100% negative margin cones with a cone thickness of 20 mm. A resection thickness between 10 and 19.9 mm led to 73% negative margin cones [9]. Oz et al. reported that cone volume, cone length and cone thickness were not associated with the margin status of the conization specimens, but they found that mean cone thickness was significantly different between margin-positive and margin-negative patients [16].

We calculated using the Youden index that the chance of margin positivity was high when the mean length of the cone was less than 0.513 cm and the mean thickness of cone was less than 0.35 cm. The chance of residual disease was less if the cone specimen had a minimum length of 0.775 cm and a minimum thickness of 0.65 cm. A few studies, however, recommend frozen section examination during the procedure and performing procedures with more experienced surgeons as useful options for high-risk patients to minimize surgical

margin positivity rates and maximize cure rates from one-step intervention [17,18].

In conclusion, we suggest that when we are in doubt regarding the margins, it is always better to perform multiple passes for lesions with a high Swede score with an initial smear of HSIL. When we get a margin positivity for LEEP specimen in postmenopausal women and if the inner margin is positive, the chance of residual disease is higher and should always be kept on very strict and close follow-up or consider a repeat procedure and to reduce residual disease, a minimum thickness of 0.65 cm and a length of 0.77 cm are needed.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest relevant to this article to disclose.

Informed consent Informed consent was obtained from all the cases.

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