
GYNAECOLOGY

Prevalence and Risk Factors for Positive Surgical Margin after Loop Electrosurgical Excision Procedure (LEEP) in Patients with High Grade Squamous Intraepithelial Lesion

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ABSTRACT

Objective: To determine the prevalence and risk factors for positive surgical margin after LEEP in patients with high grade squamous intraepithelial lesion (HSIL).

Material and Methods: Medical records of all women (n = 575) who underwent LEEP and histopathological diagnosed HSIL between January 2008 and December 2012 in our institution were reviewed. The margins of surgical specimens were re-evaluated by a pathologist. Clinical data and status of surgical margin were recorded. The prevalence and risk factors for positive surgical margin were analyzed.

Results: Complete data of 547 women with HSIL who underwent LEEP were obtained. Mean age of the women was 41.8 ± 12.5 years (ranging from 17 to 75 years). The majority of them were multiparous (n = 405 or 74.1%) and premenopause (n = 464 or 84.8%). Positive LEEP surgical margin was found in 167 cases (30.5%). In multivariable analysis, multiparity and glandular involvement were two independent risk factors for positive LEEP surgical margin; adjusted relative risk of 8.10 (95% confidence interval, 3.82-17.20) and 14.10 (95% confidence interval, 8.34-23.83), respectively.

Conclusions: The prevalence of positive margin in women with HSIL who underwent LEEP was 30.5%. Multiparity and glandular involvements were significant factors associated with the margin involvement.

Keywords: HSIL, positive margin, LEEP

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Introduction

Cervical cancer is a major global health burden. Each year, an estimated 520,000 new cases of cervical cancer were discovered worldwide⁽¹⁾. Among this, approximately 85% of them occur in developing countries⁽¹⁾. Cervical cancer is considered a preventable cancer because it has a long interval of progression from normal cervical epithelium, passing a certain period of precancerous lesion, until it becomes invasion⁽²⁻³⁾. It is well-accepted that the prevention of cervical cancer is to detect and treat patients in a precancerous stage. Pap smear is the widely used method which is proved effectively for screening and detects the precancer of the cervix⁽⁴⁾. Women, who have abnormal Pap smear, will need further investigation using a colposcopy to confirm the diagnosis. In those who are diagnosed with Cervical Intraepithelial neoplasia (CIN) 2-3 (or high grade squamous intraepithelial lesion [HSIL]), cervical conization is required for the treatment.

Conization can be performed with cold-knife conization (CKC), loop electrosurgical excision procedure (LEEP) or laser. LEEP is widely accepted for the diagnosis and treatment of CIN because of its simplicity, efficacy and being a method that can be performed in an outpatient setting with only minimal blood loss. The results of LEEP have been supported to be comparable to CKC⁽⁵⁻⁷⁾. Evidences suggested that women with incomplete excision were at risk of persistence or recurrence of cervical dysplasia after LEEP⁽⁸⁻⁹⁾. Patients with positive surgical margin after LEEP had more than three times risk of recurrence of the disease⁽⁹⁾.

In clinical practice, knowing characteristic features that associate with positive surgical margin might be useful because this information could be used to achieve optimal surgical technique in order to minimize an incomplete excision as well as to counsel the patients regarding management plan. The primary aim of this study was to determine the prevalence of positive surgical margin after LEEP in patients with high grade squamous intraepithelial lesion (HSIL). Factors associated with positive surgical margin were also

evaluated.

Materials and Methods

The present study was a retrospective descriptive study. It was conducted after receiving approval from the Vajira Institutional Review Board. All patients who underwent LEEP and were diagnosed with CIN 2-3 (HSIL) by histopathological examination between January 2008 and December 2012 in our institution were reviewed. Clinical data were extracted include age, parity, menopausal status, HIV infection, depth of conization and glandular involvement.

From a study of Sheanakul et al⁽¹⁰⁾, the prevalence of positive surgical margin after LEEP was 41%. We obtained this information along with a 5% chance of making a type I error and the maximum allowable error of 5% to calculate the sample size. We added 20% to the number calculated in the event that some subjects were excluded. This resulted in at least 447 women needed. As we desired to include as many women as we could reviewed, we therefore obtained data from all women who underwent LEEP over a 5-year period.

The cervical specimens were re-evaluated by a single experienced pathologist to confirm the pathological result and determine surgical margins. The presence of HSIL at the edge of specimen was defined as a positive margin. In case of equivocal result, another pathologist was consulted to confirm the status of the surgical margins. Women who had incomplete medical records were excluded.

Data were analyzed by parametric statistics using SPSS statistical software version 22.0 (IBM corporation, Armonk, NY, USA). Descriptive statistics were used to determine demographic data and summarized as mean with SD and minimum and maximum values as well as number and percentage. Categorical variables were composed using the Chi-square test. The characteristic features which were significantly associated with a positive margin by Chi-square test as well as potential confounding factors were entered into a multiple logistic regression model. The risk factors for positive surgical margin were presented as relative risk (RR) with 95% confidence intervals (CIs). A P-value

of less than 0.05 was considered statistical significant.

Results

During the study period, there were 575 women who were diagnosed with HSIL and underwent LEEP. Twenty eight cases were excluded because of incomplete data; the remaining 547 cases were

analyzed. The mean age of the women was 41.8 ± 12.5 years (ranging from 17 to 75 years). The characteristics of the study population were presented in Table 1. The majority of these women were multiparous (74.1%) and premenopause (84.8%). It was found that 18.8% of them had HIV infection.

Table 1. Characteristic features of the study population (n = 547)

Characteristic		Positive margin		
		Ectocervix (n = 89)	Endocervix (n= 34)	Both (n = 44)
Age (years)				
Mean (range)	41.81 (17-75)	45.51 (25-75)	39.56 (22-64)	42.50 (23-71)
Parity, n (%)				
Nulliparous	142 (25.9)	2 (22.2)	4 (44.5)	3 (33.3)
Multiparous	405(74.1)	87 (55.1)	30 (19.0)	41 (25.9)
Menopausal status, n (%)				
Yes	83 (15.2)	17 (51.5)	5 (15.2)	11 (33.3)
No	464 (84.8)	72 (53.7)	29 (21.7)	33 (24.6)
HIV infection, n (%)				
Yes	103 (18.8)	18 (52.9)	7 (20.6)	9 (26.5)
No	444 (81.2)	71 (53.4)	27 (20.3)	35 (26.3)

Of these 547 women, positive surgical margins were identified in 167 cases (30.5%). The positive margins were most commonly reported at the endocervix (89 cases or 53.3%) whereas 34 cases (20.4%) were found to have lesions at the ectocervix. Approximately one fourth of the women (44 cases or 26.3%) had lesions at both ecto- and endocervix.

A univariable analysis demonstrated that multiparity and glandular involvement were significant

factors for positive surgical margin after LEEP. After adjustment for potential confounding factors, these two variables were identified as independent risk factors for positive LEEP surgical margins, with adjusted RR of 8.10 (95% CI, 3.82-17.20) and 14.10 (95% CI, 8.34-23.83), respectively. In contrast, the menopausal status, HIV Infection and depth of conization were not found to be significant factors. (Table 2).

Table 2. Uni- and multivariable analyses to determine significant factors for positive surgical margins after LEEP

Factors	Negative margin n	Positive margin n	RR (95% CI)	adjusted RR* (95% CI)
Parity, n (%)				
Nulliparous	133 (93.7)	9 (6.3)	6.16	8.10
Multiparous	247 (61.0)	158 (39.0)	(3.23-11.72)	(3.82-17.20)
Menopausal status, n (%)				
Yes	52 (62.7)	31(37.3)	1.27	0.69
No	328 (70.7)	136 (29.3)	(0.93-1.74)	(0.37-1.28)
HIV, n (%)				
Positive	67 (65.0)	36 (35.0)	1.19	0.92
Negative	313 (70.5)	131 (29.5)	(0.88-1.60)	(0.52-1.61)
Depth of conization, n (%)				
< 10 mm	227 (70.5)	95 (29.5)	1.09	0.92
≥ 10 mm	153 (68.0)	72 (32.0)	(0.84-1.40)	(0.58-1.44)
Glandular involvement, n (%)				
Yes	121 (45.5)	145 (54.5)	6.96	14.10
No	259 (92.2)	22 (7.8)	(4.59-10.55)	(8.34-23.83)

* Adjusted for variables in the table.

CI = Confidence interval, RR = relative risk

Discussion

In meta-analysis, the prevalence rates of positive surgical margins in cervical conization (CKC or LEEP or laser) specimens varied from 3% to 47%⁽¹¹⁾. Our study which included only LEEP cases revealed the prevalence of positive surgical margins in those who were diagnosed with HSIL was 30.5%, which fell within the range of previous reported percentages. Focusing on the studies which evaluated only women who underwent LEEP, Felix et al⁽¹²⁾ reported that the rates of positive surgical margins was 33.3% which was similar to our finding. Nevertheless, the 30.5% rate detected in our study was somewhat lower than a 40.6% rate previously reported by Sheanakul et al⁽¹⁰⁾ who also conducted a study in our institution in women who underwent LEEP between June 1996 and May 2001. The difference in the prevalence rates between both studies might be that women who were included in the

study of Sheanakul et al were diagnosed with either high grade cervical lesions or micro-invasive cervical cancer while we excluded those who had micro-invasive lesions.

Among the five characteristic features studied, we found that multiparity and glandular involvements were significant risk factors for positive LEEP surgical margin by multivariable analysis. Similar to our finding, Tillmanns et al⁽¹³⁾ observed a significantly increased risk of positive margins in women with increased parity. The explanation for this relationship is that the widening and slit-like cervical os as a result of vaginal delivery lead to inadequate surgical excision specimen. This explanation was supported by our study which demonstrated that positive surgical margins were more commonly observed at ectocervix than endocervix among multiparous women (Table 1). In contrast to Tillmanns et al and our results, Samneangsano et al⁽¹⁴⁾

evaluated the risk in Thai women who underwent CKC reported that nulliparity was associated with positive margins. In such a study, the authors proposed that inadequate conization due to deep endocervix might be a possible reason. Regarding an association of glandular involvement with the risk of positive LEEP margins, our finding was confirmed by a previous study of Kir et al⁽¹⁵⁾ who reported that glandular involvement was associated with the degree of severity of cervical lesions.

In this study, menopausal status, HIV infection, and depth of conization were not identified as significant risk factors for positive surgical margins. Unlike our results, Lu et al⁽¹⁶⁾ reported that the postmenopause was a risk factor associated with a positive margin. Aside from this, Boardman et al⁽¹⁷⁾ observed that HIV-positive women were more likely to undergo conization for an abnormal endocervical curettage specimen, persistent CIN I, or inadequate colposcopic examination. Kietpeerakool et al⁽¹⁸⁾ who performed a study in Thai women reported that the invasive cancer either on cytology or LEEP specimens with a cone length of less than 10 mm was a significant predictor of incomplete excision.

The strengths of our study were that the number of our sample size was larger than those in many previous studies. In addition, the margins of surgical specimens of all cases were re-evaluated, so the results were reliable and consistent. Despite this, we were aware of some limitations of this study. First, the sample size of this study was calculated to determine the prevalence of positive surgical margin. Hence, it might not yield adequate power to evaluate some factors contributing to positive margin. Second, as it was a retrospective study, some data that could be the risk factors of positive LEEP surgical margin were unavailable or missed, e.g. area of abnormal finding from colposcopy, endocervical involvement from endocervical curettage, route of delivery, surgeon's experience, transformation zone type, type of anesthesia, width of cone biopsy etc. Third, we did not assess the rates of persistent and recurrent (both precancerous and cancerous) lesions in women who

had a positive surgical margin. Hence, further prospective research with certain period of follow up is required to determine an association between these possible influence factors and positive margin, and also the significant of margin involvement to the persistent or recurrent of the disease.

In conclusions, the prevalence of a positive margin in women with HSIL who underwent LEEP was 30.5%. Multiparity and glandular involvement were significantly associated with margin involvement. These factors might be useful for counselling and decision making regarding the suitable procedure for each case scenario. For example, multiple loop cutting or CKC might yield advantage in terms of reducing the positive surgical margin in a multiparous woman who has a widening cervix or ectropian. Since our study had limited number of women, further research with larger sample size is needed to determine other factors which may affect positive surgical margin.

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ความชุกและปัจจัยที่มีผลต่อการตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อหลังการตัดปากมดลูกด้วยห่วงไฟฟ้าในผู้ป่วยที่วินิจฉัย High Grade Squamous Intraepithelial Lesion (HSIL)

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วัตถุประสงค์: เพื่อศึกษาความชุกและปัจจัยที่มีผลต่อการตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อปากมดลูกจากการตัดด้วยห่วงไฟฟ้าในผู้ป่วย HSIL

วิธีดำเนินการวิจัย: ศึกษาข้อมูลย้อนหลังของผู้ป่วยที่วินิจฉัย HSIL และได้รับการตัดปากมดลูกด้วยห่วงไฟฟ้า จำนวน 575 คน ในช่วงเวลา 1 มกราคม 2551 ถึง 31 ธันวาคม 2555 โดยนำสไลด์ชิ้นเนื้อปากมดลูกทั้งหมดมาตรวจและอ่านผลใหม่อีกครั้งโดยพยาธิแพทย์ และนำข้อมูลที่ได้ไปวิเคราะห์

ผลการวิจัย: ในช่วงเวลาดังกล่าวพบผู้ป่วยที่วินิจฉัย HSIL และได้รับการตัดปากมดลูกด้วยห่วงไฟฟ้า ที่มีข้อมูลครบถ้วนจำนวน 547 คน อายุเฉลี่ย 41.81 ปี (ตั้งแต่ 17 ถึง 75 ปี) ส่วนใหญ่ของผู้ป่วยมีบุตร (405 คน หรือร้อยละ 74.1) และยังมีประจำเดือน (464 คนหรือร้อยละ 84.8) ผู้ป่วยที่มีรอยโรคที่ขอบชิ้นเนื้อ มีจำนวน 167 คน (ร้อยละ 30.5) โดยปัจจัยที่มีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติกับผู้ป่วยที่มีรอยโรคที่ขอบชิ้นเนื้อ ได้แก่ การมีบุตรและ glandular involvement โดยพบค่า adjusted relative risk เท่ากับ 8.10 (ระดับความเชื่อมั่นร้อยละ 95 คือ 3.82-17.20) และ 14.1 (ระดับความเชื่อมั่นร้อยละ 95 คือ 8.34-23.83) ตามลำดับ

สรุป: ความชุกของการตรวจพบพยาธิสภาพ ที่ขอบชิ้นเนื้อปากมดลูกจากการตัดด้วยห่วงไฟฟ้าในผู้ป่วยที่วินิจฉัยระยะ HSIL คือร้อยละ 30.5 ปัจจัยที่มีความสัมพันธ์กับผู้ป่วยที่มีรอยโรคที่ขอบชิ้นเนื้อและมีนัยสำคัญทางสถิติได้แก่การมีบุตรและผลตรวจชิ้นเนื้อที่มี glandular involvement