Tumor Persistence in High Grade Squamous Intraepithelial Lesion Patients with Positive Surgical Margin Post Loop Electrosurgical Excision Procedure

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Objective: *To determine the rates of persistent and recurrent tumors in patients with High Grade Squamous Intraepithelial Lesion (HSIL) who had positive surgical margin from Loop Electrosurgical Excision Procedure (LEEP)*

Material and Method: *Clinical and pathological data of all women who underwent LEEP procedures and revealed HSIL lesions with positive surgical margin between July 1997 and December 2004 were recorded.*

Results: *Histologic diagnoses of HSIL with positive surgical margin were found in 95 cases during the study period. Residual diseases were identified at ectocervical margins in 46 cases (48.4%), endocervical margin in 26 cases (27.4%), and both margins in 23 cases (24.2%). Subsequent hysterectomy was performed in 58 cases (61.0%). The remaining 37 cases (38.9%) underwent periodic follow-up with the median follow up period of 11 months (range, 1 -74 months). Persistent diseases were identified in 18 of 58 hysterectomized cases but none in 37 follow-up cases. Recurrent disease was identified in only one case in the follow-up group. Overall the rates of persistent and recurrent disease were found in 18.9% and 1.1% respectively.*

Conclusion: *In HSIL patients with positive surgical margin from LEEP, the rate of persistent disease was 18.9%, while the rate of recurrence was 1.1%.*

Keywords: *HSIL, LEEP (loop electrosurgical excision procedure), Positive margin, Persistence, Recurrence*

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Invasive cancer of the cervix is the most common gynecologic cancer in Thailand[1]. Among various histologic types of cervical carcinoma, squamous cell carcinoma is the most common[2]. Cervical squamous cell carcinoma usually develops from the precursors or preinvasive lesions. They have been classified in a variety of ways[3] based on the degree of epithelial dedifferentiation. The older systems are the dysplasia-Carcinoma In Situ (CIS) system and the Cervical Intraepithelial Neoplasia (CIN) classification; mild dysplasia or CIN I stands on one end and severe dysplasia/CIS or CIN III on the other[3]. The newer cytology report system, known as Bethesda system categorizes cervical cytologic squamous intraepithelial abnormalities into Low grade Squamous Intraepithelial Lesion (LSIL) encompassing HPV infection and CIN I and High grade Squamous Intraepithelial Lesion (HSIL) encompassing CIN II and CIN III[2].

Certain numbers of preinvasive CIN lesions would progress to more severe lesions or invasive cancer at different percentages and time intervals if left untreated. These variations depend partly on the degree or severity of histologic abnormality. The higher degree of abnormality, the sooner and higher percentages they would progress to more severe lesions[4]. For this reason, while CIN I lesion could be managed by observation and a follow-up, CIN III must be treated by complete destruction of abnormal epithelium, preferably excision of the cervix or conization[5].

Conization or excision of the cervix can be achieved by many means; the common methods are Cold Knife Conization (CKC) and Loop Electrosurgical Excision Procedure (LEEP). Both methods provide

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tissue for histopathologic evaluation. However, LEEP becomes a more popular procedure because it can be performed in an out patient setting with only minimal blood loss. The result of LEEP is also comparable to CKC[6-8]. The efficacy of LEEP is approximately 82.1% according to reports [6]. The rates of incomplete excision or residual diseases are similar between LEEP and CKC, ranging between 14.1%and 48.0% [5,6,9-15]. Patients with incomplete excision or positive surgical margin after LEEP are found to have a higher incidence of recurrence or persistence of residual disease than those with negative surgical margins[9,12,16]. Theoretically, this group of patients should have further definite treatment or need close follow-up[11-12]. However, some authors reported the rate of recurrent or persistent disease after positive surgical excision of CIN to be only 10.9-16.5%[5, 11]. This may be caused by the coagulation diathermy that was applied for hemostasis at the cervical stump after LEEP and has further destroyed abnormal tissue at the residual margin, and provided an extramargin of safety. The inflammatory reaction of cervical tissue to LEEP that serves as a host-immune response might lead to a resolution of residual CIN at the margins[11]. Based on these possibilities, further surgical treatment such as hysterectomy is not necessary in all patients with positive margin, especially in young patients who wish to preserve fertility.

To add more information for the management decision of this particular group of patients, the authors studied the rate of persistent and recurrent disease in HSIL patients with positive surgical margins after LEEP in our institution. Factors associated with tumor persistence were also studied.

Material and Method

The present study was conducted after the approval from the Ethics Committees of our institution. All patients who underwent LEEP for their cervical HSIL at the Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira Hosptial, between July 1997 and December 2004 were identified. The patients with positive surgical margins from the LEEP specimens were eligible for the study. Generally, in our institution, LEEP was performed by a gynecologic oncologist or a resident under his or her supervision. Routinely in the Department of Pathology in our institution, the whole LEEP specimens were serially sectioned to include all ectocervical and endocervical mucosa. The number of sections depended on the size and shape of the specimens. Hysterectomy was performed at the discretion of the gynecologist. The cervix was randomly sectioned for at least 4 sections (one from each quadrant) in the hysterectomy specimens with no suspicious gross lesion. Additional sections were taken at the discretion of the pathologist. After LEEP, all patients were followed-up at a 3-month interval by pelvic examination and Pap smear. Colposcopic examination and/or biopsy were conducted as indicated.

Persistent disease in the present study was referred to residual cervical lesions after LEEP, as evidenced from hysterectomy specimens or any evidence of diseases detected $\leq$ 6 months after LEEP. Recurrence was defined when disease was detected at any time > 6 months. Data collected were: age, parity, indication and date of LEEP, histologic diagnosis from LEEP, margin site and pathology of the positive margins, pathology of hysterectomy specimens, date of hysterectomy, date of persistent or recurrent disease, and date of last follow-up. Pathological reviews were performed only in cases where the margin status or pathology of margins was not stated.

Data were analyzed by parametric and non-parametric statistics using SPSS statistical software version 11.5 (Chicago, IL). Descriptive statistics were used for demographic data and summarized as mean or median. Categorized variables were compared with the chi-squared test or Fisher's exact test as appropriate. Differences between continuous variables were evaluated with unpaired t-test for variables that were normally distributed and the Mann-Whitney U test for variables that were not normally distributed. P value of 0.05 was considered as statistical significance.

Results

During the study period**,** 176 patients underwent LEEP, and the pathological diagnosis revealed cervical HSIL. Ninety-five patients (54.0%) had positive surgical margins and were eligible for the study. Median age of these 95 patients was 43 years. The indications for LEEP were therapeutic in 53.7% and diagnostic in 46.3%. The positive margins were reported most commonly at the ectocervix in 48.4%, whereas the lesions were found at the endocervix in 27.4% and at both ecto- and endocervix in 24.2%. The pathology of the positive margins varied from Human Papilloma Virus (HPV) infection, CIN I, and CIN II, and CIN III (Table 1).

Overall, 58 out of 95 patients (61.1%) underwent hysterectomy after positive surgical margins reported from LEEP; 50 patients (86.2%) had surgery within 3 months and eight patients (13.8%) at more

than 3 months after LEEP. Median age of the patients in this group was 46 years. The most common histopathology at the margin was CIN III (62.1%) for these 58 patients. The majority of lesions (46.6%) were only at the ectocervical margin, while 31.0% were only at the endocervical margin, and 22.4% were found at both ecto- and endocervical margins (Table 1). Eighteen patients had residual diseases in the hysterectomy specimens and the pathology of these were koilocytic atypia or CIN I, CIN II in eight patients (44.4%) and CIN III in the other ten patients (55.6%).

Thirty-seven patients (38.4%) in the present study did not have further treatment for their positive LEEP surgical margins and underwent routine surveillance. The median age of patients in this group was 33 years. More than half of the patients (78.4%) had positive ectocervical or both ecto- and endocervical margins (Table 1). The most common histopathology of positive margin in this group was CIN III at 40.5%. The median duration of follow-up was 11 months (range, 1-74 months); 29.7% had a follow-up period for less than 6 months, 24.4% for 6-12 months, 27.0% for 12-24 months, and 18.9% for more than 24 months. Among these 37 patients who were followed-up, no persistent disease was found in 6 months after LEEP. Overall, 18 out of 95 (18.9%) had persistent disease.

Recurrent disease after LEEP was found in follow-up patients 1 out of 37 patients. The pathology of positive LEEP margin was HSIL with koilocytic atypia at ectocervix. The cervical Pap smear performed at 19 months during the follow-up period was class III; colposcopic directed biopsy showed LSIL with koilocytic atypia. Her subsequent Pap smears during the follow-up revealed only class I-II cytology (normal or inflammation) without evidence of disease progression. None in the hysterectomy group had recurrent disease. The rate of recurrence in the whole group was 1.1% (1/95 patients).

The authors studied the following clinicopathological factors that might affect the occurence of persistent diseases; age, parity, severity of residual lesions at the margins of LEEP, the time interval from LEEP to hysterectomy (Table 2). No factors had significant association with the rate of persistent disease. The severity of pathology of positive margin also tended to associate with higher incidence of residual disease but did not reach statistical significant level, 36.1% of CIN III positive margin had residual disease versus

Table 1. Basic characteristics of patients in the hysterectomy group, follow-up group and all patients

Characteristics	Hysterectomy Group (n = 58)	Follow-up Group (n = 37)	All patients (n = 95)
Age (years)			
Median (range)	46.6 (24-69)	33.0 (20-82)	43.2 (20-82)
≤ 40	20 (34.5%)	21 (56.8%)	41 (43.2%)
> 40	38 (65.5%)	16 (43.2%)	54 (56.8%)
Parity			
0	3 (5.2%)	5 (13.5%)	8 (8.4%)
1	10 (17.2%)	14 (37.9%)	24 (25.3%)
2	24 (41.4%)	9 (24.3%)	33 (34.7%)
> 2	21 (36.2%)	9 (24.3%)	30 (31.6%)
Indication for LEEP			
Diagnostic	31 (53.4%)	13 (35.1%)	44 (46.3%)
Therapeutic	27 (46.6%)	24 (64.9%)	51 (53.7%)
Pathological diagnosis from LEEP			
CIN II	3 (5.2%)	2 (5.4%)	5 (5.3%)
CIN III	55 (94.8%)	35 (94.6%)	90 (94.7%)
LEEP margin			
positive at ectocervix	27 (46.6%)	19 (51.4%)	46 (48.4%)
positive at endocervix	18 (31.0%)	8 (21.6%)	26 (27.4%)
positive both ectocervix and endocervix	13 (22.4%)	10 (27.0%)	23 (24.2%)
Pathology of positive margin			
CIN I and HPV	20 (34.5%)	18 (48.6%)	38 (40.0%)
CIN II	2 (3.4%)	4 (10.8%)	6 (6.3%)
CIN III	36 (62.1%)	15 (40.6%)	51 (53.7%)

Table 2. Clinical and pathological characteristics features and the presence of persistent disease in the hysterectomy specimens (n = 58)

Characteristics	Residual tumor		p value
	Absence (n = 40)	Presence (n = 18)	
Age (years)			
Median (range)	46.0 (24-67)	45.5 (30-69)	0.749*
≤ 40	15 (75.0%)	5 (25.0%)	0.471**
> 40	25 (65.8%)	13 (34.2%)	
Parity			
Median (range)	2 (0-5)	2 (1-6)	0.511*
≤ 2	27 (73.0%)	10 (27.0%)	0.381**
> 2	13 (61.9%)	8 (38.1%)	
Indication for LEEP			
Diagnostic	21 (67.7%)	10 (32.3%)	0.829**
Therapeutic	19 (70.4%)	8 (29.6%)	
Report of LEEP margin			
positive at ectocervix	17 (63.0%)	10 (37.0%)	
positive at endocervix	12 (66.7%)	6 (33.3%)	0.370**
positive both ectocervix and endocervix	11 (84.6%)	2 (15.4%)	
Pathology of positive margin			
HPV, CIN I, CIN II	17 (77.3%)	5 (22.7%)	0.285**
CIN III	23 (63.9%)	13 (36.1%)	
Interval from LEEP to hysterectomy			
≤ 3 months	33 (66.0%)	17 (34.0%)	0.413***
> 3 months	7 (87.5%)	1 (12.5%)	

* Mann-Whitney U test
** Chi-square test
*** Fisher's exact test

22.7% of HPV, CIN I, or CIN II (p value = 0.285). Although the authors found a greater number and higher percentages of patients who underwent surgery within 3 months after LEEP had residual disease in the hysterectomy specimens than those patients who underwent surgery after 3 months, 17/50 patients (34.0%) versus 1/8 patients (12.5%) respectively. This was not significantly different (p = 0.413).

Discussion

The prevalence of positive surgical margin after LEEP from various studies on cervical lesions of CIN I- CIN III ranged from 22.0-48.0%[5,6,9,11,13]. Incomplete excision or positive margins have been reported to be associated with several predisposing factors such as high grade lesion, endocervical involvement, advanced age and higher parity[9,10,15-19]. Many studies reported association between positive surgical margin and an increased risk of persistence and recurrence, with possibilities of a concealed or subsequent development of invasive cancer and decreased cure rates[5,6,9-16,18]. However, not all patients with incomplete excision develop persistent or recurrent disease. One study showed that 83.8% of patients with CIN in the resection margin experienced no recurrence after a 5-year follow-up[20]. This contradictory finding may lie on the possibilities mentioned earlier.

The present study found a positive margin in 54.0% and was higher than those reported in other studies[9,11,21]. This was because the present study focused only on the HSIL or CIN II-CIN III lesions while other studies included all CIN lesions.

Persistent diseases were evidenced at 18.9% in the present study. This figure was comparable with the results from other studies of persistent disease after LEEP, which ranged from 14.2-34.7%[14,15,18].

Many factors were reported to be associated with persistent or residual diseases after LEEP such as the site of positive margins[5,10-13,15,17,18]. The site of endocervical margin appears to be more predictive of

persistent disease than the positive margins at the ectocervix. The positive margins at the endocervix were associated with persistent or residual diseases in 32.7%, 41.4% and 61.0% compared to 2.1%, 20.0% and 30.0% if positive ectocervical margin and 1.1%, 30.0% and 8.0% if positive at both endo- and ectocervical margins in the study of Lapaquette et al, Noor et al, and Suprasert et al, respectively[10,15,18]. In contrast to these studies, the authors could not explain why more persistent diseases were found in the patients with positive ectocervical margins at 37.0% (10/27 patients) than those with positive endocervical margin or both margins.

The severity or grade of lesions at positive LEEP margin is the other risk factor for the persistent or residual tumors. Some studies found that severity of lesion was the only associated factor with positive margin; high grade lesions were associated more with persistent disease than low grade lesions 36.6-42.2% versus 0-31.0%[9,10,15-17]. Although, we found that high grade lesion had more persistent disease than low grade lesion 36.1% versus 22.7% but this did not reach statistical significance ($p = 0.285$). More patients are needed to confirm this clinical finding.

More controversial issues exist on the association of persistent disease and age. Tanompongchat et al found advanced age of $\geq$ 40 years as a significant factor for residual disease, 49.4% versus 23.5%[17]. Other studies did not corroborate this finding and found no association between age and persistent disease[14,15,19]. Although the authors found that the patients with advanced age (> 40 years) had more persistent disease, in line with the finding of former authors[17], the difference was not statistically significant.

The interval between LEEP and hysterectomy might be another important factor for persistent diseases. The authors found that patients who had delayed hysterectomy (> 90 days) has less persistent disease than those with immediate hysterectomy, 1.0% versus 17.0%. This was also found in the studies of Lapaquette et al and Noor et al who found persistent diseases 0-6.4% versus 17.0-33.0% in the delayed and immediate hysterectomy respectively[10,15]. The authors believed that the inflammatory tissue reaction as had been mentioned earlier was responsible for this difference.

Regarding the rate of recurrence after LEEP with positive surgical margins, the recurrent rate of disease in the present study was only 1.1% and was lower than the other studies that ranged from 10.2% to 47.0%[6,9,10,12,14,15]. This may partly be due to the population in the present study that included only HSIL while other studies included microinvasive or invasive disease and carry a higher risk of recurrence. The other reason for this low rate of recurrence might be due to the relatively short period of follow-up.

In conclusion, the present study found that not all patients with positive surgical margins after LEEP had persistent disease in subsequent hysterectomy specimens and the rate of recurrence was low. The patients who want to preserve fertility function can have a follow-up instead of an immediate hysterectomy. Nevertheless, the patients who have risk factors as described should be thoroughly counseled for the higher comparative risk, and the follow-up or treatment plan must be individualized.

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การคงอยู่ของพยาธิสภาพในผู้ป่วย high grade squamous intraepithelial lesion (HSIL) ที่มีพยาธิสภาพที่ขอบชิ้นเนื้อจากการผ่าตัดปากมดลูกโดยใช้ลวดไฟฟ้า

อรุณี แสนเกษม, เถาวลัย ถาวรามร, สุมนมาลย์ มนัสศิริวิทยา, ศิริวรรณ ตั้งจิตรกมล

วัตถุประสงค์: *เพื่อศึกษาอัตราการคงอยู่และกลับเป็นซ้ำของพยาธิสภาพหลังจากการผ่าตัดปากมดลูกโดยใช้ลวดไฟฟ้า ที่มีพยาธิสภาพที่ขอบชิ้นเนื้อของผู้ป่วย HSIL*

วัสดุและวิธีการ: *รวบรวมประวัติ ผลชิ้นเนื้อทางพยาธิวิทยา และข้อมูลการตรวจติดตามของสตรีที่ผ่านการผ่าตัดปากมดลูกโดยใช้ลวดไฟฟ้า และมี ผลพยาธิสภาพเป็น HSIL ร่วมกับมีพยาธิสภาพที่ขอบชิ้นเนื้อ ในช่วงเวลาตั้งแต่เดือนกรกฎาคม พ.ศ. 2540 - เดือนธันวาคม พ.ศ. 2547*

ผลการศึกษา: *ในช่วงเวลาดังกล่าวพบผู้ป่วยได้รับการวินิจฉัย HSIL ร่วมกับมีพยาธิสภาพที่ขอบชิ้นเนื้อ 95 ราย พบมีรอยโรคที่ขอบชิ้นเนื้อด้านนอก (ectocervical margin) 46 ราย (48.4%) มีรอยโรคที่ขอบชิ้นเนื้อด้านใน (endocervical margin) 26 ราย (27.4%) และมีรอยโรคที่ขอบชิ้นเนื้อทั้งด้านนอกและด้านใน (both ectocervical and endocervical margin) 23 ราย (24.2%) ผู้ป่วย 58 ราย (61.1%) ได้ทำการตัดมดลูกในเวลาต่อมา ผู้ป่วยที่เหลือ 37 ราย (38.9%) ได้ทำการตรวจติดตามการรักษา โดยมีช่วงระยะเวลามัธยฐานของการตรวจติดตาม 11 เดือน (1-74 เดือน) พบการคงอยู่ของรอยโรคในผู้ป่วยที่ทำการตัดมดลูก 18 ราย จาก 58 ราย และไม่พบเลยในกลุ่มที่ทำการตรวจติดตาม การเกิดการกลับเป็นซ้ำของรอยโรคพบ 1 ราย ซึ่งเป็นผู้ป่วยในกลุ่มที่ตรวจติดตาม อัตราการคงอยู่ของรอยโรคและการกลับเป็นซ้ำโดยรวมคิดเป็นร้อยละ 18.9 และ 1.1 ตามลำดับ*

สรุป: *ในผู้ป่วย HSIL ที่มีพยาธิสภาพที่ขอบชิ้นเนื้อจากการทำการผ่าตัดปากมดลูกโดยใช้ลวดไฟฟ้า พบอัตราการคงอยู่ของรอยโรคร้อยละ 18.9 และพบอัตราการกลับเป็นซ้ำร้อยละ 1.1*