
GYNAECOLOGY

Residual Disease in Hysterectomy Specimens after Loop Electrosurgical Excision or Cold Knife Conization in High Grade Squamous Intraepithelium Lesion and Microinvasive Cervical Carcinoma

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ABSTRACT

Objective: To study the residual disease in subsequent hysterectomy specimens after loop electrosurgical excision (LEEP) or cold knife conization (CKC) and its correlation with adequacy of margins in previously excised specimens.

Materials and Methods: Medical records and microscopic specimens of patients who were diagnosed as high grade squamous intraepithelial lesion (HSIL) or microinvasive cervical carcinoma (MIC) in LEEP or CKC specimens with subsequently hysterectomy within 6 months after the diagnosis from January 1, 1999 to April 30, 2009 were reviewed. Adequacy of margins and residual lesion were specifically evaluated.

Results: Of 156 cases, 87 of them (55.8%) had positive margin in LEEP/CKC specimens, whereas residual disease was identified in hysterectomy specimens in 73 cases (46.8%). There was no significant difference of residual tumor in the uterus between positive- and negative-margin of LEEP/CKC specimens ($p=0.61$). Comparing between LEEP and CKC, positive margin was significantly higher in LEEP specimens (72.9% vs. 47.3%, $P=0.004$), but the presence of residual diseases in hysterectomy specimens was similar between both groups and was not related to the marginal status. The numbers of positive margin sites in LEEP/CKC specimen were positively correlated to the residual disease in the uterus. Invasive squamous cell carcinoma was identified in the hysterectomy specimen of case that had negative margin of CKC specimen.

Conclusion: There was high prevalence of residual disease in uterus following LEEP/CKC. Patients with increased numbers of positive margin sites in LEEP/CKC specimens tended to have more residual disease. Positive margins were more common in patients who underwent LEEP than CKC. Negative margin status could not rule out invasive residual disease in hysterectomy specimen.

Keywords: residual disease, hysterectomy specimen, high grade squamous intraepithelial lesion, microinvasive carcinoma, conization, positive margin

Introduction

Loop electrosurgical excision (LEEP) and cold knife conization (CKC) are the most common excisional surgical methods for diagnostic and therapeutic procedures for cervical intraepithelial neoplasia (CIN)⁽¹⁻²⁾. It is well established that eradication of these lesions prevents the development of invasive cervical carcinoma. Nowadays, there is a trend towards more conservative treatment of CIN and microinvasive cervical carcinoma. Excisional cervical procedures have been advocated to be an adequate therapeutic measure for the disease irrespective of age or child requirement if the resection margins are free of cervical dysplasia⁽³⁾. Previous studies showed 20.1-47.4% residual disease in subsequent hysterectomy specimens, varying from CIN1 to invasive squamous cell carcinoma stage IA2⁽⁴⁻⁷⁾.

Adequacy of the excisional cervical specimen is often used to predict the residual disease in subsequent hysterectomy specimens. Although some studies^(7,8) found a direct correlation between positive margin and residual disease in post cone hysterectomy specimen but others failed to confirm a significant correlation^(8,9).

According to these controversial results, this study was aimed to evaluate the residual disease in subsequent hysterectomy specimens after LEEP or CKC and its correlation to the status of margins in previously excised cervical specimens.

Materials and Methods

Seven hundred and thirty-nine cases of LEEP and CKC diagnosed as high grade squamous intraepithelial lesion (HSIL) or microinvasive squamous cell carcinoma (MIC) from January 1, 1999 to April 30, 2009 were retrieved from surgical pathology files of the Division of Gynecologic Pathology and Cytology, Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital. There were 311 cases of LEEP and 428 cases of CKC specimens. Only 241 patients who underwent subsequent hysterectomy at King Chulalongkorn Memorial Hospital within six months after the diagnosis were included in this study. Medical records and pathological reports were initially

reviewed and 79 cases were excluded from this study due to HIV infection (62 cases) and coexisting of adenocarcinoma in situ (AIS) of cervix (17 cases). Six cases were subsequently excluded due to missing Hematoxylin-eosin (H&E) slides and paraffin blocks. The remaining 156 cases were enrolled in this study, consisting of 48 cases from LEEP and 108 cases from CKC. H&E-stained sections from each case was reviewed by an experienced pathologist (ST) who did not know previous pathological results to confirm the histological diagnosis and to assess pathological features, particularly adequacy of the margins in LEEP/CKC specimens and residual disease in hysterectomy specimens. Positive margin was defined by the presence of CIN1 or human papilloma virus (HPV) infection or more severe lesion at margins of excisional specimens. The diagnosis of residual disease was based on the presence of CIN1 or HPV infection or more severe lesion in cervical tissue of hysterectomy specimens.

Statistical analyses were performed with the SPSS for Windows software (version 15; SPSS Inc, Chicago, IL, USA). Data were evaluated as descriptive statistics. The correlation between variables was assessed with the Chi-square and Fisher's exact test. Statistical significance was defined as a probability value ($p < 0.05$).

This study had been approved by Ethical Committee, Faculty of Medicine, Chulalongkorn University.

Results

Among 156 cases of HSIL or MIC in LEEP/CKC specimens with subsequent hysterectomy within 6 months without coexisting HIV infection or AIS, and had available H&E slides to evaluate, 48 cases were LEEP and 108 cases were CKC. The mean age (\pm SD) of the patients was 45.0 (\pm 8.9) years old (range = 29-75 years old). Sixteen patients (10.2%) were nulliparous and 47 cases (30.1%) were in premenopausal period. Overall median duration between excisional and hysterectomy procedures was 41 days, ranging from 2 to 180 days. Patients' demographic data of both LEEP and CKC

groups were not difference except for the mean duration between excisional and hysterectomy procedures (54.1 vs. 34.8 days, $p = 0.003$, Table 1). Mean pathological sections taken from LEEP and CKC were 22.6 and 22 sections, respectively, while mean sections of cervix in hysterectomy specimens was 12.9 sections.

CIN3 was the most common pathologic diagnosis in both LEEP and CKC specimens, followed by MIC and CIN2, with rather similar proportion in both groups (Table 2). The overall rate of residual disease in hysterectomy specimens was 46.8% (73 out of 156 cases), classified into 36.6% (19 out of 48 cases) of LEEP group and 50.0% (54 out of 108 cases) of CKC group. The residual diseases in both groups were statistically significant ($p=0.04$). Positive margin of LEEP/CKC specimens was observed in 87 cases (55.8%). Based on margin status, residual disease was higher present in patients with positive-margin of excision specimens, but there was no statistically significant difference (54.0% vs. 37.7%, $p = 0.61$)

Comparison between types of excisional procedure, positive margin was more frequently found in specimens from LEEP than that from CKC with statistically significant difference (72.9% vs. 47.3%, $p = 0.004$). In 108 patients with CKC procedure, residual disease was present in 32 out of 52 positive-margin

cases (61.5%) and 22 out of 56 negative-margin cases (39.3%) with statistically significant difference between both groups ($p = 0.03$) (Table 3). Although residual lesion was more common in LEEP cases with positive margin than those with negative margin, there was no statistically significant difference (42.9% vs. 30.8%, $p = 0.67$).

Correlation between number of positive margins and residual disease in hysterectomy specimens was shown in Table 4. Majority of positive-margin cases had only one site involvement The most common site was endocervix. Increasing numbers of positive margin sites in LEEP/CKC specimens was positively correlated to higher rate of residual disease in the hysterectomy specimens. Residual disease was observed in 50.7% of cases with one site of positive margin and stepped up to 100% in case with three sites of positive margin.

Of all 87 cases that had positive margin from excisional procedure, 8 cases revealed more severe lesion of residual disease than the margin pathology (Table 5). It was of interest that residual diseases were found in 26 cases (37.7%) with negative margin. The residual lesions were as following: CIN1 and HPV infection (6 cases), CIN2 (8 cases), CIN3 (10 cases), AIS (1 case) and invasive squamous cell carcinoma stage Ib1 (1 case) following CKC.

Table 1. Patients' demographic data between LEEP and CKC group

	LEEP (n = 48)	CKC (n = 108)	p-value
Age (year, mean±SD)	45.6±9.1	44.9±8.9	0.67
Premenopause	11(22.9%)	36(33.3%)	0.19
Nulliparous	5(2.1%)	11(10.2%)	0.96
Median duration between excisional and hysterectomy procedures (days)	54	34	0.003

Table 2. Histologic diagnosis in LEEP and CKC specimens

	LEEP (n = 48)	CKC (n = 108)	Total (n = 156)
CIN2	1 (2.1%)	1 (0.9%)	2 (1.3%)
CIN3	29 (60.4%)	61 (56.5%)	90 (57.7%)
MIC	18 (37.5%)	46 (42.6%)	64 (41.0%)

CIN = cervical intrepithelial neoplasia, MIC = microinvasive cervical carcinoma

Table 3. Excisional margin status and residual disease in hysterectomy specimens

	LEEP (n = 48)			CKC (n = 108)		
	Positive margin (n = 35)	Negative margin (n = 13)	p-value	Positive margin (n = 52)	Negative margin (n = 56)	p-value
Positive residual disease	15/35 (42.9%)	4/13 (30.8%)	0.67	32/52 (61.5%)	22/56 (39.3%)	0.03
Negative residual disease	20/35 (57.1%)	9/13 (69.2%)		20/52 (38.5%)	34/56 (60.7%)	

Table 4. Correlation between positive margins and residual disease in hysterectomy specimens

Positive margin site	Residual disease in hysterectomy specimens		Total
	Yes (n=73)	No (n=83)	
-ectocervix / -endocervix / -deep	27 (37.0%)	42 (50.6%)	69
-ectocervix / +endocervix / -deep	27 (37.0%)	26 (31.3%)	53
+ectocervix / -endocervix / -deep	7(9.6%)	8(9.6%)	15
-ectocervix / -endocervix / +deep	3(4.1%)	2(2.4%)	5
+ectocervix / +endocervix / -deep	4 (5.5%)	2(2.4%)	6
+ectocervix / -endocervix / +deep	1(1.4%)	0(0%)	1
-ectocervix / +endocervix / +deep	3(4.1%)	3(3.6%)	6
+ectocervix / +endocervix / +deep	1 (1.4%)	0 (0%)	1

Table 5. Severity of margin lesion and residual disease in subsequent hysterectomy specimens

Residual disease	Margin lesions				
	Negative (n = 69)	CIN1 (n = 2)	CIN2 (n = 3)	CIN3 (n = 67)	MIC (n = 15)
No lesion	43 (62.3%)	1 (50.0%)	0	33 (49.2%)	6 (40.0%)
CIN1/HPV	6 (8.8%)	0	0	1 (1.5%)	0
CIN2	8 (11.6%)	1 (50.0%)	2 (66.7%)	3 (4.5%)	0
CIN3	10 (14.5%)	0	1 (33.3%)	24 (35.8%)	5 (33.3%)
MIC	0	0	0	4 (6.0%)	4 (26.7%)
AIS	1 (1.4%)	0	0	2 (3.0%)	0
SCC	1 (1.4%)	0	0	0	0

CIN = cervical intraepithelial neoplasia

HPV = Human papilloma virus

AIS = Adenocarcinoma in situ

MIC = Microinvasive cervical carcinoma

SCC = Squamous cell carcinoma

Discussion

The residual disease in cervix in this study is 46.8% which is similar to the results from previous reports⁽⁴⁻⁷⁾. Our study also showed higher cases of positive margin in the patients underwent LEEP than CKC. This may due to limitation of the LEEP to excise extensive lesion.

Previous studies suggested that surgical margins of excisional specimens were reliable predictors for presence or absence of the residual disease in hysterectomy specimens^(10,11). However, this concept was different from several studies^(12,13). The absence of expected residual lesion in positive margin cases can be explained by two main mechanisms. First, this regression process may occur due to immune response triggered by the excisional procedure. The second mechanism may be the possible destruction of residual dysplastic cells by cauterization for hemostasis and removal of this tissue by post-cone endocervical curettage⁽¹²⁾. Similarly, there are several possible explanations for the presence of residual disease after apparently complete excisional procedure⁽¹³⁾. First, if the pathologist overlooks an involved margin, complete excision is falsely diagnosed. The second reason is

friable dysplastic epithelium can be easily stripped off the cervical stroma by the excisional surgical procedure. In addition, the lesion may be originally multifocal changes in natures.

In this study, the rate of residual disease was significantly higher in positive-than negative-margin groups of CKC procedure. However, no significant difference was detected in the LEEP group. This result may be explained by the small number of LEEP cases in this study. Moreover, electrical fulguration in LEEP may destroy residual dysplastic epithelium, resulting in decreased rate of residual lesion in hysterectomy specimens. In addition, mean duration between LEEP and hysterectomy procedure is statistically longer than post CKC group. This may have effect on less frequency of residual disease in post LEEP uterus.

However, negative excisional margin can not guarantee the absence of residual or invasive lesion in subsequent hysterectomy specimens. We found 37.7% of residual disease in negative margin group which is higher than 10.1% - 23% of previous studies⁽⁴⁻⁷⁾. The possibility is that in our institute, we routinely do serial sectioning of the entire cervix in post-conization or post-LEEP hysterectomy specimens instead of

selective positive quadrant sampling technique. This technique may increase opportunity to find more residual lesions as we did find one case of invasive squamous cell carcinoma.

Importantly, high prevalence of residual tumor after free margin of excisional procedures was demonstrated in this study. Close follow-up by cytology and colposcopic examination should be strictly considered after excisional procedure without subsequent hysterectomy, regardless of margin status.

However, the main weak point in this study is that hysterectomy was not subsequently performed in all LEEP/CKC cases which were diagnosed as HSIL or MIC. So, there may be some selective bias. Further studies are needed to support these findings in order to be able to establish the appropriate guideline for patients with these conditions.

Conclusion

High prevalence of residual disease in the cervix following LEEP/CKC was demonstrated. Positive margins were significantly more common in LEEP than CKC procedures. There was tendency to have more residual disease in cases with increased number of positive margin sites, and negative margin status could not rule out invasive residual disease in hysterectomy specimen.

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การเหลือรอยโรคในชิ้นเนื้อมดลูกภายหลังการรักษาด้วยการตัดรอยโรคที่ปากมดลูก ในผู้ป่วยที่มีรอยโรคขั้นสูงก่อนเป็นมะเร็งและมะเร็งปากมดลูกระยะแรก

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วัตถุประสงค์ : เพื่อศึกษารอยโรคในชิ้นเนื้อปากมดลูกหลังการรักษาด้วยการตัดรอยโรคที่ปากมดลูก

วัสดุและวิธีการ : ศึกษาชิ้นเนื้อหลังจากเวชระเบียนของผู้ป่วยที่ได้รับการตัดรอยโรคที่ปากมดลูกและได้รับการวินิจฉัยว่าเป็นรอยโรคขั้นสูงก่อนเป็นมะเร็ง และมะเร็งปากมดลูกระยะแรก ตามด้วยการตัดมดลูกภายในระยะเวลา 6 เดือน ที่โรงพยาบาลจุฬาลงกรณ์ตั้งแต่วันที่ 1 มกราคม 2542 ถึง 30 เมษายน 2552

ผลการศึกษา : จากผู้ป่วยทั้งหมด 156 รายที่ได้รับการตัดปากมดลูกเป็นรูปกรวยหรือห่วงไฟฟ้า มี 87 ราย (ร้อยละ 55.8) เหลือรอยโรคที่ขอบของชิ้นเนื้อ และ 73 ราย (ร้อยละ 46.8) เหลือรอยโรคในชิ้นเนื้อปากมดลูก โดยไม่พบความแตกต่างของการเหลือรอยโรคในปากมดลูกระหว่างกลุ่มที่มีและไม่มีรอยโรคที่ขอบของชิ้นเนื้อ ($P=0.61$) พบว่ามีการเหลือรอยโรคที่ขอบของชิ้นเนื้อในกลุ่มที่ได้รับการตัดปากมดลูกด้วยห่วงไฟฟ้ามากกว่าตัดปากมดลูกเป็นรูปกรวย (ร้อยละ 72.9 vs ร้อยละ 47.3, $P=0.004$) แต่การเหลือรอยโรคในมดลูกเหมือนกันทั้งสองกลุ่มโดยไม่สัมพันธ์กับรอยโรคที่ขอบชิ้นเนื้อ มีโอกาสพบรอยโรคในชิ้นเนื้อปากมดลูกมากขึ้นในกลุ่มที่พบรอยโรคที่ขอบของชิ้นเนื้อหลายตำแหน่ง พบเซลล์มะเร็งปากมดลูกชนิดสแควมัสได้ในชิ้นเนื้อปากมดลูกแม้ว่าจะไม่เหลือรอยโรคที่ขอบของชิ้นเนื้อในการตัดปากมดลูกเป็นรูปกรวย

สรุป : มีอุบัติการณ์สูงที่จะเหลือรอยโรคที่ขอบของชิ้นเนื้อภายหลังการตัดปากมดลูกทั้งวิธีตัดด้วยห่วงไฟฟ้า และตัดปากมดลูกเป็นรูปกรวย พบการเหลือรอยโรคที่ขอบของชิ้นเนื้อภายหลังการตัดปากมดลูกด้วยห่วงไฟฟ้ามากกว่าการตัดปากมดลูกเป็นรูปกรวย การเหลือรอยโรคที่ชิ้นเนื้อปากมดลูกมากขึ้นในกลุ่มที่เหลือรอยโรคที่ขอบของชิ้นเนื้อหลายตำแหน่งของปากมดลูก การไม่เหลือรอยโรคที่ขอบของชิ้นเนื้อหลังตัดปากมดลูกเป็นรูปกรวยไม่ได้ประกันว่าจะไม่เหลือรอยโรคที่ชิ้นเนื้อจากการตัดมดลูก