Thai Journal of Obstetrics and Gynaecology
October 2019, Vol. 27, No. 4, pp. 187-194

GYNECOLOGY

Prevalence and Associated Factors of Positive Margins of Cervical Tissue from Loop Electrosurgical Excision Procedure

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ABSTRACT

Objectives: The primary objective was to find the prevalence of positive margins of cervical tissue from loop electrosurgical excision procedure (LEEP) for conization and the secondary objective was to determine its associated factors.

Materials and Methods: Medical records of 350 patients who underwent LEEP at Udonthani Hospital form March 2016 to July 2018 were reviewed. Data collection included baseline characteristics, preoperative cytology, colposcopic finding, colposcopic directed biopsy histology, histopathological diagnosis, margin of surgical specimens and all related histologic results. The prevalence and associated factors for positive margins were analyzed.

Results: There were 323 patients who underwent LEEP and had complete data. The mean age was 42.3 ± 10.6 years. The majority of them had a body mass index < 30 kg/m2 (94.1%), multiparous (88.8%), negative test of human immunodeficiency virus antibody (91.3%) and premenopausal status (76.2%). The prevalence of positive margins of cervical tissue form LEEP was found in 80 cases (24.8%), and the most positive margin site was endocervix (48.8%). From multivariate logistic regression analysis, colposcopic directed biopsy histology > cervical intraepithelial neoplasia 2 was the only significant factor associated with the positive margins (adjusted odds ratio 3.91, 95% confidence interval 1.35-11.27).

Conclusion: The prevalence of positive margins of cervical tissue from LEEP was almost one-fourth. The high grade of the colposcopic directed biopsy histology was a significant factor associated with having positive margins.

Keywords: positive margin, loop electrosurgical excision procedure, preinvasive squamous cell carcinoma, cervical intraepithelial neoplasia, carcinoma of cervix.

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Received: 24 September 2018, **Revised:** 2 December 2018, **Accepted:** 3 December 2018

ความชุกและปัจจัยที่เกี่ยวข้องกับการตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อของปากมดลูกจากการตัดปากมดลูกด้วยห่วงไฟฟ้า

รวิสรา จำปาวงค์, เสาวณีย์ ตั้งมโนวุฒิกุล, สุรพงศ์ แสนโภชน์, ศรีสุดา ทรงธรรมวัฒน์, เมธา ทรงธรรมวัฒน์

บทคัดย่อ

วัตถุประสงค์: *วัตถุประสงค์หลักคือเพื่อศึกษาความชุกของการตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อของปากมดลูกจากการตัดปากมดลูกด้วยห่วงไฟฟ้าเป็นรูปกรวย และวัตถุประสงค์รองเพื่อศึกษาปัจจัยที่เกี่ยวข้อง*

วิธีการวิจัย: *ศึกษาข้อมูลย้อนหลังของผู้ป่วยที่ได้รับการตัดปากมดลูกด้วยห่วงไฟฟ้าในโรงพยาบาลอุดรธานี ตั้งแต่ เดือนมีนาคม 2559 ถึง เดือนกรกฎาคม 2561 จำนวน 350 คน ทำการบันทึกข้อมูลได้แก่ ข้อมูลพื้นฐาน, ผลตรวจคัดกรองมะเร็งปากมดลูก, ผลการส่องกล้องตรวจปากมดลูก, ผลชิ้นเนื้อจากการตัดปากมดลูกขณะส่องกล้องตรวจปากมดลูก, ผลชิ้นเนื้อปากมดลูกจากการตัดปากมดลูกด้วยห่วงไฟฟ้าและรอยโรคที่ขอบชิ้นเนื้อ นำข้อมูลมาวิเคราะห์หาความชุกและปัจจัยที่มีความสัมพันธ์กับการตรวจพบรอยโรคที่ขอบชิ้นเนื้อปากมดลูก*

ผลการวิจัย: *ในช่วงเวลาดังกล่าวมีผู้ป่วยที่ได้รับการตัดปากมดลูกด้วยห่วงไฟฟ้าและข้อมูลครบถ้วนจำนวน 323 คน อายุเฉลี่ย 42.3 ปี ส่วนใหญ่ของผู้ป่วยมีดัชนีมวลกาย < 30 kg/m^2 (304 คน หรือ ร้อยละ 94.1) ไม่เป็นผู้ติดเชื้อ HIV (295 คน หรือ ร้อยละ 91.3) และยังมีประจำเดือน (246 คน หรือ ร้อยละ 76.2) ผู้ป่วยที่มีรอยโรคที่ขอบชิ้นเนื้อมีจำนวน 80 คน (ร้อยละ 24.8) ส่วนใหญ่เป็นรอยโรคที่ขอบชิ้นเนื้อด้านใน ร้อยละ 48.8 โดยปัจจัยที่เกี่ยวข้องอย่างมีนัยสำคัญทางสถิติกับการตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อของปากมดลูกจากการตัดปากมดลูกด้วยห่วงไฟฟ้าคือ ผลชิ้นเนื้อปากมดลูกจากการส่องกล้องตรวจปากมดลูกรุนแรงกว่าระดับ cervical intraepithelial neoplasia 2 โดยพบว่า adjusted odds ratio เท่ากับ 3.91 (ระดับความเชื่อมั่นร้อยละ 95% คือ 1.35-11.27)*

สรุป: *พบความชุกของการตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อของปากมดลูกจากการตัดปากมดลูกด้วยห่วงไฟฟ้าประมาณหนึ่งในสี่ของผู้ป่วย โดยปัจจัยที่มีผลกับการตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อปากมดลูกได้แก่ ผลพยาธิวิทยาจากการส่องกล้องตรวจปากมดลูกที่มีความรุนแรงกว่าระดับ CIN 2*

คำสำคัญ: *การตรวจพบพยาธิสภาพที่ขอบชิ้นเนื้อ, การตัดปากมดลูกด้วยห่วงไฟฟ้า, มะเร็งปากมดลูกระยะยังไม่มีการรุกราน, ระยะก่อนมะเร็งของปากมดลูก, มะเร็งปากมดลูก*

Introduction

Cervical cancer is the third most common cause of death for woman in developing countries[1] and the second highest incidence of cancer in Thailand[2]. Cervical cancer is a preventable cancer because it takes a long time to progress from normal cervical epithelium to precancerous lesion and finally becoming an invasive pattern. Pap smear has been used effectively for screening and detection of the precancerous lesions of the cervix following the Bethesda system[3]. Cervical intraepithelial neoplasia (CIN) is frequently diagnosed and treated by cervical conization according to the American Society for Colposcopy and Cervical Pathology (ASCCP) guideline for managing abnormal cervical cancer screening tests and cancer precursors (2012)[4].

Cervical conization can be performed using either cold-knife conization (CKC), loop electrosurgical excision procedure (LEEP) or laser conization. LEEP is widely used, because it can be performed in an outpatient setting, minimal bleeding, cost-effective and its results are comparable with the CKC and laser conization[5]. However, a common problem with LEEP is the positive margin of cervical tissue specimen which is a risk for persistence or recurrence of cervical dysplasia that can progress to squamous cell carcinoma[6]. Management of positive margin is controversial, including follow-up with cytology, endocervical sampling, re-excision or hysterectomy if it cannot be re-excised[4, 7].

Many studies have reported the prevalence of positive margin after LEEP, varying from 12.3 to 47.0% and inconclusive associated factors[8-15]. Therefore, the primary objective was to find the prevalence of positive margins of cervical tissue from LEEP for conization and the secondary objective was to determine its associated factors. This knowledge will be used by the gynecologists for awareness of high risk cases in the patient's treatment and follow-up process.

Materials and Methods

This study was a retrospective descriptive study. After the study protocol was approved by Udonthani Research Ethics Committee, the medical records were reviewed. The inclusion criteria was patients who underwent LEEP for indications according to ASCCP guideline at the Department of Obstetrics and Gynecology, Udonthani Hospital, Thailand, from March 2016 to July 2018. According to the ASCCP guideline, colposcopy was done in case of cervical cancer screening test was positive for abnormal cervical cytology ≤ LSIL and high risk HPV type 16 and 18. LEEP conization was done without colposcopy in case of abnormal cervical cytology ≥ HSIL who age ≥ 25 years. The sample size was calculated by the formula for a descriptive study using the estimated prevalence of positive margin after LEEP of 14.3%[8, 16], a 5% chance of making a type 1 error and acceptable error of 5%. One hundred and eighty nine women were needed for the study.

Baseline characteristics were recorded which included age, body weight, height, parity, menstrual status, human immunodeficiency virus (HIV) status, history of smoking and level of surgeon. Other information included the women's pathologic information, preoperative cytology, colposcopic finding, preoperative histology, LEEP histology and surgical margin. The exclusion criteria was incomplete data of patient's medical records.

The statistical analysis was performed using Stata version 13. Continuous variables were presented by the mean ± standard deviation. Categorical variables were presented by number and percentage. The chi-square test, Fisher exact or student t-test were performed to evaluate the discrete variables. The associated factors of positive margin were evaluated by multivariate logistic regression, and were presented as odd ratios (ORs) with 95% confidence intervals (95%CI). A p value < 0.05 was considered statistically significant.

Results

From March 2016 to July 2018, there were 350

women who underwent LEEP at the Department of Obstetrics and Gynecology, Udonthani Hospital, Thailand. Twenty seven of these women were excluded from the study because of incomplete data. A total of 323 patient's records were analyzed. Baseline characteristics are shown in Table 1. The mean age was 42.3±10.6 years, mean body weight was 56.5±9.5 kilograms (kg), mean height was 155.5±8.6 centimeters (cm) and mean body mass index (BMI) was 23.9±10.9 kg/m^2. Most patients had a BMI < 30 (n = 304; 94.1%) and were multiparous (n = 287; 88.8%), HIV negative (n = 295; 91.3 %) and premenopausal status (n = 246; 76.2%).

Preoperative cytology is presented in Table 2. Most patients had high grade squamous intraepithelial lesion (HSIL) (51.4%). A Colposcopy was done in 169 patients (52.3%) with 78 patients (46.2%) having an unsatisfied colposcopic finding and 91 patients (53.8%) having a satisfied colposcopic finding. A total of 118 patients were colposcopic directed biopsy, preoperative histology are presented in Table 2.

Postoperative histology is presented in Table 3. Most patients had cervical intraepithelial neoplasia (CIN) 3 (43.6%). The prevalence of positive margins of cervical tissue form LEEP was found in 80 cases (24.8%), the most positive margin site was endocervix (48.8%). Data of preoperative associated factors are presented in Table 4 as positive and negative margin groups. Univariate and multivariate logistic regression analysis was done in possibly associated factors with positive margins as shown in Table 4. A significant characteristic was colposcopic directed biopsy histology > CIN 2 with the adjusted ORs of 3.91 (95%CI 1.35-11.27).

Table 1. Baseline characteristics.

Characteristics	Total (N=323)	$^+$ve magin (N=80)	$^-$ve margin (N=243)	p value
Age (years), mean±SD	42.3±10.6	43.3±10.7	42.0±10.6	0.34
BW (kg), mean±SD	56.5±9.5	57.8±10.0	56.1±9.3	0.18
Height (cm), mean±SD	155.5±8.6	155.5±6.4	155.5±9.2	0.99
BMI (kg/m^2), mean±SD	23.9±10.9	23.9±3.8	23.9±12.4	0.98
- BMI < 30	304(94.1%)	74(24.3%)	230(75.7%)	0.48
- BMI ≥ 30	19(5.9%)	6(31.6%)	13(68.4%)	0.48
Nulliparous	36(11.2%)	9(25%)	27(75%)	0.97
Postmenopause	77(23.8%)	22(28.6%)	55(71.4%)	0.38
Anti HIV +ve	28(8.7%)	10(35.7%)	18(64.3%)	0.16
Level of surgeon				
Resident	122(37.8%)	38(31.1%)	84(68.9%)	0.04
Staff	201(62.2%)	42(20.9%)	159(79.1%)	

Data are presented in term of N (%) unless specified otherwise

- p value was calculated by student's t test for continuous data and Pearson chi square or Fisher exact test for categorical data
- $^+$ve: positive, $^-$ve: negative, SD: standard deviation, BW: body weight, BMI: body mass index, HIV: human immunodeficiency virus.

Table 2. Preoperative cytology and histology.

Characteristics	Total (N=323)	+ve magin (N=80)	-ve margin (N=243)	p value
Cervical cytology*				
+ve HPV 16 or 18	10 (3.1%)	3 (30%)	7 (70%)	0.70
ASC-US	39 (12.0%)	6 (15.4%)	33 (84.6%)	0.15
LSIL	34 (10.5%)	6 (17.6%)	28 (82.4%)	0.31
ASC-H	49 (15.1%)	9 (18.4%)	40 (81.6%)	0.26
HSIL	166 (51.2%)	46 (27.7%)	120 (72.3%)	0.21
SCCA	7 (2.2%)	3 (42.9%)	4 (57.1%)	0.26
AGC	13 (4.0%)	4 (30.8%)	9 (69.2%)	0.61
AIS	6 (1.9%)	3 (50%)	3 (50%)	0.15
Staff				
Colposcopic finding				
Not done	154 (47.7%)	45 (29.2%)	109 (70.8%)	0.17
Satisfied	91 (28.2%)	17 (18.7%)	74 (81.3%)	
Unsatisfied	78 (24.2%)	18 (23.1%)	60 (76.9%)	
Colposcopic directed biopsy histology**				
Not done	205 (63.1%)	53 (25.9%)	152 (74.1%)	0.04
No CIN	2 (0.6%)	0	2 (100%)	
CIN 1	15 (4.6%)	0	15 (100%)	
CIN 2	36 (11.1%)	6 (16.7%)	30 (83.3%)	
CIN 3	44 (13.5%)	16 (36.4%)	28 (63.6%)	
CIS	17 (5.2%)	4 (23.5%)	13 (76.5%)	
AIS	6 (1.8%)	5 (83.3%)	1 (16.7%)	

Data are presented in term of N (%) unless specified otherwise.

- +ve: positive, -ve: negative, HPV: Human papilloma virus, ASC-US: Atypical squamous cells of undetermined significance, LSIL: Low grade squamous intraepithelial lesion, ASC-H: Atypical squamous cells cannot exclude HSIL, HSIL: High grade squamous intraepithelial lesion, AGC: Atypical glandular cells, SCCA: Squamous cell carcinoma, AIS: Adenocarcinoma in situ, CIN: Cervical intraepithelial neoplasia, CIS: Carcinoma in situ

* 1 case of HSIL with AIS

**1 case of CIN 3 with AIS, 1 case of CIS with AIS

Table 3. Postoperative histology.

Characteristics	Total	$^{+}$ve margin	$^{-}$ve margin	p value
LEEP pathology*				
No CIN	29 (8.9%)	0	29 (100%)	< 0.01
CIN 1	24 (7.4%)	6 (25.0%)	18 (75.0%)	
CIN 2	47 (14.4%)	12 (25.5%)	35 (74.5%)	
CIN 3	142 (43.6%)	40 (28.2%)	102 (71.8%)	
CIS	62 (19.0%)	9 (14.5%)	53 (85.5%)	
AIS	11 (3.4%)	5 (45.5%)	6 (54.5%)	
SCCA	9 (2.8%)	6 (66.7%)	3 (33.3%)	
Adenocarcinoma	2 (0.6%)	2 (100%)	0	
Type of $^{+}$ve margin				
Endocervix		39 (48.8%)		
Ectocervix		21 (26.3%)		
Both		18 (22.5%)		
Not specified		2 (2.5%)		

Data are presented in term of N (%) unless specified otherwise.
- $^{+}$ve: positive, $^{-}$ve: negative, LEEP: loop electrosurgical excision procedure, CIN: Cervical intraepithelial neoplasia, CIS: Carcinoma in situ, AIS: Adenocarcinoma in situ, SCCA: Squamous cell carcinoma
* 3 cases of CIS with AIS

Table 4. Preoperative associated factors of positive margin of LEEP specimen.

Factors	$^{+}$ve margin (N=80)	$^{-}$ve margin (N=243)	Crude OR (95%CI)	Adjusted OR (95%CI)	p value
Age (years), mean±SD	43.3±10.7	42.0±10.6	1.01 (0.99-1.04)	1.00 (0.94-1.07)	0.79
BMI (kg/m^2), mean±SD	23.9±3.8	23.9±12.4	1.00 (0.98-1.02)	1.00 (0.95-1.04)	0.86
Nulliparous	9 (25.0%)	27 (75.0%)	1.01 (0.46-2.26)	0.67 (0.16-2.84)	0.59
Postmenopause	22 (28.6%)	55 (71.4%)	1.30 (0.73-2.31)	0.78 (0.16-3.84)	0.76
HIV positive	10 (35.7%)	18 (64.3%)	1.78 (0.78-4.05)	1.33 (0.25-6.92)	0.74
Level of surgeon					
Resident	38 (31.1%)	84 (68.9%)	1.71 (1.03-2.86)	1.60 (0.59-4.35)	0.36
Staff	42 (20.9%)	159 (79.1%)			
Preoperative cytology*					
≤ LSIL	15 (18.1%)	68 (81.9%)	1.68 (0.90-3.15)	1.06 (0.42-2.69)	0.91
> LSIL	65 (27.0%)	176 (73.0%)			
Colposcopic directed biopsy histology**					
≤ CIN2	6 (11.3%)	47 (88.7%)	3.74 (1.38-10.12)	3.91 (1.35-11.27)	0.01
> CIN2	25 (37.3%)	42 (62.7%)			

- LEEP: loop electrosurgical excision procedure, +ve: positive, -ve: negative, ORs: odds ratio, SD: standard deviation, BMI: body mass index, HIV: human immunodeficiency virus, LSIL: Low grade squamous intraepithelial lesion, CIN: Cervical intraepithelial neoplasia
*1 case of HSIL with AIS, **1 case of CIN 3 with AIS, 1 case of CIS with AIS

Discussion

Prevalence of positive margin of cervical tissue form LEEP at Udonthani Hospital was 24.8% which was similar to 12.3-44.0% from the other studies. For example, Chen, et al reported 35.8% of positive margin at Jining No.1 People's Hospital, China[9]. Kietpeerakool, et al reported 44.0% of positive margin at Chiang Mai University Hospital[11]. Panna, et al reported 12.3% of positive margin at Srinangarind Hospital[14]. Tanompongchat, et al reported 35.3% of positive margin at Siriraj Hospital[15]. These results were varied by the characteristics of study population, hospitals, surgeons and histological type.

In this study, the associated factor of positive margin of cervical tissue form LEEP was colposcopic directed biopsy histology > CIN 2 which was similar to Chaijindaratana, et al[8] and Panna, et al[14] studies. The reason of higher risk of positive margin in this group was the greater degree of pathology might have more extension of disease. However, this study did not found the association of positive margin with nulliparous, age or post menopause that might affect the transformation zone of cervix which were reported in Chaijindaratana, et al[8] Chen, et al[10] and Tanompongchat, et al studies[15]. The skill and experience of surgeon was also reported as the associated factors in Chaijindaratana, et al[8] and Panna, et al[14] studies, which was not found in this study. Others associated factors, such as human papilloma virus (HPV) positive, history of HIV, history of smoking that might interfere the immunological factor were also reported in previous studies[8, 9, 12]. However, these were not found in this study. The reason of difference might be from the different population, surgeons and also the sample size of study which had small cases in some factors such as history of HIV or nulliparous.

The clinical application of this study is for the gynecologists to be concerned about the positive margin of LEEP specimen especially in the high grade preoperative histology. The top hat of LEEP might be needed in the > CIN 2 case to reduce the positive endocervical margin which was found in more than one-third of case compared with 11.3% in the ≤ CIN 2. The wider cervical tissue specimen might also be needed in this situation to avoid positive ectocervical margin. However, multiple factors such as size, amount of lesion and colposcopic finding should be considered to avoid excessive surgery and increased complications. The limitation of this study was the retrospective data collection which some associated factors were not collected such as site, quadrant, size of lesion and the size of cervical tissue specimens. The postoperative histology and surgical margins were also reported by many pathologists and this might cause some variation in diagnosis. Moreover, colposcopy was not done in many cases in this study due to the ASCCP guideline which treated abnormal cervical cytology > HSIL by LEEP without colposcopy.

Conclusion

The prevalence of positive margins of cervical tissue form LEEP was almost one-fourth. The high grade colposcopic directed biopsy histology was a significant factor associated with the positive conization margins.

Acknowledgment

We gratefully acknowledge Dr.Thammanoon Wisittanawat Director of Udonthani Hospital for permission and grant support. Thanks for Udonthani Hospital staff and all participants who assisted in this study. None of the authors has any conflict of interest relative to this work. This study did not receive pharmaceutical company support

Potential conflicts of interest

The authors declare no conflict of interest.

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