Prevalence and Risk Factors for Residual Cervical Neoplasia in Subsequent Hysterectomy Following LEEP or Conization

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Objectives: *The purposes of the present study were to determine the prevalence of residual disease in the hysterectomy specimens following cold knife conization (CKC) or loop electrosurgical excision procedure (LEEP) and to evaluate the predictive factors for residual disease.*
Design: *Descriptive study*
Setting: *Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital.*
Subjects: *A total of 120 patients who underwent hysterectomy after either LEEP or CKC.*
Material and Method: *The medical records of 120 women were reviewed to estimate the prevalence of residual disease.. The patients' characteristic and pathologic parameters were analyzed for the risk factors of residual disease. Chi square test and Student t test were used for statistical analysis.*
Results: *Of the 120 patients, 46 cases had residual disease in their hysterectomy specimens so the prevalence was 38.3% (95% CI 29.5, 47.2). Invasive cervical cancer was found in the hysterectomy specimens in 4 cases (8.7%). Only ectocervical margin was the predictive factor of residual disease in the hysterectomy specimen (p = 0.002). Age, conization pathologic findings, glandular involvement, endocervical margin status, stromal invasion, and endocervical curettage results were not predictive factors for residual disease in the hystectomy specimens.*
Conclusion: *Residual disease was found in 38.3% of hysterectomy specimens after conization. Also undiagnosed invasive cervical cancer was found. Careful examination for residual disease in hysterectomy specimens should be performed, especially among those with positive cone margin.*

Keywords: *Cervical intraepithelial neoplasia, Cold knife conization, Loop electrosurgical excision procedure, Residual disease*

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Invasive cervical cancer is a significant public heath problem and the leading cause of cancer death in Thai women. Invasive cervical cancer is considered a preventable cancer because it has a long preinvasive state also cervical cytology screening program are available and the treatment for preinvasive lesion is effective. There are many options for cervical intraepithelial neoplasia (CIN) eradication varying from ablative methods, i.e. cryotherapy, electrocautery and laser vaporization to excisional methods, i.e. cold knife conization (CKC), laser conization and loop electrosurgical excision procedure (LEEP). The loop electrosurgical excision procedure (LEEP) and cold knife conization of the cervical transformation zone can be used for both diagnostic and therapeutic purposes[1].

Currently, the trend in the management of CIN is conservative. Optimal management of CIN after CKC or LEEP remains controversy especially when surgical margins are not free from disease. Hysterectomy or repeated conization may be considered if surgical margins are not free or the results of endocervical

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curettage positive for dysplasia after excisional procedures.

Examination of hysterectomy specimens for residual disease revealed great clinical importance. Residual disease has been reported to increase the recurrent rate and worsen the prognosis of the patients. Reliable predictors of residual dysplasia in the cervix after CKC or LEEP have not been consistently identified.

The purposes of the present study were to determine the prevalence of residual disease in the hysterectomy specimens following CKC or LEEP and to evaluate predictive factors of residual disease.

Materials and Method

Medical record review of women who underwent either LEEP or cold knife conization (CKC) and subsequently simple hysterectomy at the Department of Obstetrics and Gynecology, Siriraj Hospital from January 1999 to December 2003 were performed. A retrospective review of medical records was conducted under ethical board review permission. A total of 120 patients who underwent both LEEP or CKC and subsequent hysterectomy were enrolled in the present study. All patients had abnormal cervical smears and 117 patients underwent colposcopic examination before the conization. The indications for conization included unsatisfactory colposcopy, positive endocervical curettage, discrepancies of greater than two levels between Pap smear and colposcopic examination or suspicion of microinvasive disease[2]. Ninety-two patients underwent LEEP while 28 patients underwent cold knife conizaton. All conization and LEEP specimens were fixed in formalin and processed in a standard fashion. Hysterectomy was performed through the abdominal route as indicated between 1.5 months and 12 months after conization. The specimens were submitted for histopathologic examination including maximal neoplastic severity, extension to margins and thermal damage. All histologic slides were reviewed by a well experienced pathologist at the Department of Pathology. Residual disease was defined as the presence of cervical intraepithelial neoplasia or invasive cancer in the hysterectomy specimens.

Data on patients' characteristics, previous cytological report, colposcopic and pathologic finding were extracted from the medical records. Prevalence with 95% confidence interval (CI) of residual disease were calculated. Certain characteristics were compared between those with and without residual disease to determine possible risk factors.

Descriptive statistics were used to describe the patients' characteristics using mean, standard deviation, number and percentage. Chi square test and Student t test were used to determine the differences between the groups as appropriate. A p-value of < 0.05 was considered statistically significant in the present study.

Results

From January 1999 to December 2003, a total of 120 patient's profiles were available for analysis. Characteristics of the patients are shown in Table 1. Mean age of these patients was 44.3 years. The majority of the patients were parous (94.2%), whereas 5.8% were nulliparous.

Table 2 shows the result of the initial Pap smear and colposcopic findings. High- grade squamous intra-epithelial lesion (HSIL) was reported in 80 cases (66.7%) while 25 cases (20.8%) were reported as invasive cancer. Colposcopy was performed in 117 cases and 81 cases were reported as CIN III. Invasive cancer was reported in only 2 cases (1.7%).

Table 1. Baseline characteristics of the patients (N = 120)

Characteristic	Number (%)
Age (mean age $\pm$ SD)(years)	44.3 $\pm$ 6.9
Parity	
0	7 (5.8)
1	17 (14.2)
2	60 (50.0)
3	21 (17.5)
$\geq$ 4	15 (12.5)

Table 2. Initial cytology and colposcopic results (N = 120)

	N (%)
Pap smear	
ASCUS	3 (2.5)
LSIL	12 (10.0)
HSIL	80 (66.7)
Invasive CA	25 (20.8)
Colposcopy	
Not done	3 (2.5)
CIN I	9 (7.5)
CIN II	25 (20.8)
CIN III	81 (67.5)
Invasive CA	2 (1.7)

Table 3 shows the pathologic findings from conization or LEEP. CIN III was reported in 93 cases (77.5%). Glandular involvement was found in 87 cases (75.7%). Positive endocervical margin was present in 63 cases (78.8%). Stromal invasion was reported in 33 cases (57.9%). Positive endocervical curettage was reported in 14 cases (36.8%).

Of the 120 patients who had a subsequent hysterectomy performed, 46 cases had residual disease in their hysterectomy specimens, hence the prevalence was 38.3% (95%CI 29.5,47.2).

Table 4 shows the histology of residual disease in the hysterectomy specimens. The majority was CIN III (73.9%), and 4 cases (8.7%) had invasive cancer.

Table 3. Pathological findings from CKC or LEEP

	N (%)
Pathology (N = 120)	
CIN I	9 (7.5)
CIN II	18 (15.0)
CIN III	93 (77.5)
Glandular involvement (N = 115)	
Positive	87 (75.7)
Negative	28 (24.3)
Ectocervical margin status (N = 112)	
Positive	87 (77.7)
Negative	25 (22.3)
Endocervical margin (N = 80)	
Positive	63 (78.8)
Negative	17 (21.2)
Stromal invasion (N = 57)	
Positive	33 (57.9)
Negative	24 (42.1)
Endocervical curettage (N = 38)	
Positive	14 (36.8)
Negative	24 (63.2)

Table 4. Histology of subsequent hysterectomy (N = 46)

Histologic finding	N (%)
CIN I	6 (13.1)
CIN II	2 (4.3)
CIN III	34 (73.9)
Invasive cancer	4 (8.7)

Table 5 shows the comparison of certain characteristics between those with and without residual disease. Only positive conization or LEEP margin status was significantly correlated with residual disease in the hysterectomy specimens. Those with positive ectocervical margin were more likely to have residual disease than negative margin (47.1% and 12% respectively, p = 0.002). Other factors, such as age, severity of disease, glandular involvement, endocervical margin, stromal invasion, endocervical curettage (ECC) did not show significant association with residual disease.

Discussion

In the management of CIN by CKC or LEEP, the negative margins of excised tissue may indicate total excision of neoplasia[3]. Involved conization margins are often interpreted as highly predictive of residual disease in the cervix, necessitating further therapy, including reconization or hysterectomy. However, a review study could not identify any strong predictive factor for residual disease[3].

Table 5. Factors associated to residual disease in subsequent hysterectomy

	Residual N (%)	No residual N (%)	p value
Age (Mean age ± SD)	45.6 ± 6.4	43.5 ± 7.0	0.113
Pathology			
CIN I	2 (22.2)	7 (77.8)	0.489
CIN II	6 (33.3)	12 (66.7)	
CIN III	38 (40.9)	55 (59.1)	
Glandular involvement			
Positive	31 (35.6)	56 (64.4)	0.121
Negative	15 (53.6)	13 (46.4)	
Ectocervical margin			
Positive	41 (47.1)	46 (52.9)	0.002
Negative	3 (12.0)	22 (88.0)	
Endocervical margin			
Positive	29 (46.0)	34 (54.0)	0.107
Negative	4 (23.5)	13 (76.5)	
Stromal Invasion			
Positive	18 (54.5)	15 (45.5)	0.178
Negative	8 (33.3)	16 (66.7)	
ECC			
Positive	8 (57.1)	6 (42.9)	0.318
Negative	9 (37.5)	15 (62.5)	

In the present study, the prevalence of residual disease in the post-cone hysterectomy specimens was 38.3%. This could be compared with those previously reported (29 to 48%)[3-7]. Invasive cancer in the post cone hysterectomy specimens was found in 4 of 120 patients (3.3%) in the present study while Husseinzaden et al reported residual cervical cancer in only 1 of 106 specimens[5]. The appearance of invasive cancer follow ing treatment of cervical dysplasia may be considered a failure of management. There are several possible explanations for the presence of residual invasive cancer after excision of cervical dysplasia by conization. Inexperienced surgeons may have difficulties in recognizing invasive cervical lesions and in determining the true completeness of a cone biopsy. It is also possible that the cervical dysplasia are multifocal within the transformation zone[4,8], so the invasive foci could be missed. With this regard, the patients may receive inadequate treatment if ablative methods of therapy are used[4,8]. Reexcision of the transformation zone may be necessary in positive cone margin. Microinvasion of squamous lesions at the surgical margin or involved margins in adenocarcinoma in situ requires repeat excision before either conservative follow up or hysterectomy. Because frank invasion could be found in these cases, repeat excision is necessary to make an accurate diagnosis before selecting appropriate clinical management.

The results of the present study showed the ectocervical margin status was the only significant pre-dicting factor for residual disease. But Moore et al[3] identified age as a predictor for residual dysplasia and Kalogirou et al[9] found that increasing age and severity of disease were the factors that accurately predicted residual dysplasia[3,9].

Some limitations should be noted. There were not many cases of CKC and LEEP with subsequent hysterectomy at the time of the study at Siriraj Hospital,so the authors did not separately analyze between CKC and LEEP in the aspect of different on residual dysplasia in hysterectomy specimens. Also subsequent hysterectomy was not performed in all cases who underwent CKC or LEEP. This could have some effects to the prevalence of the present study.

In conclusion almost 40% of hysterectomy post conization had residual disease and undiagnosed invasive cervical cancer was also found. Ectocervical margin was the only predictive factor of residual disease in hysterectomy specimen. Careful examination for residual disease in hysterectomy specimens should be performed to reveal this important clinical information.

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ความชุกและปัจจัยเสี่ยงของการมีรอยโรคที่เหลืออยู่ของปากมดลูก ในมดลูกที่ได้รับการผ่าตัดภายหลังการตัดปากมดลูกด้วยห่วงไฟฟ้าหรือด้วยมีดเป็นรูปกรวย

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วัตถุประสงค์: *เพื่อศึกษาความชุกและปัจจัยเสี่ยงของการมีรอยโรคที่เหลืออยู่ ในมดลูกที่ได้รับการผ่าตัดภายหลังการรักษาด้วยการตัดปากมดลูกด้วยห่วงไฟฟ้าหรือด้วยมีดเป็นรูปกรวย*

ชนิดของการวิจัย: *การวิจัยเชิงพรรณนา*

สถานที่ทำการวิจัย: *ภาควิชาสูติศาสตร์- นรีเวชวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล*

กลุ่มตัวอย่าง: *สตรีที่ได้ผ่าตัดมดลูกภายหลังการรักษาด้วยการตัดปากมดลูกด้วยห่วงไฟฟ้าหรือตัดปากมดลูกเป็นรูปกรวย ตั้งแต่เดือน มกราคม พ.ศ. 2543 ถึง เดือน ธันวาคม พ.ศ. 2546 จำนวน 120 ราย*

วัสดุและวิธีการ: *ทำการทบทวนเวชระเบียนผู้ป่วยทั้ง 120 ราย เพื่อประมาณค่าความชุกของรอยโรค ที่เหลืออยู่ในมดลูก โดยประเมินจากรายงานทางพยาธิวิทยาของมดลูกที่ได้รับการผ่าตัด ตรวจสอบปัจจัยเสี่ยงที่คาดว่าจะมีส่วนเกี่ยวข้องกับการมีรอยโรคเหลืออยู่แล้วนำผลดังกล่าวไปวิเคราะห์ทางสถิติ*

ผลการวิจัย : *ในผู้ป่วยที่ได้ผ่าตัดมดลูก 120 ราย พบ 46 รายมีรอยโรคเหลือในมดลูก คิดเป็นความชุก 38.3% (95%CI 29.5, 47.2) และมีเพียงปัจจัยเดียวที่สามารถพยากรณ์ได้ถึงการมีรอยโรคเหลืออยู่ คือ การมีรอยโรคที่ขอบกรวยในขณะที่อายุ ผลพยาธิวิทยาจากการตัดปากมดลูก glandular and stromal involvement ผลเนื้อเยื่อปากมดลูกไม่สามารถทำนายได้ว่าจะมีรอยโรคเหลืออยู่หรือไม่*

สรุป: *ตรวจพบรอยโรคเหลืออยู่ 38.3% ในมดลูกที่ได้รับการผ่าตัด ภายหลังการรักษาด้วยการตัดปากมดลูกเป็นรูปกรวย และพบว่ามีรายที่เป็นมะเร็งร่วมด้วยโดยในรายที่มีรอยโรคที่ขอบกรวย ควรจะได้รับการตรวจหารอยโรคที่เหลืออยู่ในมดลูกอย่างละเอียด ก่อนทำการตัดมดลูก*