

Predictors of the Residual Disease of High-Grade Lesions and Microinvasive Squamous Cell Carcinoma of the Cervix Following Conization

Nungrutai Saeab MD*, Sathana Boonyapipat MD*,
Kobkul Tungsinnunkong MD**, Tippawan Liabsuetrakul MD, PhD***

* Department of Obstetrics and Gynecology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand

** Department of Pathology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand

*** Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand

Objective: To determine the predictors of residual disease of high-grade lesion (HGL) and microinvasive squamous cell carcinoma of the cervix (MICA) in subsequent hysterectomy following conization.

Material and Method: The medical records of women who underwent any conizations diagnosed of HGL and MICA and followed by subsequent hysterectomy within 6 months were retrospectively reviewed. A case and control was defined as whether or not a residual disease of HGL or more was detected in cervical tissue from hysterectomy after conization. Demographic characteristics and pathological features of cases and controls were recorded independently and blindly. Univariate and multivariate analysis were used. The Receiver Operating Characteristics curve of predictors was created using the fitting value obtained from a logistic regression model.

Results: A total of 185 women were diagnosed during January 1, 1997 and July 31, 2008 including 102 women without a residual disease and 83 with residual disease at cervical tissue from hysterectomy. The multivariate analysis showed that postmenopausal status (OR = 3.5, 95% CI = 1.8-6.7), number of quadrant involvement (OR = 3.8, 95% CI = 1.8-8.3), internal margin involvement (OR = 3.8, 95% CI = 1.7-8.2), severe nuclear atypia (OR = 2.0, 95% CI = 1.1-3.8) and high mitotic activity (OR = 2.1, 95% CI = 1.1-3.7) were the predictors of residual disease in hysterectomy specimens after conization. Three or more predictors involved predicted the detection of residual disease.

Conclusion: The presence of postmenopause, three or four quadrants involved, positive internal margin, severe nuclear atypia and high mitotic activity could be used to predict residual lesions after conization.

Keywords: Cervical dysplasia, Conization, Subsequent hysterectomy, Predictor

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Cancer of the cervix is the most common cancer in Thai women with an estimated 5,593 new cases in 1990, 5,462 new cases in 1993, 6,268 new cases in 1996 and 6,746 new cases in 1999⁽¹⁾. Due to a long duration of the pre-invasive stage, an effective screening program and proper management of

detected preinvasive lesions, in particular of the high-grade lesions (HGL), are major preventive measures. The estimated progression rate of HGL if left untreated is 5 to 40 percent⁽²⁾.

In the past, the standard therapy for patients with HGL and microinvasive carcinoma (MICA) was usually hysterectomy, especially for women no longer likely to bear children. More recently, the diagnostic excisional procedure is recommended for women with a histological diagnosis of HGL, however, there has been a trend toward more conservative surgery including cold-knife conization (CKC), loop electrosurgical

Correspondence to: Boonyapipat S, Department of Obstetrics and Gynecology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90112 Thailand. Phone: 074-429-617, Fax: 074-429-617, E-mail: sathana.t@psu.ac.th, kobkult@hotmail.com, ltippawa@yahoo.com, snungrut@medicine.psu.ac.th

excision procedures (LEEP) or large loop excision of the transformation zone (LLETZ), laser conization, and electrocautery needle conization⁽³⁾.

The treatment failure rate for HGL using either ablative or excision methods vary between 1% and 25%. In the past, patients with residual disease after excision procedures had given a poor prognosis usually requiring more intensive follow-up and more frequent subsequent radical surgery. One of the most predictive factors for residual lesion is the marginal status of excision specimen. The choice of treatment in women with a positive margin include interval assessment using cytology with endocervical sampling after treatment, repeated diagnostic excisional procedures or even hysterectomy if a repeat diagnostic procedure is not feasible⁽³⁾.

Although there are other demographic and clinicopathological factors including marginal status or positive endocervical curettage (ECC) that have been used to predict recurrent/residual disease after an excision procedure, the results of previous studies remain controversial. The purpose of the present study was to determine the demographic and clinicopathological predictors of a residual disease in subsequent hysterectomy in women who were diagnosed of HGL and/or microinvasive cancer (MICA) from conization.

Material and Method

The present case-control study was conducted at Songklanagarind Hospital, a University Hospital, which is a tertiary center for gynecologic oncology in southern Thailand. The present study was approved by the Institute of Ethics Committee of the Faculty of Medicine at Prince of Songkla University, Hat Yai, Songkhla, Thailand. The medical records of women who underwent any conizations diagnosed of high-grade lesion and microinvasive squamous cell carcinoma of the cervix and followed by subsequent hysterectomy within 6 months were retrospectively reviewed between January 1, 1997 and July 31, 2008. According to the proportion of factors related to the risk of residual disease in previous studies⁽³⁾, at least 81 specimens from women who underwent both conization and hysterectomy in each residual and non-residual lesion were needed.

A case and control group was defined as whether or not a residual disease was detected from cervical tissue of hysterectomy specimen. The residual disease was diagnosed if the presence of CIN II, CIN III, MICA, AIS or invasive cancer in the hysterectomy

specimens was noted. A pathologist reviewed the specimens of hysterectomy of all eligible records to identify the case and control. Demographic characteristics and clinicopathological features of conization were reviewed by the same pathologist and recorded independently and blindly from case ascertainment.

Demographic characteristics included age at diagnosis, pre or postmenopausal status and parity. Clinicopathological features were methods of conization (LEEP or CKC), diameter and depth of conization, number of quadrant involvement (one or two versus three or four), marginal status involved (ectocervical, endocervical or internal), presence of endocervical glandular involvement, percentage of involved section, percentage of involved mucosal length using an ocular micrometer, growth patterns (flat or bulbous), presence or absence of pseudogland formation or central necrosis, severe nuclear atypia, number of mitotic activity per 10 high power fields (HPFs), severe inflammatory cell infiltration, cytoplasmic maturation, lymphovascular involvement and performed ECC⁽⁴⁾.

Routinely, the specimens of conization were inked at the resection margin, serial sectioned and entirely submitted for pathological examination. Paraffin blocks were cut at 5- μ m intervals at two to three levels and were stained with hematoxylin and eosin. If conization showed a positive cone margin, associated gynecologic disease, cancer phobia, completed childbearing, expected poor compliance for follow-up and an inability to repeat the re-excision of the specimens, a following hysterectomy was indicated. Cervical specimens of the post-cone hysterectomy specimens were cut depending on the previous cone marginal status. If negative margins were detected, the tissue was incised into two to three sections per quadrant. The tissue was incised entirely if positive margins were seen. The final pathological diagnosis as the gold standard was defined as the most severe lesion of all specimens.

All data were double entered into EpiData 2.0 and analyzed by R software version 2.7.0 (the R Foundation for Statistical Computing 2008, Austria). Demographic characteristics and clinicopathological features between case and control groups were analyzed using univariate and multivariate analysis. The normal distribution of continuous data was tested then unpaired t-test or the Mann-Whitney U-test was used as appropriate. The categorical data were analyzed using Chi-square or Fisher's exact test as

Table 1. Relationship of final pathological findings between conization and hysterectomy

Conization	Hysterectomy					
	≤ CIN I	CIN II	CIN III	MICA	SCCA	AIS
CIN II	1	0	0	0	0	0
CIN III	65	3	44	1	1	0
MICA	22	0	14	10	5	0
AIS	4	0	0	1	0	2
AIS and CIN III	9	1	1	0	0	0
AIS and MICA	1	0	0	0	0	0

appropriate. A backward stepwise logistic regression model was used to identify the independent predictors of residual disease with a p value of less than 0.05 as a significant difference. The scoring index of significant predictors was estimated using the presence of predictors scored as one and absence of predictors scored as zero. Then the Receiver Operating Characteristics (ROC) curve of predictors was created using fitting value obtained from logistic regression model. Finally, the sensitivity and specificity of prediction was calculated.

Results

Of 185 eligible women in the present study period, 102 women were diagnosed of non-residual disease and 83 women diagnosed of residual disease. The subjects' age ranged from 24 to 80 with a mean of 47.2 years. Most of the women (68.6%) had a premenopausal status and the median parity was 3 (range 0-12). The results of conization were CIN II 0.5%, CIN III 67.6%, MICA 28.1%, AIS alone 3.8% and AIS with coexisting squamous lesions 6.2% (CIN III in 11 cases, and MICA in one case). Type of conization included loop conization 47% and CKC 53%.

The surgical treatments following conization were simple hysterectomy (94.1%) and radical hysterectomy with pelvic lymphadenectomy (5.9%). The average period from conization to subsequent hysterectomy was 62.2 days (range 1-183 days). The post-cone hysterectomy was performed within 1 month in 15.7% and within 2 months in 61.1%. Eighty-three (44.9%) patients had residual lesions in the subsequent hysterectomy specimens (CIN II 2.2%, CIN III 31.9%, AIS 1.1%, MICA 6.5% and invasive squamous cell carcinoma 3.2%). Most residual lesions in the post-cone hysterectomy specimens (95.9%) were similar to or less severe than the previous pathological report.

Table 2. Univariate analysis of demographic characteristics between non-residual and residual groups

Characteristics	Control n = 102	Case n = 83	p-value
	n (%)	n (%)	
Age group (year)			0.001
≤ 50	82 (80.4)	48 (57.8)	
> 50	20 (19.6)	35 (42.2)	
Reproductive status			<0.001
Premenopause	82 (80.4)	45 (54.2)	
Postmenopause	20 (19.6)	38 (45.8)	
Parity			1
Nullipara	3 (2.9)	3 (3.6)	
Multipara	99 (97.1)	80 (96.4)	

Only 8 patients (4.1%) had more advanced residual lesions. The relationship between the pathologic results of cone specimens and hysterectomy specimens is shown in Table 1.

The univariate analysis of demographic characteristics and clinicopathological features is shown in Tables 2 and 3. The final model of the multivariate logistic regression is shown in Table 4. Postmenopausal status, higher number of quadrant involvement, internal margin involvement, severe nuclear atypia and high mitotic activity were the independent predictors for remaining residual diseases of HGL of cervix or more. According to five significant factors, the ROC curve using fitting value obtained from logistic regression model is depicted in Fig. 1. The sensitivity of the presence of two or more, three or more and four or more of these five factors was 89%, 64% and 31%, respectively. The specificity of the presence of two or more, three or more and four or

Table 3. Univariate analysis of clinicopathological features between non-residual and residual groups

Features	Control (n = 102)	Case (n = 83)	p-value
	n (%)	n (%)	
Method of excision			0.65
LEEP	50 (49.0)	37 (44.6)	
CKC	52 (51.0)	46 (55.4)	
Quadrants involved			<0.001
1-2	35 (34.3)	10 (12.0)	
3-4	67 (65.7)	73 (88.0)	
Positive ectocervical margin			0.01
No	85 (83.3)	55 (66.3)	
Yes	17 (16.7)	28 (33.7)	
Positive endocervical margin			<0.01
No	56 (54.9)	27 (32.5)	
Yes	46 (45.1)	56 (67.5)	
Positive internal margin			<0.01
No	91 (89.2)	57 (68.7)	
Yes	11 (10.8)	26 (31.3)	
Gland involvement			0.64
Not involved	9 (8.8)	10 (12.0)	
Involved	93 (91.2)	73 (88.0)	
Growth pattern ^a			0.14
Flat	100 (98.0)	76 (92.7)	
Bulbous	2 (2.0)	6 (7.3)	
Pseudogland or central necrosis			0.09
No	69 (67.6)	43 (51.8)	
Yes	29 (28.4)	37 (44.6)	
Not applicable ^b	4 (4.0)	3 (3.6)	
Nuclear atypia			0.04
No	77 (75.5)	50 (60.2)	
Yes	25 (24.5)	33 (39.8)	
Mitosis (/10 HPF) ^c			0.02
≤ 23	60 (58.8)	34 (41.0)	
> 23	42 (41.2)	49 (59.0)	
Severe stromal inflammation			0.02
No	63 (61.8)	36 (43.4)	
Yes	39 (38.2)	47 (56.6)	
Cytoplasmic maturation			0.28
No	64 (62.7)	43 (51.8)	
Yes	34 (33.3)	37 (44.6)	
Not applicable ^b	4 (4.0)	3 (3.6)	
Lymphovascular space involvement			0.47
No	99 (97.1)	78 (94.0)	
Yes	3 (2.9)	5 (6.0)	
ECC results			0.01
Negative	37 (36.3)	17 (20.5)	
Positive	5 (4.9)	12 (14.5)	
Not done	60 (58.8)	54 (65.0)	
	Median (IQR)	Median (IQR)	
Diameter (mm)	20 (16.2-30)	20 (15-25)	0.06
Depth (mm)	10 (10-20)	10 (7.5-15)	0.28
Percentage of involved section	46 (28.2-68)	64 (41-88.5)	<0.001
Percentage of involved mucosal length	43.5 (29.2-66.2)	64 (40-88)	<0.001

^a Can not evaluate growth pattern in one patient

^b Not applicable: the pseudogland or central necrosis and cytoplasmic maturation could not be identified in glandular lesions

^c A median mitosis was used for a cut-off point of analysis

mm: millimeters, HPF: high power field, IQR: interquartile range

Table 4. Final model of significant predictors in multivariate analysis

Predictors	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value (Wald's test)	p-value (LR-test)
Reproductive status			<0.001	<0.001
Premenopause	1	1		
Postmenopause	3.5 (1.8, 6.7)	3.5 (1.7, 7.2)		
Quadrants involved			0.01	<0.01
One or two	1	1		
Three or four	3.8 (1.8, 8.3)	3 (1.3, 6.9)		
Positive internal margin			0.02	0.01
No	1	1		
Yes	3.8 (1.7, 8.2)	2.8 (1.2, 6.7)		
Nuclear atypia			0.02	0.02
No	1	1		
Yes	2.0 (1, 3.8)	1 (1.1, 4.5)		
High mitotic activity			0.03	0.03
≤ 23	1	1		
> 23	2.1 (1.1, 3.7)	2.1 (1.1, 4.1)		

more of these five factors was 43%, 76% and 96%, respectively. The detection of three or more factors was the most useful to predict the residual disease.

Discussion

Postmenopausal status, higher number of quadrant involvement, internal margin involvement, severe nuclear atypia and high mitotic activity are

independent predictors of residual diseases of HGL or more of the cervix. The detection of three or more predictors was clinically useful.

There is general agreement that the reporting of marginal status on a cone biopsy specimen is a reliable indicator of the residual lesions and/or their persistence⁽⁵⁻¹³⁾ which supported the finding in the present study that internal margin involvement predicted the residual disease. However, the location of the involved margin, whether ectocervical, endocervical or internal margin remains controversial^(11,14). A positive margin was not always associated with residual disease, possibly because of the eradication of residual lesions by the immune response or vaginal acidity, the removal of the lesion by endocervical curettage or electrocauterization of the cone bed, rapid cell turnover during cervical healing, false positive margin status produced by the oblique section during specimen preparation^(4,14-17).

Age, reproductive status and parity were reported as predictors of residual disease in subsequent hysterectomy in previous studies⁽¹⁴⁻¹⁶⁾ but only the postmenopausal status was significantly associated with residual disease in the present study. The high incidence of incomplete excision in elderly and menopausal women may have resulted from a deep inversion of the transformation zone of the atrophic cervix that may have caused difficulty in the removal of the entire lesion⁽¹⁴⁻¹⁶⁾. Whereas studies of Lin⁽¹⁵⁾ and Lu⁽¹⁴⁾ found that parity was significantly related to

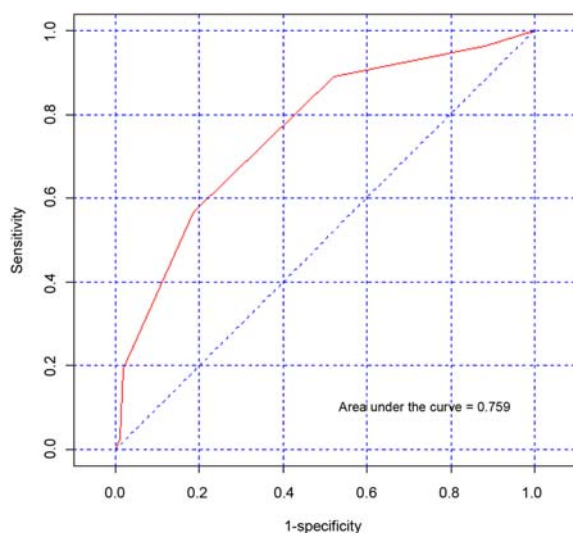


Fig. 1 ROC curve using fitting value from logistic regression model

residual disease, but in the present study, parity was not a significant predictor for residual disease similar to the finding of Park's study⁽¹⁶⁾. The reason why it was an insignificant predictive factor in the present study is possibility due to differences in the number of parity and multiparity, with the latter having a much small number.

The present study demonstrated that the involvement of more than half of the cervix was significantly associated with residual lesions; this finding was also consistent with previous studies^(13,17). There were no studies which reported severe nuclear atypia and high mitotic activity as the predictors for residual lesions. This finding might be explained by high atypia and proliferative activity related to exhibiting extensive lesions leading to remaining residual disease after conization.

A recent study, Kim 2007, has indicated that positive ECC, bulbous growth pattern, and central necrosis in the resection positive margin, but they were not significant in the present study. Likewise, a study revealed ECC as one predictor for residual lesions especially adenocarcinoma in situ⁽¹⁸⁾. On the other hand, the study of Kietpeerakool⁽¹⁷⁾, ECC was not a significant predictive factor for residual lesions due to differences in surgical techniques, experience of the surgeon, and interpretation of the pathologist. They suggested that ECC was minimally beneficial if the endocervical margin was positive. In the present study, ECC was performed only in unsatisfactory colposcopic examinations and showed significance in univariate analysis but not in logistic regression.

A systematic review demonstrated that the overall pooled treatment failure rates of CIN are about 5-15% and most failures occur within 2 years after treatment. Even treated, the incidence of invasive cervical disease remains about 56 per 100,000 for at least 20 years after treatment thus follow-up is essential⁽³⁾. As risks of treatment failure are associated with the presence of residual disease, clinicopathologic predictors for residual disease are used to identify women who may need intensive follow-up. The authors created the ROC curve using fitting value obtained from logistic regression model to make the predictors more meaningful in a clinical decision making. More predictors involved increased sensitivity but decreased specificity of residual detection. Women, who presented three or more predictors after conization, should be counseled and followed up intensively or further management due to a high chance of residual disease.

The case-control study was used in the present study because the specimens from both conization and subsequent hysterectomy within 6 months in women diagnosed of HGL and MICA was uncommon. The study period of 10 years was needed to obtain the sample size as calculation. In conclusion, the presence of postmenopause, three or four quadrants involved, positive internal margin, severe nuclear atypia and high mitotic activity can predict the residual lesions after conization in women diagnosed of HGL or more. Those women who have three or more predictors should be counseled and managed with caution.

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ศึกษาปัจจัยที่สามารถทำนายการคงเหลือของรอยโรค ในผู้ป่วยที่มีพยาธิสภาพที่ปากมดลูกในระดับรุนแรง และมะเร็งปากมดลูกระยะเริ่มแรกที่ได้รับการตัดชิ้นเนื้อที่ปากมดลูกเป็นรูปกรวย

หนึ่งฤทัย แซ่เอี้ยบ, สาธนา บุญยพิพัฒน์, กอบกุล ตั้งสินมั่นคง, ทิพวรรณ เลียบสื่อตระกูล

วัตถุประสงค์: ศึกษาปัจจัยที่สามารถทำนายการคงเหลือของรอยโรคที่ปากมดลูก ในกลุ่มผู้ป่วยที่มีรอยโรคในระดับรุนแรง และมะเร็งปากมดลูกระยะเริ่มแรกจากการตัดปากมดลูกเป็นรูปกรวย

วัสดุและวิธีการ: ค้นหาเวชระเบียนผู้ป่วยที่มีรอยโรคที่ปากมดลูกในระดับรุนแรงและมะเร็งปากมดลูกระยะเริ่มแรกจากการตัดปากมดลูกเป็นรูปกรวย และตัดมดลูกภายใน 6 เดือน จำแนกกลุ่มผู้ป่วยมีและไม่มีรอยโรคคงเหลือจากการทบทวนผลพยาธิวิทยาจากการตัดมดลูก รวบรวมข้อมูลลักษณะพื้นฐานทบทวนผลพยาธิวิทยาจากการตัดปากมดลูกเป็นรูปกรวย และนำมาคำนวณทางสถิติเพื่อค้นหาปัจจัยที่สามารถทำนายได้

ผลการศึกษา: ปัจจัยที่สามารถทำนายการคงเหลือของรอยโรค คือผู้ป่วยที่หมดประจำเดือน พบรอยโรคที่ขอบด้านลึกของชิ้นเนื้อ พบรอยโรคมกกว่าครึ่งของชิ้นเนื้อ พบนิวเคลียสที่ผิดปกติ และการแบ่งตัวที่ผิดปกติ และมีความเสี่ยงเพิ่มขึ้นหากพบร่วมกันมากกว่าหรือเท่ากับ 3 ปัจจัย

สรุป: ปัจจัยที่สามารถทำนายการคงเหลือของรอยโรคที่ปากมดลูก ในผู้ป่วยที่มีรอยโรคในระดับรุนแรง และมะเร็งปากมดลูกระยะเริ่มแรกจากการตัดปากมดลูกเป็นรูปกรวย คือ ผู้ป่วยที่หมดประจำเดือนพบรอยโรคที่ขอบด้านลึกของชิ้นเนื้อ พบรอยโรคมกกว่าครึ่งของชิ้นเนื้อ พบนิวเคลียสที่ผิดปกติ และการแบ่งตัวที่ผิดปกติ