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Cervical intraepithelial neoplasia II-III with endocervical cone margin involvement after cervical loop conization: Is there any predictor for residual disease?

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Abstract

Aim: To determine the clinicopathological predictors for residual disease in women who have had cervical intraepithelial neoplasia (CIN) II-III with endocervical cone margin involvement after loop electrosurgical excision procedure (LEEP).

Methods: All of the women who had CIN II-III on LEEP specimens with endocervical margin involvement, and underwent subsequent surgical treatment including repeat LEEP or hysterectomy at Chiang Mai University Hospital between May 2003 and June 2006 were reviewed.

Results: During the study period, 85 women who matched the study inclusion were identified. The mean age was 48.6 years. Fifty-two women (61.2%) were postmenopausal. The most common Pap smear before LEEP was high-grade squamous intraepithelial lesion (HSIL) (65.9%), followed by squamous cell carcinoma (21.2%). Twenty-five women (29.4%) had concurrent ectocervical and endocervical cone margin involvement. Residual disease was noted in 44 women (51.8%, 95%CI = 40.7–62.7) of whom six had unrecognized invasive squamous cell carcinoma, while the remaining 38 had CIN II-III. Only extensive endocervical cone margin involvement (3–4 quadrants) was noted as the significantly independent predictor for residual disease (aOR = 14.2, 95% CI = 3.6–55.8; $P < 0.001$).

Conclusion: Extensive endocervical cone margin involvement after LEEP for CIN II-III is a strong predictor for residual disease. Therefore, the number of involved quadrants should be evaluated to plan further management.

Key words: cervical intraepithelial neoplasia, endocervical margin, loop electrosurgical excision procedure, predictor, residual disease.

Introduction

Cervical intraepithelial neoplasia (CIN) II-III of the uterine cervix is now well established as a precursor lesion of squamous cell carcinoma. With the trend toward more conservative surgery, cervical conization has therefore become the treatment of choice for such lesions. Although there are various conization techniques, loop electrosurgical excision procedure (LEEP) has gained wide acceptance among gynecologic practice because it provides specimens for histological examination, can be performed in the outpatient department requiring only local anesthesia, and has a high success rate and low major surgical complication.[1] The incomplete excision of neoplastic epithelium after LEEP, however, is noted in a considerably high proportion of women and is mainly at the endocervical cone margin.[2] Previous studies reported that an incomplete

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excision at the endocervical cone margin after LEEP was a significant predictor for either persistence or recurrence of cervical dysplasia during follow-up.[3–5] The American Society for Colposcopy and Cervical Pathology (ASCCP) recommended a repeat excision as the first option in women who had CIN II-III with endocervical cone margin involvement after LEEP. If repeat excision is not feasible, hysterectomy is acceptable.[6] Based on this recommendation, an argument has been raised because a hysterectomy would be unnecessary in some cases and could be avoided with better identification of women at risk of harboring residual disease. Accordingly, this study was conducted to determine the clinicopathological predictors for residual disease in women who had CIN II-III with endocervical cone margin involvement after LEEP.

Materials and Methods

After approval from the Research Ethics Committee, the medical records of women undergoing LEEP at Chiang Mai University Hospital between May 2003 and June 2006 were reviewed. To become eligible for this study, the patients had to have CIN II-III on LEEP specimens and endocervical cone margin involvement with CIN II-III. The patients who had concurrent involvement of ectocervical and endocervical cone margin were also recruited. Abstracted data included patient characteristics, abnormal cervical cytology results, colposcopic findings, histology of LEEP specimens, and residual lesion after subsequent treatment.

LEEP was performed in an outpatient setting. The electrical power for the loop electrode was set to a blended mode. Endocervical curettage was routinely performed after LEEP. In cases of LEEP margin involvement, repeat colposcopy was carried out at 6–8 weeks postoperatively. All subsequent surgical treatment was performed within 12 weeks after the first LEEP. We attempted to perform repeat loop excision as first choice of treatment after positive cone margin. Hysterectomy was carried out when loop excision was technically impossible. The LEEP specimen diameters, including cone base and length, were measured before fixation. All specimens were opened longitudinally and sectioned serially along the entire length of the endocervix to the ectocervix at intervals of 1–3 mm and they were then embedded in paraffin. The surgical margins of the cones were marked with indelible ink. All sections were then stained with hematoxylin and eosin. Cone margin involvement in this study was defined by histological examination as the presence of neoplastic epithelium consistent with CIN II-III at the margin. The endocervical curettage (ECC) specimens were histologically interpreted as negative, positive, or inadequate. The results were negative when normal endocervical cells were presented. Positive results were those in which neoplastic cells were noted. Inadequate results were those without cells for interpretation.

Subjects with any type of histological abnormality after subsequent surgical treatment were classified as positive for residual disease. The χ^2 or Fisher exact test were used to univariately identify factors related to the presence of residual disease. For those factors with a *P*-value of less than 0.10 in univariate analysis, a multivariate analysis using a logistic model was used as well to find the independent factors. An odds ratio, with a 95% confidence interval that did not include unity, was considered statistically significant. All statistical tests were two sided and a *P*-value of less than 0.05 was considered statistically significant.

Results

During the study period, 85 women who had CIN II-III with endocervical cone margin involvement after LEEP, and had undergone subsequent surgical treatment were identified. The mean age of the women was 48.6 years (median 48.0, range 27–78 years). Fifty-two women (61.2%) were postmenopausal. Three women (3.5%) were nulliparous. The most common Pap smear before LEEP was high-grade squamous intraepithelial lesion (HSIL, 65.9%), followed by squamous cell carcinoma (21.2%), atypical squamous cells (9.4%), low-grade squamous intraepithelial lesion (2.4%), and unknown (1.2%), on which LEEP was performed due to CIN II-III on the previous biopsy from the referral hospital. The majority of women (82.4%) had unsatisfactory colposcopic examination before LEEP. Twenty-five women (29.4%) had concurrent ectocervical and endocervical cone margin involvement, while the remaining 60 (70.6%) had only endocervical cone margin involvement. The mean cone length and maximum cone base were 8.26 mm (median 8.0, range 4–15) and 21.4 mm (median 21.0, range 10–45), respectively. The abnormal ECC after LEEP was noted in 38 women (44.7%). The subsequent surgery included repeat LEEP (53), total abdominal hysterectomy (28), total laparoscopic hysterectomy (3), or vaginal hysterectomy (1). Residual disease was noted in 44 women (51.8%, 95%CI = 40.7–62.7), in whom 6 had unrecognized invasive squamous cell carcinoma, while the

Table 1 The univariate and multivariate analyses for prediction of residual disease after loop electrosurgical excision procedure (LEEP)

Variables	Category	Number (%)	Univariate *P*-value	Multivariate OR (95%CI)	*P*-value
Extents of lesion[†]	3–4 quadrants 1–2 quadrants	26/29 (89.7) 18/56 (32.1)	<0.001	14.2 (3.6–55.8)	<0.001
ECC	Positive Others[‡]	27/38 (71.1) 17/47 (36.2)	0.002	2.6 (0.8–7.7)	0.091
Cone length (mm)	<10 ≥10	34/53 (64.2) 10/32 (31.3)	0.004	3.1 (0.9–9.7)	0.053
Pap results	SCCA Others	12/18 (66.7) 32/67 (47.8)	0.190	Variable removed	
Age (years)	≥50 <50	21/35 (60.0) 23/50 (46.0)	0.271	Variable removed	
Menopausal status	Postmenopausal Premenopausal	19/33 (57.6) 25/52 (48.1)	0.505	Variable removed	
Margin involvement	Endo/ectocervical Endocervical	14/25 (56.0) 30/60 (50.0)	0.642	Variable removed	
Colposcopic finding[§]	Abnormal Others[¶]	4/8 (50.0) 40/77 (51.9)	1.000	Variable removed	

[†]The extent of endocervical cone margin involvement with CIN II-III. [‡]There were 28 negative and 19 inadequate specimens for evaluation. [§]After first LEEP. [¶]There were 74 unsatisfactory and 3 normal colposcopies. ECC, endocervical curettage; LEEP, loop electrosurgical excision procedure; SCCA, squamous cell carcinoma.

remaining 38 had residual CIN II-III. All 6 women with residual invasive lesions underwent total abdominal hysterectomy because repeat loop excision was technically impossible. Five women had a tumor depth of 3 mm or less and width of 7 mm or less (FIGO stage IA1), while the remaining one had a tumor diameter of 4.7 mm in depth and 10 mm in width (FIGO stage IB1).

Twelve (14.1%) women did not return to follow-up after the completion of treatment. At the median follow-up time of 11.2 months (range: 4–24 months), there was no evidence of recurrent disease detected by either Pap smear or physical examination in the remaining 73 women.

The univariate analysis, which included the age at diagnosis, menopausal status, type of abnormal Pap smear, site of cone margin involvement, cone length, extent of CIN II-III at endocervical cone margin, results of endocervical curettage, and colposcopic finding after LEEP was performed. Extensive endocervical cone margin involvement (3–4 quadrants), short cone length (less than 10 mm), and abnormal results of endocervical curettage were found to have a *P*-value of less than 0.10. Multivariate analysis using a logistic regression model, which included all the above significant covariates, was then performed. Only extensive endocervical cone margin involvement remained a statistically significant predictor for residual lesion after LEEP ($P < 0.001$). Women with such lesions had approximately 14 times the risk of having residual disease on subsequent surgical specimens (Table 1).

Discussion

In this study, we noted that 51.8% of women undergoing LEEP for CIN II-III, in whom the endocervical cone margin was involved, had residual disease on subsequent surgical treatment. This finding was similar to the reported incidence of approximately 50% in previous studies.[7,8] Additionally, the incidence of unrecognized invasive cervical carcinoma (7.1%) in this study was also comparable to that previously reported of 0.9% to 9.6%.[7,9–11]

The authors systematically evaluated the demographic, colposcopic, and pathological variables to determine the relationship with residual disease on subsequent treatment. A logistic regression analysis revealed that only extensive involvement of CIN II-III at the endocervical cone margin (3–4 quadrants) was a significant independent predictor for residual disease. Women with such extensive lesions at the endocervical cone margin had approximately 14 times the risk of having residual lesions on subsequent surgical evaluation. To our knowledge, an association between the number of quadrant involvement of the endocervical

cone margin after LEEP for CIN II-III and a risk of having residual disease on subsequent surgical treatment has not been reported previously. This finding is biologically plausible because a large amount of CIN II-III at the endocervical cone margin may indicate an increased chance of having a residual lesion that is too large to be completely eradicated when compared to a small lesion. Unsurprisingly, women with extensive involvement of the endocervical cone margin were more likely to have a residual lesion after LEEP, as demonstrated in our multivariate analyses.

Interestingly, on our multivariate analyses, the short cone length (less than 10 mm) was a marginally significant predictor for residual disease after LEEP for CIN II-III with endocervical cone margin involvement (P = 0.053). An explanation for this observation may be related to the high incidence of either unsatisfactory colposcopy before LEEP (82.4%) or the incidence of menopausal women (61.2%) in this study, which suggested that the abnormal cervical epithelium was more likely to situate high in the endocervical canal in the majority of cases. Consequently, shallow excision of the endocervix would result in incomplete removal of the entire lesion. Therefore, our findings indicated that deeper endocervical excision in such women using other conization techniques, such as apical excision of the transformation zone after the first pass, the so-called top-hat LEEP, or cold-knife conization, may be more appropriate than the traditional LEEP in reducing the incidence of endocervical cone margin involvement.

Theoretically, ECC after LEEP appears to be a strong predictor for residual disease on post-LEEP specimens, however currently the available data is mixed. Felix *et al*.[3] and Kalogirou *et al*.[12] pointed out that the post-LEEP ECC could predict residual lesions on subsequent treatment. Conversely, Natee *et al*.[11] and Vierhout and de Planque[13] reported that ECC did not provide significant value in predicting residual lesions. In this study, ECC was not a significantly independent predictor for residual disease from multivariate analyses (P = 0.09). The heterogeneity of these results may be partially explained by the difference in surgical technique, experience of the surgeon and interpretation of the pathologist.

In this study, there was no significant difference in the incidence of residual lesion after LEEP in women who had only endocervical cone margin involvement, when compared to those with concurrent endocervical and ectocervical cone margin involvement from univariate analyses (50 and 56%, respectively, P = 0.64). This observation was consistent with findings from previous reports.[14–16] An explanation for this finding may be the result of thermal destruction of the peripheral ectocervical lesion during electrical fulguration after LEEP. This hypothesis does not similarly apply to residual lesion at the endocervical lesion because it cannot be seen and vaporized as easily as those at the ectocervical margin. In addition, the colposcopist generally avoids vaporizing close to the endocervical os in order to minimize the risk of endocervical stenosis after LEEP.

The major aim of the postconization surveillance for CIN II-III is the early detection of residual and recurrent disease. The selection of follow-up methods, i.e. cervical cytology alone and combined cytology and human papillomavirus (HPV) testing generally depends on the available resource of each setting. Recently, Bar-Am *et al*.[17] reported that adding HPV testing to cervical cytology could increase the detection rate of residual CIN II-III after conization. Our findings suggested some important practical considerations for women who had endocervical cone margin involvement with CIN II-III and for whom repeat conization is clinically impossible. The post-treatment surveillance without hysterectomy may be an alternative in those with 1–2 quadrants involvement because only 30% of such women had residual disease. On the other hand, because of the high incidence of residual disease (89.7%) in women who have had extensive endocervical cone margin involvement (3–4 quadrants), hysterectomy is strongly advised.

In conclusion, extensive endocervical cone margin involvement after LEEP for CIN II-III is a strong independent predictor for residual disease. Therefore, apart from the evaluation of endocervical cone margin involvement, the number of involved quadrants should also be assessed and reported to the physician, with an explicit comment about the significant risk of harboring residual disease when extensive involvement is noted.

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