
GYNAECOLOGY

Prevalence and Risk Factors of LEEP Margin Involvement

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ABSTRACT

Objective To determine the prevalence and factors associated with incomplete margins in women with CIN undergoing LEEP.

Design Cross-sectional study.

Setting Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University.

Subjects A total of 187 women who underwent LEEP between January 1, 1998 and December 31, 2000.

Methods Medical records of 187 women were reviewed. Data collection included baseline characteristics, Pap smear results, colposcopic findings, and all related cytologic and histologic results.

Results The prevalence of cervical LEEP margin involvement was 35.3%. Positive ectocervical and endocervical margins were found in 19.3% and 16.0% respectively. In addition, 10.7% showed positive on both ectocervical and endocervical margins. Independent risk factors for any margin involvement were age ≥ 40 years (OR 3.0 and 2.9 respectively), endocervical extension of lesions (OR 2.8 and 3.5 respectively), and invasive results from Pap smear (OR 3.9 and 6.9 respectively). On the other hand, invasive results from Pap smear was the only independent risk for ectocervical margin involvement (OR 4.6).

Conclusion Cervical LEEP margin involvement was found in approximately one-third of women underwent LEEP (35.3%). Important risk factors associated with incomplete excision were older age, endocervical extension of lesions, and invasive cancer on Pap smear. Such factors should be considered in all women indicated for LEEP and appropriate technique should be used to reduce the risk of margin involvement.

Key words: loop electrosurgical excision procedure (LEEP), margin involvement, cervical intraepithelial neoplasia (CIN)

Invasive cervical cancer is the leading cause of cancer death in Thai women and still a significant public health problem in Thailand. Cancer prevention efforts were required by early detection and eradication of cancer precursor lesions, i.e., cervical intraepithelial neoplasia (CIN).⁽¹⁾ Pap smear is the

fundamental method for early detection of CIN. However, there are so many options for CIN eradication varying from ablative methods (cryotherapy, electrocautery and laser vaporization) to excisional method (cold knife conization, laser conization and loop electrosurgical excision procedure or LEEP). Similar

success rates were observed between cryotherapy, laser vaporization, and LEEP.^(2,3)

LEEP is an alternative surgical technique to cold knife conization for CIN treatment. The technique uses a low voltage, high-frequency electrical current to excise the entire transformation zone. This technique is relatively simple and very cost-effective since it is performed with local anesthesia as an outpatient service in the gynecologic office or in an operating room. LEEP can be used for both diagnostic and therapeutic purposes. Large series have shown that LEEP had over 90% cure rate for all grades of CIN with low rate of complications such as hemorrhage or cervical stenosis compared to cold-knife conization.^(3,4) However, incidence rate of incomplete excision and residual disease were similar between LEEP and cold-knife conization.⁽²⁻⁴⁾

Pathological margin status is widely accepted as an important risk factor for recurrent or persistent CIN.^(1,5-10) In one large study of 381 women who underwent cold-knife conization, the rate of recurrent or persistent CIN were 16% among women with positive margins and only 4% among those with negative margins.⁽⁹⁾ There was also a report showing that the cure rate for incomplete excision at ectocervical margin was 86% and at the endocervical margin was 68% and only 40% if excision was incomplete at both margins.⁽¹¹⁾

Up to 40% of women undergoing LEEP had incomplete excision of their CIN lesion on the basis of histopathologic interpretation.^(7,8,12,13) Incomplete resection or positive LEEP margin have been reported to be associated with several factors, including severity of referral Pap smear,⁽¹⁴⁾ involvement of the endocervix,^(12,14,15) high-grade lesion^(12,16-19) more extensive lesion size,^(12,14,15,20) conization technique,⁽²¹⁾ and surgeon's expertise.^(15,19)

The objectives of this study were to determine the prevalence of incomplete margins among women who underwent LEEP, and to evaluate factors associated with incomplete LEEP margins.

Materials and Methods

Retrospective review of medical records was

conducted under ethical board review permission. Women who underwent LEEP between January 1, 1998 and December 31, 2000 at Siriraj Hospital were enrolled for this collective review.

All women enrolled had already been evaluated by colposcopy prior to LEEP by experienced colposcopists and colposcopic diagnoses were made with or without cervical biopsy. If indicated, LEEP was scheduled and performed as an outpatient service in operating room by the same gynecologist. Loop diameter selection was made based on the size of the lesion. One, two or more passes were allowed on the cut procedure. Endocervical curettage (ECC) was performed selectively after the LEEP according to surgeon's judgement.

All data were extracted from medical record including baseline characteristics, Pap smear results, colposcopic findings, and all related cytologic and histologic results. Important variables were pre-defined as follows:

- Pap smear results were reported according to the 1991 Bethesda System.⁽²²⁾
- Cervical lesion site was classified as lesion involving ectocervix, endocervix, or both, as recorded from colposcopic findings.
- Cervical lesion size was classified by number of quadrants the lesion involved.
- Colposcopic diagnoses were determined either from histologic results, or from colposcopic characteristics observed by colposcopist if cervical biopsy was not performed.
- Margin involvement was defined as the presence of CIN at excision margin or less than 1 mm close to margin.
- All tissue specimens, including colposcopic-directed biopsy, LEEP specimen and margin involvement, were reviewed and interpreted by one pathologist in the Department of Pathology

Data were described using descriptive statistics, including mean, standard deviation, number, and percentage. Univariate comparison of potential risk factors between those with and without margin involvement was made using Chi square test. Logistic regression analysis was performed to determine

independent risk factors for margin involvement. Odds ratios and their 95% confidence intervals were estimated. Statistical significance was considered when p value was less than 0.05.

Results

During January 1, 1998 and December 31, 2000,

a total of 187 patient's profiles were available for analysis. Characteristics of the women were shown in Table 1. Mean age of these women was 39.5 years and 13.4% were nulliparous. Initial Pap smear results were available in 177 cases and HSIL was reported in the majority of cases (72.2%). Invasive cancer on Pap smear were found in 13.4% of cases.

Table 1. Baseline characteristics of women in this study (N = 187)

Characteristic	Number (%)
Mean age \pm SD (yrs)	39.5 \pm 10.1
Parity	
0	25 (13.4%)
1-2	100 (53.5%)
≥ 3	62 (33.2%)
Pap smear result	
LSIL	16 (8.6%)
HSIL	136 (72.7%)
Invasive	25 (13.4%)
Missing	10 (5.3%)

Colposcopy was performed in all women prior to LEEP. Colposcopic findings were shown in Table 2.

Table 2. Colposcopic findings prior to LEEP (N = 187)

Colposcopic findings	Number (%)
Transformation zone	
Adequate	112 (59.9%)
Inadequate	75 (40.1%)
Lesion site	
No lesion seen	19 (10.2%)
Ectocervix only	115 (61.5%)
Ectocervix and Endocervix	53 (28.3%)
Lesion size (quadrants)	
0-1	75 (40.1%)
2	76 (40.6%)
3-4	36 (19.3%)
Colposcopic diagnosis	
Normal	18 (9.6%)
Low grade (HPV, CIN I)	27 (14.4%)
High grade (CIN II, CIN III, Invasive cancer)	142 (75.9%)
Glandular involvement	(N = 44)
No	30 (68.2%)
Yes	14 (31.8%)

Transformation zone was adequately visualized in 60% of cases. Cervical lesion involved ectocervix only in 61.5% of cases and involved both ectocervix and endocervix in 28.3% of cases. The lesion extensively involved more than 2 quadrants in 19.3% of case. The majority was diagnosed with high-grade lesions on colposcopic examination (75.9%). Cervical biopsy was performed in 44 cases and 31.8% revealed glandular involvement on histologic results.(Table 2.)

Results on margin involvement were shown in Table 3. Ectocervical and endocervical margins were reported to be free of the disease in 121 cases (64.7%), and the prevalence of positive margin was 35.3%. Positive ectocervical and endocervical margins were found in 19.3% and 16.0% respectively. In addition, 20 cases (10.7%) showed positive on both ectocervical and endocervical margins.

Table 3. Margin involvement

Margin involvement	Number (%)
Negative margins	121(64.7%)
Positive margins	66(35.3%)
Ectocervical margin	36(19.3%)
Endocervical margin	30(16.0%)
Ectocervical and endocervical margins	20(10.7%)

Factors possibly associated with LEEP margin involvement were evaluated as shown in Table 4. Significant characteristics that increased the probability of margin involvement were age of 40 years or more, increased severity of Pap smear results, more extensive lesions (involved 3 quadrants or more, and endocervical involvement), and inadequate

visualization of transformation zone. Similar results were observed among those with endocervical margin involvement. On the other hand, among those with ectocervical margin involvement, significant factors associated with positive margin were older age and severity of Pap smear results.

Table 4. Factors associated with LEEP margin involvement (66 cases)

Risk factors	N	No. of cases with margin involvement (%)		
		Any margin	Ectocervix	Endocervix
Age (years)				
< 40	102	24 (23.5%)	14(13.7%)	18(17.6%)
≥ 40	85	42 (49.4%)*	22(25.9%)*	32(37.6%)*
Parity				
Nulliparous	25	5 (25.0%)	4(16.0%)	2(8.0%)
Multiparous	162	61 (37.7%)	32(19.7%)	48(29.6%)*
Pap smear				
LSIL	16	5(31.2%)	4(25.0%)	2(12.5%)
HSIL	136	39(28.7%)	18(13.2%)	28(20.6%)
Invasive cancer	25	18(72.0%)*	11(44.0%)*	18(72.0%)*

Risk factors	N	No. of cases with margin involvement (%)		
		Any margin	Ectocervix	Endocervix
Lesion size (quadrants)				
0-2	151	48(31.8%)	25(16.6%)	35(23.1%)
3-4	36	18(50.0%)*	11(30.6%)	15(41.7%)*
Lesion site				
None / Ectocervix	134	38(28.4%)	24(17.9%)	25(18.7%)
Ectocervix / Endocervix	53	28(52.8%)*	12(22.6%)	25(47.2%)*
Transformation zone				
Adequate	112	28(25.0%)	18(16.1%)	21(18.7%)
Inadequate	75	38(50.7%)*	18(24.0%)	29(38.7%)*
Colposcopic diagnosis				
Normal / Low grade	45	14(31.1%)	10(22.2%)	7(15.6%)
High grade	142	52(36.6%)	26(18.3%)	43(30.8%)
Glandular involvement				
No	30	8(26.7%)	6(20.0%)	7(23.3%)
Yes	14	5(35.8%)	3(21.4%)	4(28.6%)

* Statistical significance, using Chi square test

Logistic regression was performed to determine the independent risk for margin involvement. The results were shown in Table 5. For involvement of any LEEP margin and endocervical margin involvement, independent risk factors were old

age, lesions with endocervical extension, and invasive cancer on Pap smear. On the other hand, invasive cancer on Pap smear was the only independent risk for ectocervical margin involvement.

Table 5. Logistic regression analysis of factors associated with LEEP margin involvement

Margin involvement	Risk factors	Odds ratio (95% CI)
Any margin	- Age \geq 40 years	3.0 (1.5 - 6.1)
	- Ectocervix and Endocervix involvement	2.8 (1.3 - 5.9)
	- Invasive cancer on Pap smear	3.9 (1.5 - 10.6)
Ectocervix	- Invasive cancer on Pap smear	4.6 (1.9 - 11.5)
Endocervix	- Age \geq 40 years	2.9 (1.3 - 6.3)
	- Ectocervix and Endocervix involvement	3.5 (1.6 - 7.9)
	- Invasive cancer on Pap smear	6.9 (2.5 - 18.9)

Discussion

LEEP is an alternative surgical technique to cold knife conization for CIN management. It can be used for both diagnostic and therapeutic purposes. However, clinical management problems arise when

squamous or glandular lesions extend to the excision margins. In this study, prevalence of LEEP margins involvement was 35.3%. This prevalence was similar to previous reports which had LEEP margins involvement range from 14 to 48%.^(7,8,12,13,23-25)

Ectocervical involvement was found slightly more common than endocervical involvement (19.3% and 16.0% respectively). Involvement of both ectocervical and endocervical margins was found in only 10.7% of all cases.

There was a report that 83.8% of patients with CIN in the resection margin were free of recurrence after a 5-year follow up period.⁽⁹⁾ However, evidence exists that involved margins are associated with residual and recurrent disease.^(5,16) A decrease in cure rate among those with incomplete excision has been reported. Success rate of LEEP has been reported to drop remarkably to only 69.2% when endocervical margins of the specimen were involved as compared to 83.1% in those with uninvolved margins.⁽³⁾ In addition, cure rate for incomplete excision at ectocervical margin was 86% and at the endocervical margin was 68% and dropped to only 40% if excision was incomplete at both margins.⁽¹¹⁾ Recurrence rate has been reported to be significantly increased with involvement of endocervical margin.⁽¹⁸⁾

The results showed that independent risk factors for overall margin involvement and endocervical margin involvement in this study were older age, extension of lesions into endocervical canal, and invasive cancer on Pap smear. For ectocervical involvement, only invasive cancer on Pap smear was significant. This was similar to those from previous studies. Severity of Pap smear and involvement of endocervix have been reported to be associated with LEEP margin involvement.^(12,14,15) High-grade lesion from colposcopy only slightly increased risk of incomplete LEEP resection, but was not significant statistically. This was different from those reported by others.^(12,16-19) Advanced age of 40 years or older was another significant risk factor found in this study, while others did not report such association.^(12,15-16) Older age might be indirectly related to increased disease severity since there is still lack of national cervical cancer screening in Thailand. Extensive lesion size that involved multiple quadrants was another factor that has been reported by some to increase the risk of positive margin as

well.^(12,14,15,20) However, it was not a significant risk in this study. Surgeon's expertise has also been reported to be a risk factor as well. However, this should not have any impact on the results of this study since all procedures were performed by highly-experienced gynecologists.

These risk factors should be considered in patients who are indicated for excisional biopsy of cervix for diagnosis and treatment of CIN. Incomplete excision should be anticipated when LEEP is used. Technique for excisional biopsy of cervix should also be considered carefully and efforts should be made to reduce the risk of margin involvement in these patients. Cold-knife conization provides a deeper cone biopsy (large volume excised) that might be an alternative for the management of patients with large lesions or lesions that extend to endocervical canal. Although most cases of positive margin will also be cured, the importance of further follow up should be explained to these patients. The more intensive follow up schedule should be arranged carefully to ensure that all recurrence would not be missed.

References

1. Wright TC Jr, Cox JT, Massad LS, Carlson J, Twigg LB, Wilkinson EJ. 2001 consensus guidelines for management of women with cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 2003; 189: 295-304.
2. Mitchell MF, Tortelero-Luna G, Cook E, Whittaker L, Rhodes-Morris H, Silva E. A randomized clinical trial of cryotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. *Obstet Gynecol* 1998; 92: 737-44.
3. Gold M, Dunton CJ, Murray J, Macones G, Hanau C, Carlson JA Jr. Loop electrocautery excisional procedure: Therapeutic effectiveness as an ablation and a conization equivalent. *Gynecol Oncol* 1996; 61: 241-4.
4. Ferenczy A. Management of patients with high grade squamous intraepithelial lesions. *Cancer* 1995; 76: 1928-33.
5. Jakus S, Edmonds P, Dunton C, King SA. Margin status and excision of cervical intraepithelial neoplasia. *Obstet Gynecol Surv* 2000; 55:520-7.
6. Felix JC, Muderspach LI, Duggan BD, Roman LD. The significance of positive margins in loop electrosurgical cone biopsies. *Obstet Gynecol* 1994; 84: 996-1000.
7. Zaitoun AM, Mckee G, Coppen MJ, Thomas SM, Wilson PO. Completeness of excision and follow up cytology in patients treated with loop excision biopsy. *J Clin Pathol*

- 2000; 53: 191-6.
8. Gardeil F, Barry-Walsh C, Prendiville W, Clinch J, Turner MJ. Persistent intraepithelial neoplasia after excision for cervical intraepithelial neoplasia grade III. *Obstet Gynecol* 1997; 89: 419-22.
9. Vedel P, Jakobsen H, Kryger-Baggesen N, Rank F, Bostofte E. Five-year follow up of patients with cervical intra-epithelial neoplasia in the cone margins after conization. *Eur J Obstet Gynaecol Reprod Biol* 1993; 50: 71-6.
10. Gonzalez DI Jr, Zahn CM, Retzlaff MG, Moore WF, Kost ER, Snyder RR. Recurrence of dysplasia after loop electrosurgical excision procedures with long-term follow-up. *Am J Obstet Gynecol* 2001; 184: 315-21.
11. Mohamed-Noor K, Quinn MA, Tan J. Outcomes after cervical conization with complete and incomplete excision of abnormal epithelium: a review of 699 cases. *Gynecol Oncol* 1997; 67: 34-8.
12. Murdoch JB, Morgan PR, Lopes A, Monaghan JM. Histological incomplete excision of CIN after large loop excision of the transformation zone (LLETZ) merits careful follow up, not retreatment. *Br J Obstet Gynaecol* 1992; 99: 990-3.
13. Lapaquette TK, Dinh TV, Hannigan EV, Doherty MG, Yandell RB, Buchanan VS. Management of patients with positive margins after cervical conization. *Obstet Gynecol* 1993; 82: 440-3.
14. Naumann RW, Bell MC, Alvarez RD, Edwards RP, Partridge EE, Helm CW, et al. LLETZ is an acceptable alternative to diagnostic cold-knife conization. *Gynecol Oncol* 1994; 55: 224-8.
15. Costa S, De Nuzzo M, Terzano P, Santini D, De Simone P, Bovicelli A, et al. Factors associated with cone margin involvement in CIN patients undergoing conization-equivalent electrosurgical procedure. *Acta Obstet Gynecol Scand* 2000; 79: 586-92.
16. Phelps JY III, Ward JA, Szigeti J II, Bowland CH, Mayer AR. Cervical cone margins as a predictor for residual dysplasia in post-cone hysterectomy specimens. *Obstet Gynecol* 1994; 84: 128-30.
17. Abdul-Karim FW, Nunez C. Cervical intraepithelial neoplasia after conization: a study of 522 consecutive cervical cones. *Obstet Gynecol* 1985; 65: 77-81.
18. Andersen ES, Pedersen B, Nielsen K. Laser conization: the result treatment of cervical intraepithelial neoplasia. *Gynecol Oncol* 1994; 54: 201-4.
19. Santos C, Galdos R, Alvarez M, Verarde C, Barriga O, Dyer R, et al. One-session management of cervical intraepithelial neoplasia: a solution for developing countries. *Gynecol Oncol* 1996; 61: 11-5.
20. Haung M, Anderson P. Positive margins after cervical conization as an indicator of residual dysplasia. *Prim Care Update Ob Gyn* 1998; 5: 160-1.
21. Alvarez RD, Helm CW, Edwards RP, Naumann RW, Partridge EE, Shingleton HM, et al. Prospective randomized trial of LLETZ versus laser ablation in patients with cervical intraepithelial neoplasia. *Gynecol Oncol* 1994; 52: 175-9.
22. Kurman RJ, Solomon, D. The Bethesda system for reporting cervical/vaginal cytologic diagnosed: definition, criteria, and explanatory notes for terminology and specimen adequacy. New York: Springer-Verlage; 1994.
23. White CD, Cooper WL, William RR. Cervical intraepithelial neoplasia extending to the margins of resection in conization of the cervix. *J Reprod Med* 1991; 36: 635-8.
24. Narducci F, Occelli B, Boman F, Vinatier D, Leroy JL. Positive margins after conization and risk of persistent lesion. *Gynecol Oncol* 2000; 76: 311-4.
25. Brun JL, Youbi A, Hocke C. Complications, sequelae and outcome of cervical conizations: evaluation of three surgical techniques. *J Gynecol Obstet Reprod Biol* 2002; 31: 558-64.