Loop Electrosurgical Excision Procedure (LEEP) at Maharaj Nakorn Chiang Mai Hospital : Problems in Pathologic Evaluation

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Abstract

Background : Loop electrosurgical excision procedure (LEEP) is widely used in diagnosis and management of cervical lesions. Difficulties in histopathologic evaluation of LEEP specimens, particularly for the margin status, have been reported to be a significant disadvantage of the procedure.

Method : The histologic slides of the specimens from 163 patients who underwent LEEP at Maharaj Nakorn Chiang Mai Hospital from August 1995 to November 1997 were retrospectively reviewed for the degree of thermal artefact and the margin status. Follow-up data after a 6-month-period were correlated with the margin status.

Results : Thermal artefact was present in all cases (mild 51.5%, moderate 36.2%, and severe 12.3%). In only one case, histologic diagnosis of the lesion was not possible due to severe thermal artefact. Nine cases (5.5%) had non-evaluable margins due to either thermal artefact (7 cases) or improper orientation of fragmented tissue (2 cases). Of 90 cases with subsequent surgical specimens, residual diseases were present in 4 of 21 (19.0%) with negative LEEP margins, in 31 of 64 (48.4%) with positive margins, and in 4 of 5 (80.0%) with non-evaluable margins.

Conclusions : Pathologic evaluation of the specimens from LEEP was limited in only a minority of cases. Thermal artefact was not a critical disadvantage of LEEP. The positive or negative margin status was correlated with the risk of residual disease.

Key word : LEEP, Uterine Cervix, Thermal Artefact

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Loop electrosurgical excision procedure (LEEP) is a surgical procedure that is widely accepted as a technique in diagnosis and management of cervical lesions[1,2]. It has a potential to replace traditional cold-knife conization (CKC) with several advantages[3]. The specimen obtained by LEEP is inevitably accompanied by thermal artefact that may significantly interfere with the pathologic evaluation[2,4]. Furthermore, multiple fragments obtained by the procedure may be difficult to orientate[5]. The studies regarding LEEP addressed different levels of concern for difficulties in histopathologic assessment of the specimens. We evaluated the results of this procedure performed in our hospital for the presence of factors that interfered with the pathological diagnosis with emphasis on the margin status and its relation to the residual disease.

MATERIAL AND METHOD

Patients included in the study underwent colposcopy and LEEP at Maharaj Nakorn Chiang Mai Hospital from August 1995 to November 1997. LEEP was performed by rotating residents in Obstetrics and Gynecology under supervision of the gynecologic oncologists. The clinical information and the pathological reports of all cases were available for review. The histopathologic slides were retrieved from the surgical pathology files of the Department of Pathology. The cases of which the original histopathologic materials were incomplete or not available were excluded. The follow-up data including the histologic diagnosis of specimens from further biopsy or surgery and the results of subsequent cervical cytologic smears within 6 months after LEEP were collected.

The pathology reports were reviewed for the number of tissue fragments received and the number of histologic slides. Pathologic re-evaluation of all specimens obtained by LEEP was performed by one pathologist (S.S.) without knowledge on the clinical information. All cases were reviewed for the histologic diagnosis, the presence of squamo-columnar junction, degree of thermal artefact, and status of the surgical margin. Thermal artefact was graded into 3 categories according to the degree of cellular alteration and distortion of tissue architecture as follows: mild (Fig. 1), moderate (Fig. 2), and severe (Fig. 3). The quality of the surgical margins was determined as evaluable or non-evaluable by the opinion of the reviewer. Non-evaluable margin was considered when the margin affected by thermal artefact had equivocal features of squamous intraepithelial lesion (SIL) or the true

Fig. 1. Mild thermal artefact is characterized by cellular edema and vacuolar degeneration with minimal architectural distortion. (Hematoxylin & Eosin stain [H&E], original magnification, x200)

Fig. 2. Moderate thermal artefact. Coagulative change is characterized by eosinophilic granular cytoplasm and distorted nuclei with degenerated nuclear chromatin. (H&E, original magnification, x200)

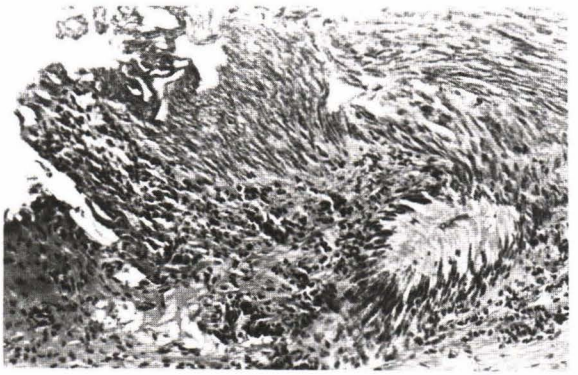

Fig. 3. Severe thermal artefact is characterized by marked cellular degeneration with severe distortion of all cytologic details. (H&E, original magnification, x200)

Table 1. Indications for LEEP in 163 patients.

Unsatisfactory colposcopy	56
Confirmation of SIL diagnosis	49
Therapeutic excision	13
Discrepancy between cervical cytology and biopsy	12
Microinvasive SCC or exclusion of invasion	29
AIS	4

SCC : squamous cell carcinoma, AIS: adenocarcinoma *in situ*.

Table 2. Histologic diagnosis of 163 LEEP specimens.

Benign change	10
Atypical squamous metaplasia	2
Low-grade SIL	28
High-grade SIL	90
Microinvasive SCC	15
SCC	11
AIS	2
Invasive adenocarcinoma	4
Non-evaluable	1

surgical margin could not be identified. Positive surgical margin was diagnosed when either margin of the specimen showed the presence of SIL.

The results of the margin status were compared with the presence of residual lesion in further surgical specimens obtained within 6 months after LEEP. The presence of at least low-grade SIL was required as an indication for positive outcome. Statistical analysis was performed using Chi square with Yates' correction or Fisher's exact test. Statistical significance was considered when p value was less than 0.05.

RESULTS

A total of 163 cases of LEEP specimens during that period met the inclusion criteria for the study. The patients' ages ranged from 18 to 67 years (mean, 39.6). All cases had a history of abnormal cervical smear or biopsy prior to colposcopy. Indications for LEEP are presented in Table 1. The LEEP specimens were mostly obtained in one piece (120 cases). Forty-three cases (26.4%) had multiple tissue fragments (up to 4 pieces in 4 cases). Based on histologic review, squamocolumnar junction was present in 146 cases (89.6%). In the remaining 17 cases, only endocervical tissue was included. The histologic diagnosis of LEEP specimens is shown in Table 2. In one case, pathologic diagnosis was not possible due to the presence of severe thermal artefact at the lesion. The surgical margin in this case was, however, evaluable as negative.

Thermal artefact was present in all specimens from LEEP and was usually confined to the margins of the tissue. Of 163 cases, 84 (51.5%) had mild degree of thermal artefact, 59 (36.2%) had moderate degree, and 20 (12.3%) had severe degree. The margin status was considered evaluable in 154 cases (94.5%). Nine cases (5.5%) had non-evaluable surgical margins due to thermal artefact (7 cases) or inappropriate tissue orientation (2 cases). Relation between the surgical margin status and the degree of thermal artefact is shown in Table 3. Although the prevalence of non-evaluable margins was more frequent among the specimens with moderate to severe thermal artefact than those with mild degree, the difference was not significant (p=0.3). Of 3 cases with mild thermal artefact and non-evaluable margin, it should be noted that non-evaluable margin status was genuinely caused by thermal artefact in only one case, while the other two had non-evaluable margins due to improper tissue orientation. Of 120 cases whose specimens were received in one

Table 3. Degree of thermal artefacts and margin status of LEEP specimens.

Margin status	Degree of thermal artefacts					
	Mild	%	Moderate	%	Severe	%
Evaluable	81	96.4	54	91.5	19	95.0
Negative	49	58.3	14	23.7	4	20.0
Positive	32	38.0	40	67.8	15	75.0
Non-evaluable	3*	3.6	5	8.5	1	5.0
Total	84	100.0	59	100.0	20	100.0

*including 2 cases with non-evaluable margin due to improper tissue orientation.

Table 4. The number of tissue fragments and degree of thermal artefacts.

Degree of thermal artifacts	One fragment (120)	Multiple fragments (43)
Mild	62	22
Moderate	43	16
Severe	15	5

Table 5. Degree of thermal artefacts and margin status of ectocervical and endocervical margins in 146 cases.

	Endocervical margins (146)	%	Ectocervical margins (146)	%
Degree of thermal artefacts				
Mild	78	53.4	78	53.4
Moderate	54	37.0	54	37.0
Severe	14	9.6	14	9.6
Margin status				
Negative	87	59.6	106	72.6
Positive	56	38.4	30	20.6
Non-evaluable	3	2.0	10	6.8

piece, 6 (5.0%) had non-evaluable margins compared to 3 of 43 cases (7.0%) with two or more tissue fragments (p=0.7). When the number of fragments was related to the degree of thermal artefact (Table 4), no statistical significance was observed (p=1.0). Of 146 cases in which the surgical margins could be orientated as ectocervical or endocervical end, there was no difference in the severity of thermal artefact affecting both margins (Table 5). When each type of margin was separately considered, the endocervical margins were more frequently positive than the ectocervical ones (38.4% compared to 20.6%) but less frequently non-evaluable (2.0% compared to 6.8%). Differences in the results of the margin status between the ectocervical and endocervical margins were statistically significant (p=0.001).

Table 6. Relation between the margin status of LEEP specimens and the presence or absence of residual lesions in subsequent surgical specimens of 90 cases.

Margin status	Negative outcome (51)	Positive outcome (39)
Evaluable (85)		
Negative (21)	17	4
Positive (64)	33	31
Non-evaluable (5)	1	4

In the patients with the diagnosis of high-grade SIL or more severe lesions, 90 cases underwent further surgical procedures (82 had hysterectomy and 8 had conization) in our hospital within a 6-month-period. Comparison between the margin status of LEEP specimens and the presence of a residual lesion of at least low-grade SIL in the subsequent specimens is shown in Table 6. Only 4 of 21 cases (19.0%) with negative LEEP margins had a residual lesion in the cervix compared to 31 of 64 (48.4%) with positive margin (p=0.03). Four of 5 cases (80.0%) with non-evaluable margins had residual disease. Another 32 patients with a diagnosis of SIL in LEEP specimens and negative (29 cases) or non-evaluable (3 cases) margins were followed by cytology or colposcopy for 6 months, only two with negative margins had a positive outcome. The case with non-evaluable histologic diag-

nosis had negative follow-up smears. Follow-up data were not available either due to further treatment in other hospitals or loss to follow in 31 patients (19.0%) including one with non-evaluable margin. Five patients received radiation therapy due to invasive carcinoma. The remaining four patients had benign lesions in LEEP specimens and negative follow-up outcome.

Post-LEEP endocervical curettage (ECC) was done in only 14 cases which precluded evaluation of the efficacy of the procedure. Half of the cases with positive ECC (6 of 12 cases) had positive margin of the LEEP specimens.

Postoperative complications were identified in 26 patients, 17 of these had abnormal vaginal discharge(7) or spotty bleeding(10). Significant complications present in 9 cases (5.5%) included heavy bleeding(7), parametritis(1), and cervical stenosis(1).

DISCUSSION

LEEP has received increasing attention as a surgical management for cervical epithelial lesions. The procedure can be done for the diagnosis and treatment in a single visit at the outpatient colposcopy clinics[6]. Several advantages of LEEP compared to CKC include easier procedure technique, less operation time and hospital cost, less blood loss, exposure of the patients to only local anesthesia, and maintenance of squamocolumnar junction after the procedure in follow-up colposcopy[3,7]. The prevalence of complication of the procedure is at most comparable to CKC [6-8]. Some investigators even had a positive opinion that LEEP would be an alternative to replace CKC[3,5,9]. The major disadvantages of LEEP include the problems in pathologic evaluation and limited amount of tissue removed[4,8].

The prevalence of problems in pathologic evaluation of LEEP specimens varied remarkably from none or minimal[3,9-13] to a significant proportion (26-48%) of the cases[4,5,7]. Problems in histopathologic assessment involve both the histologic diagnosis and the evaluation of the surgical margins[1,2,4]. In our study, there was only one case whose histologic diagnosis was not possible and nine cases had non-evaluable surgical margins. In combination, the histopathologic evaluation was limited in only 10 of 163 cases (6.1%).

Difficulties in pathologic interpretation are mostly caused by thermal artefact and improper specimen orientation due to multiple fragments of specimens[1,5,8]. Although many studies of LEEP experience have been reported in the literature, details of thermal artefact and its interference with pathologic assessment are relatively limited[1,2,4, 5,8-11]. Thermal artefact usually occurs at the surgical margins where the tissue is most exposed to heat produced by the procedure. The frequency of cases with non-evaluable margins ranged from zero[3,9-11] to almost 50 per cent[4]. According to our results, significant thermal artefact that precluded pathologic evaluation affected a minority of cases, although some degree of thermal artefact was present in all. Inability to assess the margin seemed to be related with degree of thermal artefact. Only one of 84 cases (1.2%) with mild thermal artefact was truly non-evaluable compared to 6 of 79 (7.6%) with moderate to severe artefact. However, in cases with microinvasive carcinoma, thermal artefact may critically interfere with the histologic evaluation[1].

When multiple fragments of specimen were obtained without appropriate label, pathologists may not be able to identify the true surgical margin[1]. Improper tissue orientation occurred in a few cases in the early phase of this study but was resolved by increased awareness of the clinicians. The specimens were placed and labeled on a piece of paper before submission for pathologic examination. Significant relation of the number of fragments with the severity of thermal artefact and the presence of non-evaluable margins has been reported[5]. This association could not be confirmed in our study.

Another important disadvantage of LEEP is the limited amount of tissue removed, particularly of the endocervix, which makes it unsuitable for the conservative management or the diagnosis of certain lesions that predominantly involve the endocervix such as glandular neoplasms[14]. In our study, the high rate of positive surgical margin status of LEEP specimens (53.4%) was probably explained by the shallow excision of the cervical tissue, which may be associated with the skill of the performers. Preclinical training of the procedure on animal models was reported to improve the skill to achieve a satisfactory specimen[15].

Margin status is an important factor related to the persistence or recurrence of disease. In our study, the endocervical margins were more frequently positive than the ectocervical ones (38.3% compared to 20.5%). Kreb et al[8] reported a higher proportion of positive endocervical margin in specimens obtained by LEEP than in CKC specimens (32% compared to 17%). This finding correlates well with less cervical tissue removed by LEEP than by CKC[7,9]. The predictive value of residual lesions by margin status of LEEP specimens in our study was comparable to that of CKC specimens reported by Phelps et al[16]. Moore et al[17] reported the presence of residual lesions in hysterectomy specimens in more than 30 per cent of cases, even when the cone margin was negative. In our opinion, negative margin status does not guarantee the absence of a residual lesion in the cervix. It should be noted that the reports regarding correlation between the margin status and the presence of residual disease had different study criteria and designs and the results may be difficult to compare directly.

The high proportion of non-evaluable margins in some studies may raise the question regarding adequacy of LEEP specimens[4]. Although only 9 cases (5.5%) in our study had non-evaluable margins, four of five cases showed a residual lesion in the subsequent surgical specimens. This finding may correspond with our criteria for the diagnosis of "non-evaluable" margin when suspicious features were present.

In conclusion, we observed limitation of the histopathologic evaluation of specimens obtained by LEEP in a small proportion of cases (6.1%). Thermal artefact was not a critical disadvantage of the procedure. Problem in tissue orientation could be reduced by good cooperation from the clinicians. The positive or negative margin status of LEEP specimens had a potential to predict the presence of residual disease comparable to that of CKC specimens. Due to limited tissue excision, LEEP may not be an appropriate technique to remove the lesions with predominant endocervical involvement.

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REFERENCES

1. Messing MJ, Otken L, King LA, Gallup DG. Large loop excision of the transformation zone (LLETZ): A pathologic evaluation. Gynecol Oncol 1994; 52: 207-11.
2. Ioffe OB, Brooks SE, De Rezende RB, Silverberg SG. Arifact in cervical LLETZ specimens: Correlation with follow-up. Int J Gynecol Pathol 1999; 18: 115-21.
3. Turner MJ, Rasmussen MJ, Flannelly GM, Kelehan P, Lenehan PM, Murphy JF. Outpatient loop diathermy conization as an alternative to inpatient knife conization of the cervix. J Reprod Med 1992; 37: 314-6.
4. Montz FJ, Holschneider CH, Thompson LDR. Large-loop excision of the transformation zone: Effect on the pathologic interpretation of resection margins. Obstet Gynecol 1993; 81: 976-82.
5. Naumann RW, Bell MC, Alvarez RD, et al. LLETZ is an acceptable alternative to diagnostic cold-knife conization. Gynecol Oncol 1994; 55: 224-8.
6. Luesley DM, Culllimore J, Redman CW, et al. Loop diathermy excision of the cervical transformation zone in patients with abnormal cervical smears. BMJ 1990; 300: 1690-3.
7. Mathevet P, Dargent D, Roy M, Beau G. A randomized prospective study comparing three techniques of conization: cold knife, laser, and LEEP. Gynecol Oncol 1994; 54: 175-9.
8. Krebs HB, Pastore L, Helmkamp F. Loop electrosurgical excision procedures for cervical dysplasia: Experience in a community hospital. Am J Obstet Gynecol 1993; 169: 289-95.
9. Girardi F, Heydarfadai M, Koroschetz F, Pickel H, Winter R. Cold-knife conization *versus* loop excision: Histopathologic and clinical results of a randomized trial 1994; 55: 368-70.
10. Baggish MS, Barash F, Noel Y, Brooks M. Comparison of thermal injury zones in loop electrical and laser cervical excisional conization. Am J Obstet Gynecol 1992; 166: 545-8.
11. Wright TC Jr, Richart RM, Ferenczy A, Koulos J. Comparison of specimens removed by CO_2 laser conization and loop electrosurgical excision procedure. Obstet Gynecol 1992; 79: 147-53.
12. Ferris DG, Hainer BL, Pfenninger JL, Zuber TJ, DeWitt DE, Line RL. Electrosurgical loop excision of the cervical transformation zone: The experience of family physicians. J Fam Pract 1995; 41: 337-44.
13. Oyesanya OA, Amerasinghe CN, Manning EAD. Outpatient excisional management of cervical intraepithelial neoplasia: A prospective, randomized comparison between loop diathermy excision and laser excisional conization. Am J Obstet Gynecol 1993; 168: 485-8.
14. Kennedy AW, ElTabbakh GH, Biscotti CV, Wirth S. Invasive adenocarcinoma of the cervix following LLETZ (large loop excision of the transformation zone) for adenocarcinoma in situ. Gynecol Oncol 1995; 58: 274-7.
15. Ferris DG. Electrosurgical loop excision of the transformation zone: Preclinical training proficiency. Fam Med 1993; 25: 456-60.
16. Phelps JY III, Ward JA, Szigeti J, 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. Moore BC, Higgins RV, Laurent SL, Marroum M-C, Bellitt P. Predictive factors from cold knife conization for residual cervical intraepithelial neoplasia in subsequent hysterectomy. Am J Obstet Gynecol 1995; 173: 361-8.

ปัญหาการแปลผลทางพยาธิวิทยาในชิ้นเนื้อที่ได้จากการตัดปากมดลูกด้วยห่วงไฟฟ้าที่โรงพยาบาลมหาราชนครเชียงใหม่

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การตัดปากมดลูกด้วยห่วงไฟฟ้าเป็นวิธีการผ่าตัดเพื่อการวินิจฉัยและการรักษารอยโรคของปากมดลูกที่ได้รับความนิยมมากในปัจจุบัน อย่างไรก็ตามชิ้นเนื้อปากมดลูกที่ได้อาจยากต่อการแปลผลทางพยาธิวิทยาโดยเฉพาะการแปลผลบริเวณขอบชิ้นเนื้อ

ในการศึกษานี้ได้ทบทวนสไลด์จากชิ้นเนื้อปากมดลูกของผู้ป่วยที่ได้รับการตัดปากมดลูกด้วยห่วงไฟฟ้าที่โรงพยาบาลมหาราชนครเชียงใหม่ ตั้งแต่ 1 สิงหาคม 2538 ถึง 30 พฤศจิกายน 2540 เป็นจำนวน 163 ราย เพื่อประเมินระดับความรุนแรงของ thermal artefact และ ผลทางพยาธิวิทยาที่ขอบชิ้นเนื้อ และได้รวบรวมข้อมูลการตรวจทางพยาธิวิทยาเพิ่มเติมภายในระยะเวลา 6 เดือนเพื่อเปรียบเทียบกับผลทางพยาธิวิทยาของขอบชิ้นเนื้อ

ผลการศึกษาพบมี thermal artefact ในชิ้นเนื้อของผู้ป่วยทุกราย โดยมีความรุนแรงระดับน้อย 51.5% ระดับปานกลาง 36.2% และระดับมาก 12.3% มีผู้ป่วยหนึ่งรายที่ไม่สามารถให้การวินิจฉัยทางพยาธิวิทยาของรอยโรคได้เนื่องจาก thermal artefact และมีผู้ป่วย 9 ราย (5.5%) ที่ไม่สามารถแปลผลทางพยาธิวิทยาของขอบชิ้นเนื้อได้ เนื่องจาก thermal artefact (7 ราย) หรือ เนื่องจากไม่สามารถบอกตำแหน่งขอบชิ้นเนื้อที่แท้จริง (2 ราย)

เมื่อเปรียบเทียบผลทางพยาธิวิทยาของขอบชิ้นเนื้อที่ได้จากการตัดด้วยห่วงไฟฟ้ากับผลชิ้นเนื้อปากมดลูกที่ได้จากการผ่าตัดเพิ่มเติมในผู้ป่วยจำนวน 90 ราย พบรอยโรคเหลืออยู่ที่ปากมดลูกในกลุ่มที่ไม่พบรอยโรคที่ขอบชิ้นเนื้อจำนวน 4 ใน 21 ราย (19.0%) พบรอยโรคเหลืออยู่ 31 ใน 64 ราย (48.4%) ในกลุ่มที่ขอบชิ้นเนื้อมีรอยโรค และ พบรอยโรคเหลืออยู่ 4 ใน 5 ราย (80%) ในกรณีที่ไม่สามารถแปลผลขอบชิ้นเนื้อได้

ชิ้นเนื้อที่ได้จากการตัดปากมดลูกด้วยห่วงไฟฟ้าส่วนใหญ่ไม่มีปัญหาการแปลผลทางพยาธิวิทยา และไม่ใช่ข้อด้อยที่สำคัญของการตัดปากมดลูกด้วยห่วงไฟฟ้า ผลทางพยาธิวิทยาของขอบชิ้นเนื้อปากมดลูกที่ได้จากการตัดด้วยห่วงไฟฟ้ามีความสัมพันธ์กับโอกาสที่จะมีรอยโรคคงเหลืออยู่ที่ปากมดลูก

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