Treatment Failure Following Large Loop Excision of the Transformation Zone for the Treatment of Cervical Intraepithelial Neoplasia at Rajavithi Hospital

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Objective: *To evaluate the treatment failure rate of large loop excision of the transformation zone (LLETZ) in the treatment of cervical intraepithelial neoplasia (CIN) and the risk of persistence or recurrence depending on the clinicopathologic factors.*

Material and Method: *Retrospective case-record review of 250 women who had a final diagnosis of CIN and underwent LLETZ in Rajavithi Hospital from June 1st, 1998 to December 31st, 2003. Computerized files of these patients were then reviewed for clinicopathological follow-up results.*

Results: *Success rate of 86.8% was obtained. The incidence of treatment failure was 13.2%. The clinicopathologic factor associated with the persistence or recurrence was the presence of CIN at the margin of excision. Of 69 cases with incomplete excision (positive margin), treatment failure developed in 29.0%, compared to 5.2% in patients with complete excision (negative margins) ($p < 0.001$). Using multivariate analysis, incomplete excision and endocervical margin involvement of specimen were independent risk factors for the treatment failure of CIN.*

Conclusion: *LLETZ is an effective treatment for CIN. Treatment failure rate is low. Positive surgical margin is a predictor of persistence or recurrence after LLETZ. Incomplete excision and endocervical margin involvement of specimen are significant independent risk factors.*

Keywords: *LLETZ, Persistent disease, Recurrence, Treatment failure, Positive margin*

J Med Assoc Thai 2008; 91 (1): 31-6
Full text. e-Journal: *http://www.medassocthai.org/journal*

The large loop excision of the transformation zone (LLETZ) is an established modality in the diagnosis and treatment of cervical intraepithelial neoplasia (CIN). Reported success rates in the treatment of CIN with LLETZ are high, ranging from 73-98%[1-4] and are comparable with cold knife conization and other ablative procedures[2-4]. The procedure can be quickly and safely performed on an outpatient basis and is well tolerated by the patient with minimal discomfort. Compared to cold knife conization, morbidity is lowered by shorter operative time, elimination of general or regional anesthesia and reduced blood loss with the similar cure rate[5,6]. In addition, a pathologic specimen is available for histological review and confirmation[2,3].

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Many factors were reported to be associated with persistent disease or recurrence after LLETZ. Incomplete excision of dysplasia has been reported to increase the failure rate[4,7-9]. Some authors have found that margin status can be used to predict persistent disease but others have shown no association between margin status and residual dysplasia[4,8,9-12]. Other factors possibly associated with persistent or residual disease after LLETZ such as age > 40-50 years, post menopause, large lesion size, endocervical margin involvement, CIN II or more severe lesion and glandular involvement were also reported[8-12].

The purpose of the present study was to evaluate the treatment failure rate and the risk of treatment failure depending on various clinicopathologic factors after the LLETZ at Rajavithi Hospital over the 5-year period from June 1998 to December 2003.

Material and Method

Retrospective analysis of the data was carried out on medical records of the cytology, colposcopy and pathology records of women who were treated by the LLETZ in Rajavithi Hospital from June 1998 to December 2003. In Rajavithi Hospital, all women with cytologic abnormalities (ASC-US or worse) were counseled and underwent colposcopy, the findings were documented, and punch biopsies were taken from the worst affected areas via colposcopic guidance using 3% acetic acid (colposcopically directed biopsy, CDB). The indication for LLETZ, as either diagnostic or therapeutic procedure followed the standard protocol. Other options for CIN treatment in our institute are cold-knife conization, cryosurgery, excision by laser or needle electrode, laser ablation and hysterectomy.

The LLETZ was performed by staff or residents under supervision, powered by Surgitron F.F.P.F generator (Ellman international, New York, USA). Cases were eligible in the present study if they met the author's inclusion criteria. These criteria included the final histology confirmed CIN (women with histology showing HPV infection only were not included), satisfactory colposcopy, at least 12-month follow-up period. Women with treatment failure confirmed by histology of CIN before 12 months were included in the present study. In order to assess the efficacy of LLETZ as therapeutic purpose, the present study therefore included women who underwent LLETZ and followed up only. Some of the women who underwent LLETZ and later received immediate hysterectomy, cold knife conization or the second LLETZ within 8 weeks were excluded. Those small groups of women were selected for second procedure according to the clinical indication of the individual physicians such as uterine bleeding, completed childbearing, incomplete excision of LLETZ. Women diagnosed with adenocarcinoma in situ (AIS), microinvasive carcinoma (MIC) and invasive carcinoma were also excluded from the present study. The follow-up protocol consisted of a cervical cytology at 4-month post treatment. If the cytology was normal then women were seen for 2 further visits at 6-month intervals. After three negative cytology results, they had follow-up with repeated cytology every 12 months. If an abnormal cytology was found during follow-up, further colposcopy and treatment such as repeated LLETZ, cold knife conization were performed as indicated. In general, the presence of CIN on histology after treatment up to one year is likely to be persistent disease caused by inadequate treatment and this is most common. Recurrence of CIN is due to the development of a new lesion and usually become apparent after one year. In fact, there is no way, however, of distinguishing between persistent disease and true recurrence. The present study aimed to determine the failure rate from procedure and therefore, treatment failure was defined as a persistent or recurrent CIN, which was histologically confirmed during follow-up. Histology-proved human papillomavirus (HPV) infection only did not regarded as failure of treatment.

The data were analyzed using the statistical package for the social sciences (SPSS) version 11.5. Association between categorical variable were assessed using the X^2 test or the Fisher's exact test as appropriate in univariate analysis. Multivariate analysis was performed using logistic regression to determine independent risk factors for treatment failure. A p-value of less than 0.05 was used for statistical significance.

Results

During the study period, 250 patients were eligible for the present study. Age ranged from 16-75 years with a mean of 40 years (SD = 10.43). The median length of follow-up in the total study group was 18.5 months (range, 1-66) (Table 1). For those with treatment failure (37 patients) and those without evidence of disease (217 patients), the median duration of follow-up was 5 months (range, 1-38 months) and 19 months (range, 12-66 months), respectively. CIN I were diagnosed in 32 women (12.8%). CIN II and CIN III were diagnosed in 43 women (17.2%) and 175 women (70.0%), respectively.

During the follow-up period, there were 33 patients who had CDB and CIN were confirmed histologically, giving a treatment failure rate of 13.2%. Therefore, the success rate was 86.8%. Abnormal histology revealed CIN I in 13 women (5.2%), CIN II in 4 women (1.6%) and CIN III in 15 women (6.0%). One woman (0.4%) had AIS. Treatment failures were diagnosed during the first 12 months (persistence) in 24 cases (72.7%), 9 cases (27.3%) were diagnosed after that (recurrence). According to the onset of diagnosis of treatment failure, the rate of persistent disease was 9.6% while the rate of recurrence was 3.6%. The LLETZ specimens were considered as incomplete excision in 69 cases (27.6%). Among those with incomplete excisions (positive surgical margins), 33 women (47.8%) had ectocervical margins involved, 22 women (31.9%) had endocervical margins involved. Fourteen women (20.3%) had incomplete excisions but were unable to comment upon which margins were involved. In the total study group (250 women), there were 27 women

Table 1. Clinical characteristics of patients (n = 250)

Characterisitics	n (%)
Age (Mean ± SD)	40 ± 10.43 years
Range	16-75 years
Initial Pap smear	
ASC-US	9 (3.6)
AGC*	7 (2.8)
LSIL	59 (23.6)
HSIL	149 (59.6)
Invasive carcinoma	21 (8.4)
None	2 (0.8)
Unknown	3 (1.2)
Colposcopically directed biopsy	
Not done	45 (18.0)
Inadequate	8 (3.2)
Negative	17 (6.8)
Dysplastic change	2 (0.8)
LSIL	27 (10.8)
HSIL	151 (60.4)
Endocervical curettage	
Not done	232 (92.8)
Inadequate	7 (2.8)
Positive	6 (2.4)
Negative	5 (2.0)
Histology from LLETZ	
Negative	24 (9.6)
LSIL	36 (14.4)
HSIL	190 (76)
LLETZ margin	
Undetermined	27 (10.8)
Free margin	154 (61.6)
Not free margin	69 (27.6)
Length of follow-up (Median, Range)	18.5, 1-66 months

* Atypical glandular cell

(10.8%) which margins could not be assessed. Therefore, those women were excluded from analysis of recurrent CIN according to the margin status. Among the remainder (223 women), 20 of 69 (29.0%) with incomplete excisions had treatment failure after LLETZ compared with 8 of 154 (5.2%) with complete excisions. Univariate analysis showed that the incomplete excision was statistically associated with an increased rate of persistent disease ($p < 0.001$). No other factors had significant association with the rate of treatment failure (Table 2). Using multivariate analysis, the factor of histology of LLETZ had too low prevalence in the group of HPV/CIN I (2 of 36 women) and therefore was excluded from the calculation. Logistic regression was performed with the remaining four factors (age, incomplete excision, endocervical margin involvement, histology at positive margin) entering them into the equation. The analysis revealed that the factors of incomplete excision and endocervical margin involvement of specimen were independent risk factors for the treatment failure of CIN (Table 3).

Discussion

At the present time, LLETZ is the approved treatment for the management of CIN in Thailand. It is a cheap, effective, rapid and safe technique which provides a cost effective alternative to other treatment modalities[3,13]. Many studies have reported the high success rate of LLETZ, ranging from 73-98%[1-4,13]. The present study confirms those previous reports; a success rate of 86.8% was obtained. The incidence of treatment failure was 13.2%. In multiple studies, rates of recurrence or persistence of CIN ranged from 2% to 27.5%[2,3,12,13]. The presented data resembled other studies. The success rate compares well with similar follow-up studies of other treatments[4]. A comparison between LLETZ and cold knife conization found that LLETZ was quicker and caused less blood loss and complication than conization[5,14]. When LLETZ was compared with laser vaporization, the women in the LLETZ group experienced less post operative hemorrhage and less discomfort. Operative time was greatly reduced, and histological diagnosis was available[15]. Cochrane meta-analysis has concluded that there is no obviously superior surgical technique for the management of CIN. LLETZ appeared to provide the most reliable specimens for histology[16].

Regarding the margin analysis, positive surgical margins were identified in 69 cases (27.6%). The presented data resembled the previous studies which ranged from 20% to 40%[7,8,10,11,17-19]. However, margins of LLETZ specimens are often difficult to interpret[7,8]. There were 27 (10.8% of the total 250 women) excluded from margin analysis because of the inability to assess margins, which was comparable to the other reports[4,18]. Risk of persistent or recurrent disease has been traditionally considered to be related to whether the margin of the specimen is clear of the disease. There have been studies which have assessed the significance of positive margins in LLETZ[7,10-12,18-20]. Certainly, not all studies demonstrated this association. Murdoch et al[7] and Sankasem et al[20] concluded that incomplete excision of CIN by LLETZ did not equate with residual disease. Keen et al[18] found the relationship between the positive margin and higher rate of recurrence. Flannelly et al[11] found that the highest independent risk group for recurrence was women aged ≥ 50 years

Table 2. The rate of treatment failure following LLETZ according to risk factors. Values are given as n (%)

Factors	Treatment failure n %	p-value*
Age (n = 250)		
< 50 (n = 210)	28 (13.3)	0.887
≥ 50 (n = 40)	5 (12.5)	
Incomplete excision (n = 223)		
No (n = 154)	8 (5.2)	<0.001
Yes (n = 69)	20 (29.0)	
Endocervical margin involvement (n = 55)		
No (n = 33)	7 (21.2)	0.057
Yes (n = 22)	10 (45.5)	
Histology of LLETZ (n = 226)**		
LSIL (HPV/CIN I) (n = 36)	2 (5.6)	0.106
HSIL (CIN II/CIN III) (n = 190)	30 (15.8)	
Histology at positive margin (n = 55)***		
LSIL (HPV/CIN I) (n = 9)	2 (22.2)	0.537
HSIL (CIN II/CIN III) (n = 46)	15 (32.6)	

* x^2 test
** Sixteen patients had negative histology of LLETZ
*** Fourteen patients had unclassified positive margins

Table 3. Logistic regression analysis to determine the independent risk factors for the treatment failure of CIN*

Factors	Odds ratio	95% CI (low-high)	p-value
Age ≥ 50 yrs	1.58	0.29-8.67	0.596
Incomplete excision	7.44	3.08-17.98	<0.005
Endocervical margin involvement	3.43	1.01-11.63	0.048
Histology at positive margin	0.92	0.14-6.02	0.932

* Included persistence or recurrence of CIN

with CIN at the margin. Felix et al[10] stated that the status of the internal margin predicted residual disease. With positive endocervical margin, the cure rate was approximately 70%[17]. In the present study, of 69 cases with positive margin, after ongoing follow up, residual disease developed in 29.0%, compared to 5.2% in patients with negative margins (Table 2). This difference reached statistical significance. In the present study, univariate analysis revealed that only one risk factor of treatment failure was the presence of CIN at the margin of excision. The other clinicopathologic factors such as age, involved endocervical margin, histology of LLETZ specimen were not associated with an increased treatment failure rate (Table 2). Those risk factors have been identified in the previous reports only inconsistently. Some studies reported the factors of high-grade dysplasia involving margins and histology of LLETZ as risk factors for recurrence of CIN[9-12]. In multivariate analysis, the factors of endocervical margin involvement of specimen and incomplete excision were independent risk factors for the treatment failures. However, other multivariate analysis studies failed to confirm these findings[8,19]. The majority of women with involved margins remain disease-free during follow-up[7,8,19,20]. Also, the histological report of complete excision of CIN should not imply definite cure of CIN[7]. In the present study, 5.2% of women with negative LLETZ margin had treatment failure at follow-up. The duration of follow-up is another factor that might affect the rate of treatment failure in each study

because there are variations among studies regarding definitions of cure, length of follow-up. Some studies showed low treatment failure rate at short-term follow up[13,15]. An other study revealed that the longer the follow-up time, a greater percentage of patients whose LLETZ showed incomplete excision, suffered recurrences. In addition, the more patients with positive margins had recurrence than did those whose margins were negative[18]. Therefore most studies have recommended that women with positive LLETZ margins should be counseled regarding the risks of observation versus repeat excision and the decision should be individualized[11,19].

In conclusion, LLETZ is an effective modality of treatment for CIN. The treatment failure rate in the present study is similar to previous studies. Incomplete excision and endocervical margin involvement of specimen are independent risk factors. Women with those risk factors have a higher treatment failure rate and the management should be individualized.

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ความล้มเหลวหลังการรักษา cervical intraepithelial neoplasia (CIN) โดยวิธีการผ่าตัดปากมดลูกด้วยห่วงไฟฟ้าในโรงพยาบาลราชวิถี

สธน บุญลิขิต, พจนีย์ จูงหัตถการสาธิต, สุวรรณา อัศวพิริยานนท์

วัตถุประสงค์*: เพื่อศึกษาอัตราความล้มเหลวหลังการรักษา CIN โดยวิธีการผ่าตัดปากมดลูกด้วยห่วงไฟฟ้า (LLETZ) และหาความสัมพันธ์ระหว่างอัตราการรักษาล้มเหลวกับปัจจัยเสี่ยง*

วัสดุและวิธีการ*: คณะผู้นิพนธ์ได้ศึกษาสตรีที่ได้รับการวินิจฉัยขั้นสุดท้ายว่าเป็น CIN ได้รับการรักษาโดย LLETZ ที่โรงพยาบาลราชวิถีตั้งแต่วันที่ 1 มิถุนายน พ.ศ. 2541 ถึงวันที่ 31 ธันวาคม พ.ศ. 2546 และสามารถติดตามการรักษาต่อเนื่องอย่างน้อย 12 เดือนหลังการรักษา โดยเก็บรวบรวมข้อมูลจากแฟ้มผู้ป่วยคลินิกคอลโปสโคปีและเวชระเบียน นำข้อมูลที่ได้มาศึกษาอัตราความล้มเหลวหลังการรักษา CIN โดยวิธี LLETZ และหาปัจจัยเสี่ยงที่มีผลต่อการคงอยู่หรือ การกลับเป็นซ้ำของโรค*

ผลการศึกษา*: มีสตรีที่เข้าเกณฑ์ในการศึกษาจำนวน 250 ราย อัตราการรักษาหาย ร้อยละ 86.8 อัตราการรักษาล้มเหลว ร้อยละ 13.2 สตรีจำนวน 69 รายได้รับการประเมินว่าตัดรอยโรคออกไม่หมดเนื่องจากตรวจพบ CIN ที่ขอบชิ้นเนื้อ ในสตรีกลุ่มนี้เมื่อได้รับการติดตามการรักษาพบว่ามีอัตราการรักษาล้มเหลว ร้อยละ 29 เมื่อเปรียบเทียบกับกลุ่มสตรีที่ได้รับการตัดรอยโรคออกได้หมด พบอัตราการรักษาล้มเหลวเพียง ร้อยละ 5.2 ($p < 0.001$) เมื่อวิเคราะห์ตัวแปรแบบ multivariate การตัดรอยโรคออกไม่หมด และการตรวจพยาธิวิทยาพบ CIN ที่ขอบชิ้นเนื้อที่ตำแหน่ง endocervix เป็นปัจจัยเสี่ยงที่มีนัยสำคัญทางสถิติต่ออัตราการรักษาล้มเหลว*

สรุป*: การผ่าตัดปากมดลูกด้วยห่วงไฟฟ้าในการรักษา CIN มีอัตราความล้มเหลวต่ำ การตัดรอยโรคออกได้ไม่หมด ซึ่งประเมินจากการตรวจทางพยาธิวิทยาพบ CIN ที่ขอบชิ้นเนื้อ และการตรวจพบ CIN ที่ขอบชิ้นเนื้อในตำแหน่ง endocervix เป็นปัจจัยเสี่ยงที่มีนัยสำคัญทางสถิติต่ออัตราการรักษาล้มเหลว*