

RESEARCH ARTICLE

Long-term Outcomes of a Loop Electrosurgical Excision Procedure for Cervical Intraepithelial Neoplasia in a High Incidence Country

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Abstract

Aim: To evaluate the operative, oncologic and obstetric outcomes of the loop electrosurgical excision procedure (LEEP) in cases with cervical neoplasia. **Materials and Methods:** A retrospective cohort study was conducted on patients who were suspected of cervical neoplasia and therefore undergoing LEEP at Siriraj Hospital, Mahidol University, Thailand, during 1995-2000. Outcome measures included operative complications in 407 LEEP patients and long-term outcomes in the 248 patients with cervical intraepithelial neoplasia (CIN) who were treated with only LEEP. **Results:** There were 407 patients undergoing LEEP; their mean age was 39.7±10.5 years. The histopathology of LEEP specimens revealed that 89 patients (21.9%) had lesions ≤CIN I, 295 patients (72.5%) had CIN II or III, and 23 patients (5.6%) had invasive lesions. Operative complications were found in 15 patients and included bleeding (n=9), and infection (n=7). After diagnostic LEEP, 133 patients underwent hysterectomy as the definite treatment for cervical neoplasia. Of 248 CIN patients who had LEEP only, seven (2.8%) had suffered recurrence after a median of 16 (range 6-93) months; one had CIN I, one had CIN II, and five had CIN III. All of these recurrent patients achieved remission on surgical treatment with re-LEEP (n=6) or simple hysterectomy (n=1). A significant factor affecting recurrent disease was the LEEP margin involved with the lesion (p=0.05). Kaplan-Meier analysis showed 5-year and 10-year disease-free survival (DFS) estimates of 99.9%. Twelve patients became pregnant a total of 14 times, resulting in 12 term deliveries and two miscarriages - one of which was due to an incompetent cervix. **Conclusions:** LEEP for patients with cervical neoplasia delivers favorable surgical, oncologic and obstetric outcomes.

Keywords: Cervical neoplasia - loop electrosurgical excision procedure - outcomes - Thailand

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Introduction

Cervical conization is the standard procedure performed to obtain cervical specimens for the histologic diagnosis of cervical intraepithelial neoplasia (CIN) or microinvasive cervical cancer. Furthermore, it was considered to be a therapeutic procedure for CIN. Originally, cold knife conization (CKC) was the standard procedure; laser conization was used subsequently. In 1981, Cartier et al reported a method called "loop diathermy" to obtain cervical biopsies and treat premalignant lesions (Prendiville et al., 1989). Later, Prendiville et al. (1989) introduced a large and thin wire loop called "large loop excision of the T-zone (LLETZ)" which presented low complications and high success rates (Prendiville et al., 1989). Wright et al. (1992) later suggested the use of the loop electrosurgical excision procedure (LEEP), and this became accepted worldwide (Wright et al., 1992). LEEP gained popularity over conventional CKC or laser

conization because it is easier to perform, there is no need for complicated anesthetic methods as in cold knife conization, and it costs much less than conventional conization. Currently, LEEP has been proven to be feasible and safe for both diagnostic and therapeutic purposes, accompanied by with the ability to provide high quality specimens (Wright., 1992; 2007a; 2007b). However, there are still only few data reports of long-term outcomes.

LEEP was introduced to clinical practice in our institute in 1993. The purposes of the present study were to investigate complications and outcomes of LEEP, particularly the long-term oncologic outcomes.

Materials and Methods

A retrospective cohort study was conducted in the Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand, a tertiary care medical school. After approval from the Siriraj Institutional Review Board (SIRB),

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the medical records of patients who underwent LEEP from 1st January 1995 to the 31st December 2000 were reviewed. The present study collected data on the baseline characteristics of the patients, surgical outcomes, pathologic reports, and follow-up data until 31st December 2011.

In our institute, the cervical cytology was collected by residents, fellows or faculty staff. After the cytology showed abnormalities, patients were counseled to undergo colposcopy and LEEP according to ASCCP guidelines (Wright et al., 2007a; 2007b). In brief, the patients who had abnormal cytology results would undergo further diagnostic measures, either follow-up cytology, colposcopy with or without biopsy, or LEEP, as appropriate. The colposcopy with or without biopsy was the standard procedure used to make the diagnosis of cervical neoplasia. In cases of high-grade abnormal cervical cytology and had no invasive cervical cancer according to the colposcopic features, a LEEP might be provided in the same setting - the so-called "see-and-treat approach". Moreover, in the patients whose colposcopic-directed biopsy specimens revealed glandular involvement, the diagnostic LEEP incorporating a "top hat excision" would be performed.

Colposcopy with or without biopsy and LEEP were performed by faculty staff or fellows/residents under supervision. Electrical generator and loop electrodes were selected appropriately according to the size of the cervical lesion and the preference of physicians. Intraoperative bleeding was controlled by a ball electrode in the coagulation or cut-coagulation mode. In the case of massive bleeding, the operators individually considered suturing or vaginal packing. If the patients had a high-grade lesion (CIN II or III) at the conization margins, clinicians considered re-LEEP first. Hysterectomy was considered in cases in which re-LEEP had technical limitations or the patients had concurrent diseases, such as symptomatic myoma uteri.

Complications such as bleeding or infection were recorded at the time of LEEP and during the follow-up period. The complication of bleeding was defined as one that needed suturing or transfusion or admission. Infection was diagnosed by attending physicians who provided antibiotic treatment. Cervical stenosis was diagnosed when the attending physician could not pass a 3-mm dilator through the cervical canal.

The pathologic diagnoses were made from the most severe of lesions. Our management algorithm for CIN was developed from the ASCCP guidelines (Wright et al., 2007). When the cases of cervical carcinoma were diagnosed, patients were counseled for clinical staging and treatment according to the recommendations of the International Federation of Gynecologic Oncology (FIGO) (Pecorelli et al., 2009). In cases of CIN, the patients were scheduled for follow-up. The follow-up protocol during the first two years, included physical and pelvic examination±cytology±colposcopy every 6 months. CIN patients were examined every year after the third year. If the patients had abnormal physical or cytologic findings, an aggressive work up was recommended. The recurrence of diseases was defined by histologic results as ≥ CIN I,

after a primary treatment period of >6 months. If the new episode of neoplasia occurred within a 6-month period after the first treatment, we considered it as a persistent lesion.

The accumulated data were analyzed with SPSS version 14.0 (IBM, New York, USA). The operative complications during the early postoperative period were evaluated from data of all patients undergoing LEEP. The delayed complications and other long-term outcomes were derived from data of the patients with CIN who were primarily treated with LEEP and had follow-up data. The data were presented as the mean±standard deviation (SD), median, range, number (n) and percentage (%), or odds ratio (OR) and a 95% confidence interval (CI), as appropriate. Factors affecting recurrent diseases were analyzed using a Chi-squared or Fisher's exact test and multiple logistic regression analysis. The Kaplan-Meier method was used for survival analysis to estimate 5-year and 10-year disease-free survival (DFS) rates and the mean time of DFS. All analyses were 2-sided and a p value of <0.05 was considered to be statistically significant.

Results

From 1995 to 2000, 407 patients suspected of having cervical neoplasia underwent LEEP. The baseline characteristics and pathology of 407 LEEP patients are presented in the Table 1. The mean age was 39.7±10.5 years old (range 15-81; median 38 years old). 53 patients were nulliparous and 248 patients (60.9%) had >one parity with a maximum parity of 9. The cytologic results before LEEP were 0.2% atypical squamous cell (ASC), 8.9% low-grade squamous intraepithelial neoplasia (LSIL), 69.5% high-grade squamous intraepithelial neoplasia (HSIL), 16.5% squamous cell carcinoma (SCCA), 0.7% adenocarcinoma, respectively. A total of 17 patients (4.2%) had clinical evidence of suspected cervical lesions such as chronic inflammation, post coital bleeding, or a bizarre appearance. LEEP was performed under the see-and-treat approach in 221 patients (54.3%).

Overtreatment by LEEP was found for 89 women (21.9%) which means the specimens did not contain

Table 1. Characteristics of 407 Patients Who Underwent LEEP at Siriraj Hospital During 1995 to 2000

| Characteristics | Mean±SD/n (%) |
|--------------------------------------|---------------|
| Age (years) (range 15-81; median 38) | 39.7±10.5 |
| Parity | |
| Multiparous | 354 (87.6) |
| ASC | 1 (0.2) |
| Cytologic results | |
| LSIL | 36 (8.9) |
| HSIL | 283 (69.5) |
| SCCA | 67 (16.5) |
| Adenocarcinoma | 3 (0.7) |
| Others | 17 (4.2) |
| Histopathologic results | |
| No cervical neoplasia | 26 (6.4) |
| CIN I | 63 (15.5) |
| CIN II | 31 (7.6) |
| CIN III | 264 (64.9) |
| SCCA | 22 (5.4) |
| Adenocarcinoma | 1 (0.2) |

*Abbreviation; ASC, atypical squamous cell; CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure; LSIL, low-grade squamous intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial neoplasia; SCCA, squamous cell carcinoma

cervical cancer or high-grade intraepithelial lesions. The most common pathologic reports were CIN III (264 patients, 64.9%), of which 161 had glandular involvement. The present study found cervical cancer from LEEP specimens in 23 patients, of which 22 were SCCA. A total of 260 patients (63.9%) had free margins of LEEP specimens. The diseases involved the endocervical margin, ectocervical margin, and both margins were found in 22.1%, 5.4% and 8.6%, respectively. The rate of disease involved at the LEEP margins of CIN III disease when compared with CIN I- II diseases was 42.8% vs 14.9%, p value < 0.001.

During the first instance of LEEP in each woman, nine patients (2.2%) had bleeding complication; four patients received blood transfusions, four patients underwent suturing, and four patients underwent vaginal packing. Seven patients (1.7%) had surgical site infections, of whom one patient had bleeding complications before acquiring a local infection.

After the first LEEP, 133 patients underwent hysterectomy for the treatment of cervical neoplastic diseases, which were divided into 115 simple hysterectomy, six modified radical hysterectomy, and 12 radical hysterectomy. Overall, 407 patients achieved an initial complete response. The median length of the follow-up period was 36 months with a range of 1-197 months. Late complications in 248 women after LEEP did not require hysterectomy; one patient was diagnosed with cervical stenosis and one patient had cervical incompetence. Twelve patients became pregnant a total of 14 times, resulting in 12 term pregnancies and two abortions, of which one abortion was occurred at 24 weeks of gestation due to cervical incompetence. At the time of first LEEP, all women who pregnant were 27-32 years old.

LEEP was considered to be the primary therapy for the remaining 248 patients who had cervical neoplasia and who had not received hysterectomies, therefore they were eligible for the analysis of long-term oncologic outcomes. Seven patients (2.8%) had disease recurrence as shown in Table 2; the median time to recurrence was 16 months, with a range of 6-93 months. One patient had CIN I, one patient had CIN II, five patients had CIN III. Six patients who had recurrent CIN were treated by re-LEEP, while a patient who had CIN III was treated by simple hysterectomy. All of recurrent patients had complete response. The

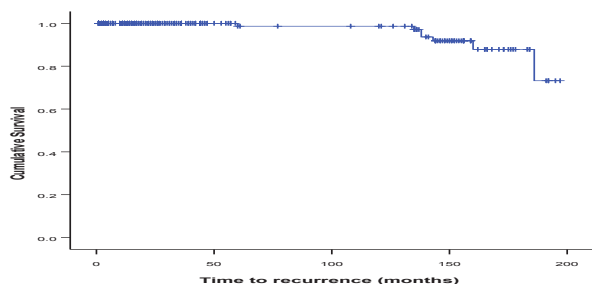


Figure 1. Kaplan-Meier Curve of 248 Patients with Cervical Intraepithelial Neoplasia (CIN) Treated with Only Loop Electrosurgical Excision Procedure (LEEP) at the Faculty of Medicine Siriraj Hospital, Mahidol University During 1995 to 2000 and Follow-up Until 2011

Table 2. Characteristics of 7 Recurrent Patients from 248 CIN Patients with Primarily Treated with LEEP

| No. | Age (yrs) | LEEP pathology | Margin status | DFI (mo) | Recurrent pathology | Treatment of recurrences |
|-----|-----------|----------------|---------------|----------|---------------------|--------------------------|
| 1 | 55 | CIN III | Free | 90 | CIN III | Re-LEEP |
| 2 | 44 | CIN III | Endo. | 16 | CIN III | Re-LEEP |
| 3 | 35 | CIN III | Free | 90 | CIN II | Re-LEEP |
| 4 | 33 | CIN II | Free | 6 | CIN III | Re-LEEP |
| 5 | 31 | CIN III | Free | 93 | CIN III | Re-LEEP |
| 6 | 30 | CIN III | Endo. | 16 | CIN I | Re-LEEP |
| 7 | 26 | CIN III | Ecto. | 9 | CIN III | TAH |

*Abbreviation: CIN, cervical intraepithelial neoplasia; DFI, disease free interval; Ecto., lesions present at ectocervical margin; Endo., lesions present at endocervical margin; LEEP, loop electrosurgical excision procedure; TAH, total abdominal hysterectomy

Table 3. Factors Affecting Recurrence Diseases in 248 Patients with CIN Primarily Treated with LEEP

| Factors | N | Recurrent rate (%) | p value |
|--------------------------------|--------------------|--------------------|---------|
| Age (years) | ≤35 | 5 (4.0) | 0.25 |
| | >35 | 2 (1.6) | |
| Parity | Nulliparity | 0 (0) | 0.59 |
| | Multiparity | 7 (3.3) | |
| Cervical cytology | <HSIL | 0 (0) | 0.59 |
| | ≥HSIL | 7 (3.3) | |
| Cervical pathology | CIN I | 0 (0) | 0.35 |
| | CIN II-III | 7 (3.6) | |
| Margin status | Free | 4 (1.9) | 0.05 |
| | Presence of lesion | 3 (8.8) | |
| CIN with glandular involvement | No | 6 (3.7) | 0.25 |
| | Yes | 1 (1.2) | |

*Data are n (%) and analyzed using Chi-square test or Fisher's exact test; **Abbreviation: CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure

correlation among the characteristics of 248 patients' who underwent only a LEEP electrosurgical excision procedure and recurrence are shown in Table 3. Factors included in the multiple logistic regression analysis were age (≤35 vs >35 years), parity (0 vs ≥1), cervical cytology (<HSIL vs ≥HSIL), cervical histopathology (CIN I vs CIN II- III), margin status (free of diseases vs diseases present), and glandular involvement (no vs yes). The only factor with a marginally significant effect on recurrent diseases was the LEEP margin involved with the lesion ($p=0.05$).

The DFS function of 248 patients who underwent only LEEP is shown in Figure 1. The mean DFS time was 188.1±3.3 months (95% confidence interval (CI) of 181.6-194.6). The estimated 5-year and 10-year DFS rates were 99.9%.

Discussion

LEEP was incepted for the management of cervical neoplasia due to various advantages over traditional CKC or laser conization. Various techniques and instruments were developed to accomplish feasibility and safety to accompany the high quality of specimens (Prendiville et al., 1989; Alvarez et al., 1994; Dey et al., 2002). We reported outcomes of LEEP for CIN in a tertiary care university hospital. The present study focused on operative complications and long-term outcomes. Because CIN usually affects women of reproductive

age - like our patients, the management of this disease is challenging; an extensive procedure to eradicate the lesions increases operative complications and adversely affects reproductive function, but inadequate treatment puts the patients at risk of recurrence and of subsequently developing cervical cancer.

The important operative complications in our study were major bleeding, infection and an incompetent cervix; our complication rate was favorably low. Regarding the safety of conization procedures, the guidelines of the National Health Service Cervical Screening Programme (NHSCSP) stated that major bleeding complication and suturing should not be more than 5% and the admission rate for the treatment of complications should not be more than 2% (Luesley et al., 2004). Thus, the rate of complications from the present study met the requirements of NHSCSP guidelines.

The low operative complication rate was probably associated with inadequate operation. The LEEP margin status was used as a surrogate marker for operative adequacy. The adequacy of LEEP in the present study was not inferior to those of previous studies. We found that 64.5% of the patients with CIN were margin-free; such a frequency was in range with those of previous studies: 40-80% (Mathevet et al., 1994; Giacalone et al., 1999; Shin et al., 2009). We also found that the risk of the margin involved with the lesion was higher in CIN III than in CIN I-II; our finding was comparable with a previous report (Shin et al., 2009). Although our population had a high proportion of CIN III, the margin-free rate was not compromised.

The rate of second trimester loss in the present study was similar to that of a large retrospective case-control study in 742 women who underwent LEEP or laser conization from a multicenter study in Norway (Sjoberg et al., 2007). Sjoberg et al. (2007) reported a rate of second trimester miscarriage of 1%. Furthermore they found that the rate of preterm birth in studied women was 15.8% which was significantly higher than in the control group (4.6%), along with an odds ratio (OR) of 3.4 (95% CI of 2.3-5.1) (Sjoberg et al., 2007). When comparing the rate of preterm birth in the same women before and after LEEP conization, previous studies found there was a 2-fold increase in the preterm birth rate (Bevis et al., 2011). In contrast, other studies claimed that the rate of preterm birth was similar between women who underwent LEEP and those who did not (Sadler et al., 2004; Acharya et al., 2005). These inconsistencies might be due to the multifactorial causes of preterm birth such as infectious diseases, maternal chronic disease and cervical length. However, the number of pregnancies in the present study (n=14) was too small to draw a conclusion.

The recurrent rate of CIN treated with LEEP in the present study was 2.8%; this rate was substantially lower when compared with the rates of 5-24% in previous reports (Alvarez et al., 1994; Ayhan et al., 2009; Lodi et al., 2011). The glandular involvement and positive margins in the LEEP specimen were potential factors for disease recurrence (Kietpeerakool et al., 2007; Lodi et al., 2011; Kir et al., 2012). Nevertheless, the present study found that only positive margin status had a marginally

significant correlation with the recurrence ($p=0.05$). Such a discrepancy could be explained via a few reasons. First, the selection bias owing to high hysterectomy rate (30%) in our CIN population might confound the result by excluding some factors from the long-term study population. Second, the conization specimens in the present study were larger than those in the previous study, which brought all diseases to the forefront in our patients. Third, the present study used electrical cauterization to control bleeding during LEEP, destroying the residual lesions via avascular necrosis.

Interestingly, when compared with studies that had a long-term follow-up period, the present study showed a favorable PFS outcome with its long-term follow-up period. Mathevet et al studied 86 CIN patients who underwent conization using CKC, laser or LEEP techniques and who were followed-up for more than 3 years. They found a recurrent rate of 5/86 patients (5.8%) (Mathevet et al., 2003). Another study in 4,417 women with CIN III who had CKC with clear margins and were followed-up for 5-30 years, found that the rate of new CIN II-III or vulvar intraepithelial neoplasia (VAIN) III diseases was 0.63% (Reich et al., 2001). The rate of recurrent diseases depends on the definition of recurrence, either abnormal cytology or histologic abnormality of at least CIN I or CIN II.

The limitation of the present study was the retrospective design without a comparative group. The strength of our study was the completeness of important data recorded in a structured follow-up form, and the low lost-to-follow-up rate. Future studies should be conducted as in prospective or randomized controlled trials designed to assess complications, oncologic outcomes, the quality of life of patients, as well as cost analysis.

In conclusion, our institute, the early operative complications of LEEP (bleeding and infection), the delayed complications (cervical stenosis and incompetent cervix), and the recurrent rate of CIN after LEEP were lower than those of previous reports. The 5-year and 10-year DFS estimates were excellent (99.9%). The only significant factor affecting recurrent diseases was the LEEP margin involved with lesions ($p=0.05$).

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References

- Acharya G, Kjeldberg I, Hansen SM, et al (2005). Pregnancy outcome after loop electrosurgical excision procedure for the management of cervical intraepithelial neoplasia. *Arch Gynecol Obstet*, **272**, 109-12.
- Alvarez RD, Helm CW, Edwards RP, et al (1994). Prospective randomized trial of LLETZ versus laser ablation in patients with cervical intraepithelial neoplasia. *Gynecol Oncol*, **52**, 175-9.
- Ayhan A, Boynukalin FK, Guven S, et al (2009). Repeat LEEP

- conization in patients with cervical intraepithelial neoplasia grade 3 and positive ectocervical margins. *Int J Gynaecol Obstet*, **105**, 14-7.
- Bevis KS, Biggio JR (2011). Cervical conization and the risk of preterm delivery. *Am J Obstet Gynecol*, **205**, 19-27.
- Dey P, Gibbs A, Arnold DF, et al (2002). Loop diathermy excision compared with cervical laservaporisation for the treatment of intraepithelial neoplasia: a randomised controlled trial. *BJOG*, **109**, 381-5.
- Giacalone PL, Laffargue F, Aligier N, et al (1999). Randomized study comparing two techniques of conization: cold knife versus loop excision. *Gynecol Oncol*, **75**, 356-60.
- Kietpeerakool C, Khunamornpong S, Srisomboon J, et al (2007). Cervical intraepithelial neoplasia II-III with endocervical cone margin involvement after cervical loop conization: is there any predictor for residual disease? *J Obstet Gynaecol Res*, **33**, 660-4.
- Kir G, Karabulut MH, Topal CS, et al (2012). Endocervical glandular involvement, positive endocervical surgical margin and multicentricity are more often associated with high-grade than low-grade squamous intraepithelial lesion. *J Obstet Gynaecol Res*, **38**, 1206-10.
- Lodi CT, Michelin MA, Lima MI, et al (2011). Factors associated with recurrence of cervical intraepithelial neoplasia after conization in HIV-infected and noninfected women. *Arch Gynecol Obstet*, **284**, 191-7.
- Luesley D, Leeson S (2004). Guidelines for the NHS Cervical Screening Programme. 1st ed. Sheffield, UK: NHSCSP2004.
- Mathevet P, Chemali E, Roy M, et al (2003). Long-term outcome of a randomized study comparing three techniques of conization: cold knife, laser, and LEEP. *Eur J Obstet Gynecol Reprod Biol*, **106**, 214-8.
- Mathevet P, Dargent D, Roy M, et al (1994). A randomized prospective study comparing three techniques of conization: cold knife, laser, and LEEP. *Gynecol Oncol*, **54**, 175-9.
- Pecorelli S (2009). Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet*, **105**, 103-4.
- Prendiville W, Cullimore J, Norman S (1989). Large loop excision of the transformation zone (LLETZ). A new method of management for women with cervical intraepithelial neoplasia. *Br J Obstet Gynaecol*, **96**, 1054-60.
- Sadler L, Saftlas A, Wang W, et al (2004). Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. *JAMA*, **291**, 2100-6.
- Shin JW, Rho HS, Park CY (2009). Factors influencing the choice between cold knife conization and loop electrosurgical excisional procedure for the treatment of cervical intraepithelial neoplasia. *J Obstet Gynaecol Res*, **35**, 126-30.
- Sjoberg KD, Vistad I, Myhr SS, et al (2007). Pregnancy outcome after cervical cone excision: a case-control study. *Acta Obstet Gynecol Scand*, **86**, 423-8.
- Reich O, Pickel H, Lahousen M, et al (2001). Cervical intraepithelial neoplasia III: long-term outcome after cold-knife conization with clear margins. *Obstet Gynecol*, **97**, 428-30.
- Wright TC Jr, Richart RM, Ferenczy A, et al (1992). Comparison of specimens removed by CO2 laser conization and the loop electrosurgical excision procedure. *Obstet Gynecol*, **79**, 147-53.
- Wright TC Jr, Massad LS, Dunton CJ, et al (2007). 2006 consensus guidelines for the management of women with abnormal cervical screening tests. *J Low Genit Tract Dis*, **11**, 201-22.
- Wright TC Jr, Massad LS, Dunton CJ, et al (2007). 2006 consensus guidelines for the management of women with