Predictive Factors for Residual Disease in the Uterine Cervix after Large Loop Excision of the Transformation Zone in Patients with Cervical Intraepithelial Neoplasia III

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Objective: To determine predictive factors for residual disease in uterine cervix after large loop excision of the transformation zone (LLETZ) in patients with cervical intraepithelial neoplasia III (CIN III).

Material and Method: Medical records of patients who underwent LLETZ with CIN III between September 1, 1992 and December 31, 2001 in Ramathibodi Hospital were reviewed. Demographic data, colposcopic findings, and pathologic parameters were analyzed to identify the predictive factors for residual disease in uterine cervix.

Results: The total of 541 cases were enrolled in this study. Managements after LLETZ are 1) repeated LLETZ, 2) hysterectomy, and 3) Papanicolaou smear. Residual disease was detected in a total of 156 patients (28.84%), there were 21 cases of CIN I (13.46%), 22 cases of CIN II (14.10%), 107 cases of CIN III (68.59%), and 6 (3.85%) cases of microinvasive squamous cell carcinoma of cervix. 1) Age > 50 years old was significant factor associated with residual disease. The incidence of residual disease was 50.00%. 2) Unsatisfactory colposcopy was significant factor associated with residual disease with 38.44% incidence of residual disease. 3) Margins involvement of LLETZ specimen was the only pathological predictive factor identified. The incidence of residual disease with clear margin, endocervical margin, ectocervical margin, and both margins involvement were 14.74, 52.63, 57.14, and 74.19% respectively. Other parameters, including gravidity, parity, menopausal status, cervical gland involvement, and number of quadrants involvement were not predictive of residual disease.

Conclusion: 1) Age > 50 years old, 2) unsatisfactory colposcopy, and 3) margins involvement of LLETZ specimens were the predictive factors for residual disease in uterine cervix.

Keywords: CIN III, LLETZ, Residual disease

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Cervical intraepithelial neoplasia III (CIN III) was accepted to be a precursor of invasive squamous cell carcinoma of cervix. Oster reported that CIN III progressed to invasive cancer in 12% of case. Even higher rate may be expected if the follow-up period was longer[5]. So the completeness of treatment is very important. But, CIN III is a local lesion and able to be cured by complete excision procedure such as large loop excision of the transformation zone (LLETZ). LLETZ is accepted and widely used for both the diagnosis and treatment of CIN III, because it is simple, cheap, safe and effective[2-5].
A considerable number of patients with CIN III were reported to retain residual disease in the uterine cervix\(^{6-13}\) and it is generally accepted that women who have been treated with CIN have an increased risk of invasive cancer of the cervix\(^{14}\). This is more likely to be explained by the progression of inadequately treated persistent disease than the development of incident CIN, so the management after LLETZ for detection of the residual disease is also very important too. Previous reports cited increasing age, parity, positive endocervical curettage, multiple-quadrant disease, positive margins, and endocervical gland involvement as the factors that could predict residual disease, but some factors were controversial\(^{6-9}\).

The purpose of this study was to determine predictive factors for residual disease in uterine cervix after LLETZ in patients with CIN III. Basic demographic data, colposcopic findings and the pathological parameters of the CIN III patients were retrospectively reviewed.

**Material and Method**

Between September 1, 1992 and December 31, 2001, CIN III lesion were diagnosed in 564 patients who underwent LLETZ at Ramathibodi Hospital, Bangkok, Thailand. Colposcopy was performed in all patients, demographic data (age, gravidity, parity, menopausal status), colposcopic findings (satisfactory of colposcopy, location of abnormal lesions) were recorded in record forms. LLETZ was done under local anesthesia following coloscope-mapping and Schiller test in operative room as an out-patient case, by Ellman Surgitron FFPF unit with electrosurgical loop elec-trode, sized 15, 20 or 25 millimeters, depending on the surgeons’ choice. The surgeons attempted to excise the cervical lesion in one cut for better orientation and margin status interpretation. Endocervical curettage was not routinely performed, because a previous study showed there was insufficient tissue to make a diagnosis of invasive carcinoma\(^{15}\).

Hemostasis was achieved by electrocoagulation with a ball electrode. The LLETZ specimen was vertically cut at 12 o’clock of the specimen for orientation and fixed in 10% formalin for pathological examination. The surgical lines of resection on LLETZ specimens were marked with India ink and then radially divided into four quadrants. Each quadrant was then further cut into 4-6 sections. All these specimens, an average of 16-24 tissue sections for each LLETZ specimen, were stained with hematoxylin and eosin, and then microscopically examined.

The most serious lesions of LLETZ specimen, lesions presented at endocervical or ectocervical margins, endocervical gland involvement, and number of cervical quadrants involvement were described on pathologic reports. We didn’t review about width and depth of LLETZ specimen because these two parameters depended on each surgeon’s operative decisions.

Two options for management after LLETZ are re-operation (hysterectomy or re-LLETZ) and follow-up. Residual disease was defined as the pathological or cytological evidence of cervical intraepithelial neoplasia or invasive cervical cancer in uterine cervix within 1 year after LLETZ.

Patients undergoing hysterectomy or re-LLETZ, presence of residual disease or no residual disease were defined from pathological diagnosis of the specimens.

In follow-up option, patients were followed-up with Papanicolaou smears (Ayre spatula) every 4-6 months for at least one year and had at least 2 smears. If all smears were negative, we classified as no residual disease. Colposcopy, biopsy, or endocervical curettage were indicated and performed with the presence of abnormal smear. Presence of residual disease or no residual disease was diagnosed from final pathological diagnosis. Those who had no evidence of residual disease but were followed-up for less than one year were excluded from the study.

The medical records of these patients were retrieved and reviewed. Pearson \(\chi^2\) test was used to test for univariate association between various demographic data, colposcopic findings, pathologic parameters and residual disease. Multivariate logistic regression was used to identify the predictive factors for residual disease in uterine cervix. We used SPSS for Windows, version 10.0 for statistical analyses. For all statistical test, p-value less than 0.05 was considered significant. This retrospective study was approved by the local institutional ethical committee.

**Results**

Of the included 564 patients, 23 cases had inadequate follow-up and were excluded. A total of 541 cases were enrolled in this study. Missing data of some part of pathological parameters were found in 26 cases because of incomplete pathological reports.

The mean age of the patients studied was 41.51 years old (range, 20-90). The median gravidity was 2 (range, 0-14), and the median parity was 2 (range, 0-10). One hundred and five patients (19.41%) of cases
were post-menopausal women.

Residual disease was detected in a total of 156 patients (28.84%), there were 21 cases of CIN I (13.46%), 22 cases of CIN II (14.10%), 107 cases of CIN III (68.59%), and unexpectedly 6 (3.85%) cases of micro-invasive squamous cell carcinoma of cervix.

Concerning management procedures after LLETZ, hysterectomy was performed in 265 patients, 137 (53.52%) of them had residual disease. Re-LLETZ was performed in only 19 patients. The procedure was not performed in the remaining cases because of the reason may be the difficulty of procedure due to shorter or smaller of cervical portio after first LLETZ. Of the re-LLETZ cases, 15 (78.95%) had residual disease. Only 4 from 257 patients in the follow-up group had evidences of residual disease within first year after LLETZ, all of them were detected in hysterectomy specimens.

The correlation of all possible factors and residual disease in uterine cervix were univariate analyzed with χ² test (Table 1). For demographic characteristics include age, gravidity, parity and menopausal status. This study used a the cut off value for age at 50 years, follow the previous studies(6,13). The cutoff values for gravidity and parity were set at 5, because parity 5 was well known as “great parity woman”. All 4 characteristics were significant factors for residual disease.

Colposcopic findings including satisfactory or unsatisfactory colposcopy and location of lesion (ectocervical lesion, endocervical lesion, both ecto-endocervical lesion, and no lesion seen) were analyzed separately with χ² test for prediction of residual disease, both of colposcopic findings correlated with residual disease in uterine cervix (Table 1).

The correlation of pathological parameters including gland involvement, surgical margins involvement (clear margin, endocervical margin,
ectocervical margin, and both margins involvement), and number of quadrants involvement with residual disease were also shown on Table 1. In number of quadrants involvement parameter, the patients were classified into two groups according to the number of quadrants showing disease involvement (one or two quadrants and three or four quadrants) to semiquantitatively described lesion size.

The presence of gland involvement, surgical margin involvement and multiple quadrants involvement correlated with residual disease in uterine cervix. All significant predictive factors from $\chi^2$ test were analyzed with multivariate logistic regression (Table 2). Only age $\geq$ 50 years old, unsatisfactory colposcope and surgical margins of LLETZ specimen involvement were significant predictors for residual disease in uterine cervix.

Location of lesion was also a significant factor, odds ratio for residual disease with endocervical lesion, both ecto-endocervical lesion, and no lesion seen to ectocervical lesion are 2.38, 2.44, and 3.38 respectively, but this factor was quite resembled and confound to satisfactory of colposcopy. So, we chose only satisfactory or unsatisfactory colposcope which is accepted as international terminology of colposcopy for this analysis.

**Discussion**

In this study, residual disease in uterine cervix was detected in 28.84% of total 541 cases, whereas in previous reports ranged between 5.4 to 48%\(^6\)-\(^{13}\). Total of 9 factors were significant factors for residual disease in uterine cervix when univariate analyzed with $\chi^2$ test, but when we analyzed with multivariate logistic regression, only three independent risk factors of residual disease in uterine cervix were identified; age $\geq$ 50 years old, the presence of CIN at the margins of excision, and unsatisfactory colposcopy.

Age was identified as a predictor of residual disease in previous reports\(^6\),\(^{13}\),\(^{17}\) and\(^{18}\). The higher incidence of incomplete excision in elderly patients may be explained by atrophy of the genital organ as well as deep inversion of transformation zone, which may increase surgical difficulties. The other reason is a longer duration of multifocal disease, as did more extensive lesion\(^17\).

In this study, parity of 5 or more was not a predictive factor of residual disease in uterine cervix, similar to the report by Moore et al\(^17\). However, Lu et al found that parity $\geq$ 5 was a predictive factor of residual disease in uterine cervix\(^6\). The significant of this result was not clear.

Menopausal status was not correlated with a residual disease in uterine cervix in this study, although the pathophysiology was the same to the event of the elderly patients. There was no previous study about menopausal status and residual disease.

By colposcopic finding, unsatisfactory colposcopy is one of independent predictive factor for residual disease in uterine cervix, the reason may be due to the squamocolumnar junction or the epithelial lesion wasn’t entirely visible, so CIN was locate in the deeper part of endocervical canal and may increase surgical difficulties. There was no previous study about colposcopic finding, but in our opinion colposcopic finding is very important pre-LLETZ data for surgeon to design and perform the completed LLETZ.

Cervical gland involvement in LLETZ specimen as a pathological diagnosis was of no value to predict residual disease in uterine cervix, and Lu et al had similar finding\(^6\). However, some previous report\(^19\) found that cervical gland involvement was one of predictive factor of residual disease in uterine cervix. The significant of cervical gland involvement was controversial.

The literature revealed conflicting results on

<table>
<thead>
<tr>
<th>Predictive Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
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<tr>
<td><strong>Age</strong></td>
<td></td>
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<tr>
<td>&lt; 50 years</td>
<td>1.00</td>
<td>Reference</td>
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<tr>
<td>$\geq$ 50 years</td>
<td>2.61</td>
<td>1.58-4.31</td>
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<td><strong>Colposcopy</strong></td>
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<td>Satisfactory</td>
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<td>2.16</td>
<td>1.29-3.60</td>
<td>0.003</td>
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<td><strong>Margin involvement</strong></td>
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<td>Clear</td>
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<td>3.70-9.53</td>
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<td>Ectocervical margin</td>
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<tr>
<td>Both cervical margin</td>
<td>14.88</td>
<td>6.10-36.29</td>
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surgical margin. There were several previous reports, that failed to identify a correlation between positive cone margin and residual disease in uterus\(^\text{(6,10,11,13,17,20)}\) and there were several reports, that supported positive surgical margin as a predictive factor of residual disease in uterine cervix\(^\text{(7,9,12,18,23,24)}\), especially four reports specified that endocervical margin of cone specimen was the predictive factor for residual disease\(^\text{(7,21-23)}\). In this report, positive margin of LLETZ specimen was an independent predictive factor for residual disease in uterine cervix. Odds ratio for residual disease of positive both margin involvement, ectocervical margin and endocervical margin are 14.07, 7.52 and 5.51 to clear margin, respectively. In our study, both ectocervical and endocervical margins involvement was a very high risk factor for residual disease in uterine cervix after LLETZ.

Number of quadrant involvement or size of lesion was not founded to be predictive of residual disease in uterine cervix in our study. The result was different with the report of Lu et al\(^\text{(6)}\). Our explanation for our result is when the surgeon knew all patient’s data, including lesion size from colposcopy mapping, or intraoperative abnormal intraepithelial lesion, the surgeons always designed and performed LLETZ with proper size of electrosurgical loop electrode for completeness of treatment.

Age ≥ 50 years old and unsatisfactory colposcopy were both already known by surgeons before LLETZ. These 2 factors may help surgeons to design and perform completed LLETZ. Margin involvement of LLETZ specimen was the factor received after LLETZ was performed, and may help surgeons to give post-LLETZ management options to patients. So surgeons should understand about all predictive factors for completeness of treatment.

**Conclusion**

Predictive factors for residual disease in uterine cervix after LLETZ in patients with CIN III are age ≥ 50 years old, unsatisfactory colposcopy and positive surgical margins of LLETZ specimens.

**References**


ปัจจัยที่ใช้ในการทำนายพยาธิสภาพที่เหลืออยู่ที่ปากมดลูกภายหลังการตัดปากมดลูกด้วยวงวงสวัสดิ์ไฟฟ้า ในผู้ป่วยที่ได้รับการวินิจฉัยเป็น Cervical intraepithelial neoplasia III

สุทธา หานแคระ, ณัฐพงษ์ อิศรางกูร, ณัฐพงษ์ อิศรางกูร, มานะ เรืองวุฒินันท์, สุรัญชี บัลลังก์โพธิ์, สมศักดิ์ ตั้งตระกูล

วัตถุประสงค์: เพื่อหาปัจจัยที่ทำนายพยาธิสภาพเหลืออยู่ที่ปากมดลูกภายหลังการรักษา Cervical intraepithelial neoplasia III (CIN III) ด้วยการตัดปากมดลูกด้วยวงวงสวัสดิ์ไฟฟ้า (Large loop excision of the transformation zone, LLETZ)

วัสดุและวิธีการ: จากเวชระเบียนผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็น CIN III ภายหลังการรักษาด้วย LLETZ ในช่วงวันที่ 1 กันยายน พ.ศ. 2535 ถึง 31 ธันวาคม พ.ศ. 2544 นำข้อมูลพื้นฐานของผู้ป่วยมาจากการตรวจปากมดลูกด้วยกล้องขยาย และข้อมูลการวินิจฉัยทางกายวิภาคข้ามกระดาษว่าปัจจัยที่ทำนายพยาธิสภาพเหลืออยู่ที่ปากมดลูก

ผลการศึกษา: ผู้ป่วย 541 ราย ได้รับการวินิจฉัยว่าเป็น CIN III ภายหลังการรักษาด้วย LLETZ เมื่อติดตามการรักษาภายหลังการตัดปากมดลูกด้วยวงวงสวัสดิ์ไฟฟ้า พบว่ามี 156 ราย (28.84%) ที่มีพยาธิสภาพเหลืออยู่ที่ปากมดลูก โดยเป็น CIN I 21 ราย (รอยละ 13.46) CIN II 22 ราย (รอยละ 14.10) CIN III 107 ราย (รอยละ 68.99) และมะเร็งปากมดลูกระยะ I A1 6 ราย (รอยละ 3.85) พบว่ามีการมีอายุเกิน 50 ปี เป็นปัจจัยที่ทำนายพยาธิสภาพเหลืออยู่ที่ปากมดลูกอย่างมีนัยสำคัญทางสถิติ โดยพบอัตราการของพยาธิสภาพเหลืออยู่ที่ปากมดลูก 50.00% การตรวจปากมดลูกด้วยกล้องขยายพบว่า unsatisfactory colposcopy เป็นปัจจัยที่ทำนายพยาธิสภาพเหลืออยู่ที่ปากมดลูกอย่างมีนัยสำคัญทางสถิติ โดยพบอัตราการของพยาธิสภาพเหลืออยู่ที่ปากมดลูก 38.44% และพบมีการพบพยาธิสภาพที่ขอบของชิ้นเนื้อจากการทำ LLETZ เป็นปัจจัยที่ทำนายพยาธิสภาพเหลืออยู่ที่ปากมดลูกอย่างมีนัยสำคัญทางสถิติ โดยพบอัตราการของพยาธิสภาพที่ขอบของชิ้นเนื้อจากการทำ LLETZ ในกรณีไม่พบพยาธิสภาพที่ขอบของชิ้นเนื้อ พบพยาธิสภาพที่ขอบของชิ้นเนื้อส่วนนอกสุดที่ติดอยู่บริเวณ ectocervix พบพยาธิสภาพที่ขอบของชิ้นเนื้อส่วนในสุดของ endocervical canal และพบพบพยาธิสภาพที่ขอบของชิ้นเนื้อส่วน 2 ส่วน เป็นรอยละ 14.74, 52.63, 57.14 และ 74.19 ตามลำดับ รวมจำนวนการตั้งครรภ์ จำนวนการคลอดบุตร ภาวะการหมดประจำเดือน cervical gland involvement และจำนวนของ quadrant involvement ไม่เป็นปัจจัยที่ทำนายพยาธิสภาพเหลืออยู่ที่ปากมดลูก

สรุป: 1) การมีอายุ ≥ 50 ปี, 2) unsatisfactory colposcopy และ 3) พยาธิสภาพที่ขอบของชิ้นเนื้อที่ได้จากการตัดปากมดลูกด้วยวงวงสวัสดิ์ไฟฟ้าเป็นปัจจัยที่ทำนายพยาธิสภาพเหลืออยู่ที่ปากมดลูก.