Correlation between Colposcopically Directed Biopsy and Large Loop Excision of the Transformation Zone and Influence of Age on the Outcome

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Objectives: To assess the accuracy and correlation between Colposcopically Directed Biopsy (CDB) and Large Loop Excision of the Transformation Zone (LLETZ) and the influence of age.

Material and Method: A comparative analysis was conducted from the 352 women referred to Rajavithi Hospital from January 1998 to December 2003, to compare between CDB and LLETZ. Correlation was assessed by the percentage of concordance (accuracy), Spearman's rank correlation coefficient (r) and Kappa statistics (K). A subgroup analysis was performed in women aged ≥ 50 years to evaluate the influence of age on the correlation.

Results: A 66.2% concordance was found between CDB and LLETZ. The correlation and agreement between the two procedures were low ($r = 0.32$, $p < 0.0001$; $K = 0.24$, $p < 0.0001$). In women aged ≥ 50 years, the accuracy was 60.7% and stronger correlation and agreement were noted ($r = 0.50$, $p < 0.0001$; $K = 0.31$, $p = 0.001$).

Conclusion: CDB is an inadequate diagnosis tool for Squamous Intraepithelial Lesion (SIL) in woman below 50 years of age. In women aged 50 years or more with satisfactory colposcopy, the accuracy and correlation between two procedures are not compromised.

Keywords: LLETZ, Correlation, Colposcopically directed biopsy

Colposcopically directed biopsy (CDB) is a standard for diagnosis of cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesion (SIL). Management algorithms are based on the colposcopic findings and the histology from biopsies. However, since Large Loop Excision of the Transformation Zone (LLETZ) for CIN was first described in 1981[1], the accuracy of CDB in identifying the severity of CIN has been questioned. From the literature, many under-diagnosis by CDB are done[2-10]. Disagreement between diagnosis based on CDB and specimens obtained by LLETZ has been reported[3,5,7,8]. The accuracy might depend on several factors such as age, interval between the two procedures and experience of colposcopists[2,5]. Women with more severe disease than that identified by CDB may receive inadequate treatment, with the risk of recurrence and development of invasive cancer. There are many reports of invasive disease being found in LLETZ specimens previously unsuspected at colposcopy or undetected by CDB[1,2,4,7,11]. The authors analyzed data on patients managed by colposcopy and colposcopically directed biopsy, followed by LLETZ in order to determine the accuracy of CDB compared to LLETZ and their correlation in our institute. In addition, the authors attempted to assess the influence of age on the accuracy and correlation.

Material and Method

The patients who were referred to a colposcopy clinic from January 1998 to December 2003 and underwent LLETZ treatments were reviewed. In our institute, all women with cytologic abnormalities (ASC-US or worse) were counseled and underwent colpos-

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copy by experienced colposcopists. The findings were documented. A punch biopsy was taken from the worst affected area via colposcopic guidance using 3% acetic acid. The indication for LLETZ as diagnostic or therapeutic procedure followed the standard protocol. Other options for SIL treatment are cold-knife cone biopsy, cryosurgery, laser excision, laser ablation and hysterectomy.

The LLETZ was performed by experienced operators, using a Surgitron F.F.P.F generator (Ellman international, New York, USA). The procedure was performed according to the technique described by Prendiville et al[1]. The LLETZ was used as an alternative to knife cone biopsy. However, patients were excluded from the present study if they were unsuitable for local ablative treatment because the transformation zone was not fully visible, there was evidence of glandular abnormalities such as adenocarcinoma in situ (AIS), invasive cancer was suggestive from colposcopy or biopsy-confirmed invasion. Biopsy-confirmed microinvasion (MIC) from CDB and those with large lesions were included in the present study.

Data were entered into a database and analyzed using statistical package for the social sciences (SPSS) version 11.5. Histological findings on LLETZ specimens were used to measure the accuracy, and the correlation with CDB results. McNemar testing was used to assess the association of the two procedures. Kappa statistics (K) and Spearman's rank correlation coefficient (r) were used to measure the agreement and the correlation between the grade of dysplasia from CDB and LLETZ findings. Exact agreement (K) between two procedures is reflected by a value of 0.8-1, substantial agreement; 0.6-0.79, moderate agreement; 0.4-0.59 and fair agreement; 0.2-0.39. Spearman's rank correlation coefficient > 0.7 indicates high correlation, 0.4-0.7 moderate correlation and < 0.4 indicates low correlation. A p-value of less than 0.05 was considered statistically significant.

Results

During the study period, 602 patients underwent LLETZ. At initial presentation, 142 patients (23.6%) had unsatisfactory colposcopy, and were excluded. Of the 602 patients, 76 (12.6%) had negative histology from LLETZ. Four hundred and sixty patients (76.4%) had satisfactory colposcopy. Of those with satisfactory colposcopy, 89 out of 460 were excluded because of lacking pathological results from CDB. Eighteen patients were excluded because they had pathological results from CDB showing other than normal, SIL or

MIC (i.e. AIS, invasive carcinoma). Lastly, one patient was excluded due to an inadequate LLETZ specimen. Therefore, 352 patients were eligible for the present study. The mean age of patients was 41.0 years (SD 10.50; range 16-81 years). LLETZ margins appeared to be clear in 199 women (56.5%). Margins were involved in 103 (29.3%) and uncertained in 50 (14.2%) women, respectively. Of the 352 patients, there were 48 (13.6%) with negative histology in LLETZ specimens.

Table 1 shows the comparison of histology from CDB and a significant lesion (high-grade SIL or worse) from LLETZ. Of the 352 women, CDB identified 48 (13.6%) with no evidence of SIL (no SIL), 40 (11.4%) with LSIL, 259 (73.6%) with high-grade SIL(HSIL) and 5 (1.42%) with MIC. Twenty-six out of 48 (54.2%), 30 out of 48 (62.5%) and 3 out of 48 (6.2%) of those with no SIL on CDB had HSIL, high-grade lesion or worse (HSIL+) and frank invasion, respectively. Of those with predicted LSIL on CDB, 13 out of 40 (32.5%), 14 out of 40 (35.0%) and 1 out of 40 (2.5%) had a HSIL, HSIL+, and frank invasion, respectively. Twelve out of 259 (4.6%) of those with HSIL on CDB had invasive carcinoma. There were 9 cases of MIC diagnosed by LLETZ in which 8 of these could not be diagnosed by CDB (1 patient was diagnosed as negative and 7 as HSIL). Moreover, there were 17 cases of invasive carcinoma that were not diagnosed by CDB (3,1, 12 and 1 patients were diagnosed as negative, LSIL, HSIL and MIC, respectively). The percentage of women with unexpected MIC or invasion was 24 out of 347 (6.9%). One case of unexpected AIS was also identified. Twenty-one out of 259 (8.1%) were diagnosed with high-grade SIL on CDB yet had no SIL in the LLETZ. Overall, 48 out of 352 (13.6%) women had negative LLETZ specimens.

Table 2 illustrates the accuracy, agreement and correlation between LLETZ and colposcopically directed biopsy in each patient, showing that the results concurred in 221 out of 334 cases (66.2%). The overcall rate at CDB was 18.6% with 15.3% undercall, McNemar test = 334 (p = 0.347). The K statistics and Spearman's rank correlation coefficeint for the grade of SIL on CDB and the grade of SIL on the LLETZ specimen were 0.24 and 0.32 (p < 0.0001), respectively. This indicates low agreement and correlation between the results of CDB and LLETZ findings.

The authors obtained different results when analyzing the subgroup of patients aged 50 years or more (Table 3). In this subgroup analysis, the overall percentage of CDB findings confirmed by LLETZ was 34 out of 56 cases (60.7%). The overcall at CDB was 19.6%

and the undercall was 19.6%. There was a moderate and significant correlation between CDB and LLETZ findings (r = 0.50, p < 0.0001). The K statistics also increased (K = 0.31, p = 0.001). There were 3 cases of MIC and 8 cases of invasive carcinoma diagnosed by LLETZ.

The percentage of women in this group with unexpected MIC or invasive carcinoma was 10 out of 62 (16.1%).

Discussion

The present study illustrates the limitations

Table 1. Comparison of CDB histology and LLETZ histology

CDB histology (n = 352)	LLETZ histology					
	No SIL	LSIL	HSIL/AIS	MIC	Invasive	Degree of significant lesion* (%)
No SIL (n = 48)	14	4	26	1	3	30 (62.5)
LSIL (n = 40)	13	13	13	0	1	14 (35.0)
HSIL (n = 259)	21	25	194**	7	12	213 (82.2)
MIC (n = 5)	0	0	3	1	1	5 (100.0)

* Significant lesion = HSIL or worse (HSIL+)
** include 1 case of adenocarcinoma in situ

Table 2. Accuracy, agreement and correlation of CDB histology and LLETZ histology*

CDB Histology	LLETZ Histology				Total	Accuracy (Exact agreement) (%)
	No SIL	LSIL	HSIL	MIC		
No SIL	14	4	26	1	45	31.1
LSIL	13	13	13	0	39	33.3
HSIL	21	25	193	7	246	78.5
MIC	0	0	3	1	4	25.0
Total	48	42	235	9	334	66.2

* Boldface values indicate exact agreement
McNemar test p = 0.347
The Kappa statistics = 0.244 (p < 0.0001)
Spearman's rank correlation coefficient = 0.324 (p < 0.0001)

Table 3. Accuracy, agreement and correlation of CDB histology and LLETZ histology: Sub-group analysis in women aged ≥ 50*

CDB Histology	LLETZ Histology				Total
	No SIL	LSIL	HSIL	MIC	
No SIL	6	2	3	0	11
LSIL	2	3	3	0	8
HSIL	3	5	25	3	36
MIC	0	0	1	0	1
Total	11	10	32	3	56

* Boldface values indicate exact agreement
McNemar test p = 1.00
The Kappa statistics = 0.308 (p = 0.001)
Spearman's rank correlation coefficient = 0.495 (p < 0.0001)

of colposcopically directed biopsy in assessing the severity of SIL and suggests that it has poor correlation and agreement with LLETZ. This supports the previous reports[3,5,6,10]. Nevertheless, some research showed a strong agreement and correlation[6,12,13]. However, the better correlation in those studies did exist when the results for agreement within 1 degree were compared. In the present study, a two-tiered classification defined by The Bethesda System was used, therefore, the exact agreement was consi-dered as an appropriate measure.

The literature reported accuracy of CDB compared with excision specimen between 35-90%[3-10,13,14]. The 66.2% accuracy using LLETZ, compared with the previous data, shows a satisfactory result. The accuracy was poor in the no SIL and LSIL group but it was better in women with HSIL. Possible reasons for in-accuracy in no SIL and LSIL group include failure of colposcopist to biopsy the most severe area, complete removal of a small low-grade lesion by CDB or abolition of lesions by inflammatory reaction following biopsy, the inability to detect a tiny subtle high-grade lesion occurring in a large striking low-grade lesion or immature metaplasia, high level of intraobserver and interobserver variability in histologic diagnosis of CIN 1[2,5]. The possible reason for higher accuracy in HSIL group is that there is a tendency of CIN 3 to be larger than a low-grade lesion. Therefore, the worst affected area is easier to be identified by colposcopy. In addition, the rest of lesion is not much affected by inflammatory reaction after taking biopsy because of the size of the lesion. The influence of lesion size on the correlation was studied by Buxton et al[9]. The present data are consistent with the previous reports[3-8,10,14]. Gunasekera et al[11] studied 98 women who had HSIL on biopsy and in 91 (93%) of these patients, the biopsy diagnosis agreed with the LLETZ specimens. Similarly, Chia et al, Powell et al and Costa et al[7,8,14] found that in women with CIN 3 diagnosed by CDB, the correlation between the CDB and LLETZ was better at 73% for SIL, 72.4% for LSIL and 85% for HSIL. Higgins et al[10] reported that women with HSIL on the cervical biopsy had the highest relative risk for finding HSIL by LLETZ and the accuracy for HSIL in the present study was better than LSIL. Studies using multivariate analysis confirmed a high-grade SIL to be an independent factor of concordance of CDB and final diagnosis[4,10].

Overall, the present study found that 19.32% of women with CIN on biopsy who underwent LLETZ had more severe lesions including invasion identified in LLETZ specimens. Undercall of CDB was noted in 62.50% of women with no SIL and in 35% of those with LSIL. This is a much worrisome finding because it would cause under treatment. The available literature indicated that women with biopsy-confirmed CIN1 who underwent LLETZ would have CIN 2-3 in 23% to 55% of the excised specimens[2,5-7,9,13]. The studies using the two-tiered system reported the same results. High-grade SIL was found in 21%-42% of the excised speci-men in women who were diagnosed with low-grade SIL on CDB[3,4,10]. The present data, 32.50%, is comparable to those reports. This indicates the disadvantage of using observational strategies to manage women with biopsy-proved low-grade SIL or CIN 1. Patients must understand the possibility that a higher-grade lesion may be present, with an increased risk of progression. Close follow-up for those patients is mandatory and treatment with LLETZ may be appro-priate in clinics where compliance is poor. The most serious aspect is the undiagnosed invasive cancer. In the present study, 6.25% of those with no SIL, 2.50% of those with LSIL and 4.63% of those with HSIL on CDB had invasive carcinoma. Moreover, 8 out of 9 cases of MIC were missed by CDB and 17 cases of invasive carcinoma were not diagnosed by CDB. The prevalence of unexpected MIC or invasion, at 6.92%, was greater than expected. Similar findings have been reported previously[4,6,7,9]. The significant proportion of MIC and invasive carcinoma may be missed despite careful colposcopy and CDB[1,4,6,7,9,11,13,15]. Invasive carcinoma of the cervix has been reported in patients after treatment by local ablation[2]. In the present study, if those patients were treated by local ablation, the diag-nosis of cervical carcinoma would be delayed and the risk of metastasis will certainly increase.

One of the criticisms of the LLETZ is the rate of negative histology[1,8], 13.64% in this study which might be regarded as overtreatment. This is probably due to several factors such as complete excision of the abnormality with the punch biopsy, false positive biopsy, false negative of LLETZ specimen, sponta-neous resolution in the time elapsed between CDB and LLETZ, disappearance of CIN after CDB occurs. It is suggested that the regression is related to local trauma or healing and the likelihood of regression may be greater with small lesions[5]. As found by another study, overestimation at biopsy is more frequent in the case of a small-sized lesion[9]. The present study shows a trend between the change in biopsy grade and the rate of negative histology of LLETZ (Table 1). The rates of negative histology previously reported were between 4-44%[1,3-6,8,10,13]. The National Health Service

Cervical Screening Program (NHSCSP) requires that more than 85% of all biopsies should contain CIN[16]. The present data achieved that standard.

It is shown that MIC is difficult to diagnose by colposcopy[12]. Murdoch et al[17] reported a significant increase in prevalence of MIC when LLETZ was introduced to replace ablative technique. They suggested that some cases of MIC were inappropriately treated by ablative method due to the underestimation of CDB. Upon this, the present finding confirms this matter. It has been accepted that MIC cannot be reliably diagnosed only by colposcopy with CDB. If MIC is detected by CDB, complete assessment of the cervix is required to rule out the presence of invasion. This entity must be based on conization specimen and not on CDB. In the present study, accuracy was only 25% for MIC. In multivariate analysis, the presence of MIC was the independent risk factor associated with concordance of biopsy[4].

Massad et al[5] found poor agreement and correlation between the two procedures and stated that some factors might have an influence on the results such as age or experience of colposcopists. That study was conducted among young women (mean age = 25) and all procedures were performed by trainees. Barker et al[13] assessed the effect of time between CDB and LLETZ and found that the correlation between the two tests was unaffected by a delay greater than 12 weeks. In the present study, the authors specifically analyze in the group of women aged 50 or over. Those women are usually regarded as postmenopausal cases. As is known, hormonal status could affect the preinvasive disease in terms of diagnosis, interpretation and treatment. After reanalysis of the data, the subgroup accuracy of CDB was 60.71%, which was similar to the accuracy of the total group. The correlation and agreement between two procedures apparently improved as shown in Table 2 and 3. Decreasing the percentage of undercall CDB finding in women with no SIL produced a significant increase in the correlation of two tests in the subgroup analysis. Generally, postmenopausal women often have unsatisfactory colposcopy due to aging and estrogen deprivation. However, only women with satisfactory colposcopy were eligible in the present study. Therefore, most of the older women with propensity of having undercall CDB results due to unsatisfactory colposcopy were excluded from the analysis at the enrollment. The present finding is supported by the previous study using multivariate analysis to control for contributing factors[4]. The factors such as age, parity and menopause were not the independent factors associated with concordance of biopsy but only the final diagnosis was related to the concordance[4]. Despite the positive result mentioned above, unexpected microinvasion or invasive carcinoma were more worrisome in this group of women. The rate, 16.13%, increased by 2.3 times at age 50 years or over. These contrary findings were not surprising. In fact, Costa et al[14] demonstrated that patient's age ≥ 50 years increased the possibility of nondiagnosis of carcinoma after adjustment for confounders such as visibility of the squamocolumnar junction and lesion size. They proposed that the plausible explanation was the higher incidence of invasive carcinoma in women in this age group and the menopause might further complicate diagnosis. Nevertheless, their study conversely showed that the probability of unconfirmed high-grade SIL diagnosis was not related to the patient's age. Women aged ≥ 50 years did not significantly affect the accuracy in diagnosis of high-grade SIL. Chen et al[12] observed that old age and achievement of menopausal status were associated with the nondiagnosis of early cervical cancer but not in multivariate analysis.

Many limitations preclude using the present results to all women undergoing colposcopy. First, the present study population did not completely meet all prerequisites for local ablation[15] such as pretreatment endocervical curettage was not done in every case, some patients had LLETZ performed with positive endocervical curettage, all large lesions were included in the present study and cases with Pap smears reported as invasive carcinoma were included as well. Consequently, the rate of unexpected MIC and invasive carcinoma in the present study (6.92%) was high compared to the literature[1,2,6,7,9,11,13-15]. In addition, the results of correlation and agreement were probably affected by this limitation as well. In general, to eliminate the risk of inadequately treating an occult invasive lesion, all prerequisites must be met before any ablative therapy is performed for the treatment of CIN[2,15]. Secondly, in some cases of undercall CDB, the long interval between CDB and LLETZ might cause progression of the disease. On the other hand, overcall CDB might be due to the same reason that caused the negative histology of LLETZ. The third limitation of the present study is due to the research design itself. Generally, women who undergo colposcopy with CDB reported as "no SIL" and "LSIL", are usually managed by expectant policy. Only a few cases with progressive potential, suspicion of HSIL or occult invasion will undergo LLETZ. This selection bias might explain a

high rate of HSIL and invasion diagnosed by LLETZ in those groups. In addition, a factor not considered in this analysis is the potential effect of intra- and inter-observer variability in reporting the grade of lesion. The histologic grading of SIL is well recognized that different pathologists may apply different grades to the same specimen[2,15]. To ensure consistent reporting, all specimens should be examined by the same pathologist. There should be concurrent pathological review as well.

In summary, the present study confirms that colposcopically directed biopsy is an inadequate endpoint for diagnosis of the SIL. Despite the modest accuracy, it has poor correlation and agreement with the histology found at time of LLETZ. In women aged 50 years or more with satisfactory colposcopy, the accuracy and correlation between two procedures are not compromised. MIC and invasive carcinoma following previously unsuspected colposcopy with CDB do exist. The cervical ablative procedure should be avoided especially in high-grade lesion, excision therapy is the treatment of choice. Treatment of low-grade lesion with LLETZ seems appropriate in setting where reliable follow up after colposcopy cannot be assured.

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การศึกษาความสัมพันธ์ระหว่างการตัดชิ้นเนื้อจากปากมดลูกโดยผ่านกล้องคอลโปสโคปกับการตัดปากมดลูกด้วยห่วงไฟฟ้าและผลของอายุของผู้ป่วยต่อความสัมพันธ์

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วัตถุประสงค์: เพื่อศึกษาความสัมพันธ์ ความสอดคล้องและความแม่นยำระหว่างผลพยาธิวิทยาจากการตัดชิ้นเนื้อจากปากมดลูกโดยผ่านกล้องคอลโปสโคป (CDB) กับผลพยาธิวิทยาจากการตัดปากมดลูกด้วยห่วงไฟฟ้า (LLETZ) และศึกษาผลของอายุของผู้ป่วยต่อความสัมพันธ์

วัสดุและวิธีการ: คณะผู้ทำการวิจัยได้ทำการเปรียบเทียบผลพยาธิวิทยาจาก CDB และ LLETZ จากผู้ป่วย 352 ราย ที่เข้ารับการรักษา ณ โรงพยาบาลราชวิถีระหว่างเดือนมกราคม พ.ศ. 2541 ถึงเดือนธันวาคม พ.ศ. 2546 การศึกษาหาความสัมพันธ์ ใช้การวัด ร้อยละของความสอดคล้อง ค่าสัมประสิทธิ์สหสัมพันธ์ และ Kappa statistics และได้ทำ การศึกษาเฉพาะกลุ่มในสตรีที่มีอายุตั้งแต่ 50 ปีขึ้นไปโดยวิธีการทางสถิติเดียวกัน

ผลการศึกษา: พบว่าผลพยาธิวิทยาจาก CDB และ LLETZ มีความสอดคล้องร้อยละ 66.17 และมีค่าสัมประสิทธิ์สหสัมพันธ์ เท่ากับ 0.32 และ Kappa statistics เท่ากับ 0.24, p < 0.0001) ในสตรีอายุตั้งแต่ 50 ปีขึ้นไปพบว่าผลพยาธิวิทยาจาก CDB และ LLETZ มีความสอดคล้องร้อยละ 60.71 และมีค่าสัมประสิทธิ์สหสัมพันธ์ และ Kappa statistics เท่ากับ 0.50 และ 0.31 ตามลำดับ

สรุป: ผลพยาธิวิทยาจากการตัดชิ้นเนื้อที่ปากมดลูกผ่านกล้องคอลโปสโคปมีความสัมพันธ์กับผลพยาธิวิทยาจาก LLETZ ค่อนข้างต่ำ CDB ไม่มีความแม่นยำเพียงพอในการวินิจฉัย SIL การตรวจด้วยกล้องคอลโปสโคปในสตรีที่มีอายุตั้งแต่ 50 ปีขึ้นไป ยังมีความแม่นยำและความสอดคล้องของ CDB เทียบกับ LLETZ ใกล้เคียงกันกับการตรวจในสตรีทุกช่วงอายุ