Is direct large loop electric excision for the transformation zone reasonable in the investigation of high-grade squamous intraepithelial lesions in cervical smears?

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Summary

Purpose of investigation: To evaluate women with cytological high-grade squamous intraepithelial lesions (HGSIL) who received standard colposcopic evaluation and direct diagnostic large loop electric excision for the transformation zone (LLETZ) to determine the feasibility of using LLETZ alone (ie, skipping the colposcopic examination).

Methods: From May 1999 to May 2001, 70 women, with the mean age of 49.58 years (range, 20-82 years) and with cervical HGSIL categorized by the Bethesda system were all evaluated by colposcopic evaluation and LLETZ. Cases with a satisfactory colposcopy examination were classified as group A and those with an unsatisfactory colposcopy examination were classified as group B. "Over-treatment" was determined if the women did not need further LLETZ for evaluation or management. "Under-treatment" was determined if treatment might be potentially inadequate or invasive cancer could be ruled out during a satisfactory colposcopic evaluation.

Results: Group A consisted of ten women who were evaluated satisfactorily by colposcopy and group B consisted of 30 women who were not evaluated satisfactorily by colposcopy. Overall 8.6% of the patients (6/70) were considered "over-treated". The rate of over-treatment was 10.0% (4/40) in group A compared with 6.7% (2/30) in group B. In contrast, overall 10% of the patients (7/70) were considered "under-treated". The rate of under-treatment was 10% (1/40) in group A compared with 10% (3/30), in group B. The positive predictive values of group A and B were 90.6% and 88.0%, respectively. The negative predictive values were 33.2% and 40%, respectively.

Conclusion: Direct diagnostic and therapeutic LLETZ for the management of cervical HGSIL may be a better alternative to colposcopy. This method of treatment avoids the possibility of under-treatment and is associated with an acceptable over-treatment rate, especially for postmenopausal women with cytological HGSIL. LLETZ has a good diagnostic accuracy with minimal morbidity and, most importantly, may help reduce patient anxicty, although further studies are needed to directly examine this effect.

Key words: HGSIL; Direct diagnostic and therapeutic LLETZ.

Introduction

Cervical carcinoma is a common female malignancy in Taiwan. A mass screening program that includes the use of cervical Papanicolaou (Pap) smears is important to women's health in terms of prevention and early diagnosis of cervical malignancies. Approximately 1.5 million women undergo a Pap smear annually in Taiwan. One percent of all Pap smears show abnormalities and one third are classified as high-grade squamous intraepithelial lesions (HGSIL). The standard protocol for patients with HGSIL is a colposcopic evaluation and endocervical assessment [1, 2]; however more intensive procedures, such as various types of conization, may be performed on a case-by-case basis.

Colposcopic evaluation has several limitations. First, because this procedure involves a subjective assessment, there is a high degree of bias and observer variability. Second, approximately 25% of all colposcopic evaluations have been described as unsatisfactory examinations, necessitating the need for further evaluations [3]. Third, a relatively high number of conflicting findings appear between cytologic results and colposcopy histologic reports, which leads to the need for further assessments, such as conization [3]. Fourth, cases of cervical intraepithelial neoplasia (CIN) 2 or 3, which are confirmed by colposcopic evaluation, often are treated with immediate therapy because these cancer stages have a significant risk of progressing to invasive carcinoma. Finally, the presence of cytologic HGSIL makes women anxious, especially in Taiwan, and cancer-phobia is so strong that women should not have to wait for treatment.

It is possible that direct diagnostic large loop electric excision for the transformation zone (LLETZ) is a good alternative to colposcopic evaluation and would allow physicians to skip the colposcopic assessment. However, LLETZ is considered a more invasive and costly procedure than colposcopy. In addition, it is thought to lead to a relatively high rate of over-treatment for women with HGSIL who do not undergo colposcopic evaluation [4].

Cold-knife conization requires physicians to undergo long-term training; in addition, for patients it is an anes-

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thetic procedure, involves a longer operative time, and may lead to a higher morbidity rate than LLETZ. However, cold-knife cone specimens have been shown to be 50% longer and 100% heavier than LLETZ specimens [4]. Laser conization shares the same conveniences as LLETZ; however, it also requires physicians to undergo long-term training and costs more. Therefore, LLETZ is often considered a better choice, and it is reported to be better than colposcopic evaluation in detecting more invasive cervical lesions including micro-invasive and invasive cancer [5, 6]. It has also been proven to be as effective as cryotherapy and laser therapy with minimal complications and similar or even better cure rates [7]. Most importantly, it provides cone specimens for pathologic diagnosis.

To clarify the above-mentioned issues and to study the feasibility, potential benefits, and possible risks of direct LLETZ for HGSIL detected during a Pap smear, we retrospectively evaluated women with HGSIL who received standard colposcopic evaluation and LLETZ treatment in a community-based teaching hospital.

Patients and Methods

We retrospectively reviewed all women (n = 70) with HGSIL detected on their Pap smears who received colposcopic evaluation and LLETZ treatment at the same time in our community teaching hospital from May 1999 to May 2001. The study was approved by the ethics committee of the Department of Obstetrics and Gynecology, Cardinal Tien Hospital, and written informed consent was obtained from all patients enrolled in the study. For all patients, if the entire squamocolumnar junction of the cevix was visualized, the examination was considered satisfactory and an endocervical curettage was unnecessary [8]. If the colposcopic examination was unsatisfactory, an endocervical curettage was performed in addition to the directed cervical biopsy. Patients with a satisfactory colposcopic evaluation were classified as group A and those with an unsatisfactory colposcopic evaluation were classified as group B. Colposcopic evaluation included cervical biopsies for group A. Colposcopic evaluation included biopsies and endocervical curettage for group B.

LLETZ was performed with an ELMED ES30 electrosurgical system with a blended cutting and coagulation output of 30W and 50W, respectively. All patients were placed under local anaesthesia, which consisted of paracervical injections of 1% lidocaine at the 3, 5, 7 and 9 o'clock positions around the cervix [9]. Colposcopic evaluation was performed first and then the transformation zone was excised with a fine wire loop in one sweep, if possible. Endocervical curettage was also performed after the procedure. Homeostasis of the wound was performed by the coagulation mode with ball electrode or by using Monsel's solution. The excised specimens were sent for pathologic examination. "Over-treatment" was determined if the women did not need further LLETZ for evaluation or management, including colposcopic examination revealing low-grade squamous intraepithelial lesions (LGSIL) and squamous cell carcinoma (SCC). "Under-treatment" was determined if treatment might be potentially inadequate or invasive cancer could be ruled out during a satisfactory colposcopic evaluation (colposcopy revealed LGSIL and LLETZ revealed HGSIL or colposcopic evaluation revealed HGSIL and LLETZ revealed SCC).

Results

The 70 women with cervical HGSIL categorized by the Bethesda system were all initially evaluated by colposcopic evaluation and then managed with LLETZ in our setting. Patient characteristics, including age, parity, and menopausal status in each group are shown in Table 1. The mean age of group A was 46.9 ± 10.9 years, and that of group B was 54.4 ± 10.9 years ($p = 0.031$). Fourteen of 40 women in group A (35.0%) were menopausal compared with 17 of 30 women (56.7%) in group B ($p = 0.023$). There were no significant differences in terms of parity between the two groups. We found that age and menopausal status contributed to the increased risk of unsatisfactory colposcopic evaluation.

Figures 1 and 2 demonstrate the histologic results of the two groups. Overall 8.6% of the patients (6/70) were considered over-treated because they had cervical lesions of which the severity was CIN 1 or the lesion was invasive cancer. Theoretically, both conditions can be easily identified by colposcopic evaluation. Therefore, further conization might not be necessary. Four of these over-

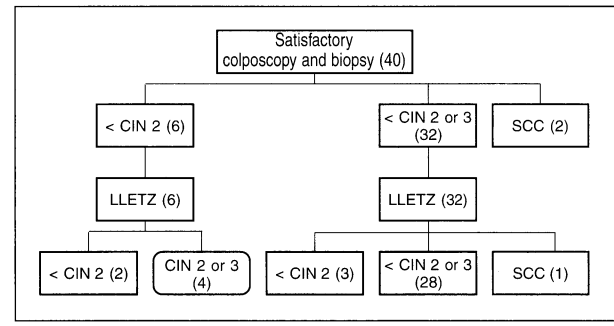

Figure 1. — Histological results of group A (patients with a satisfactory colposcopic evaluation, whose colposcopic evaluation included a cervical biopsy).
CIN = cervical intraepithelial neoplasia;
SCC = squamous cell carcinomas;
LLETZ = large loop electric excision for the transformation zone.

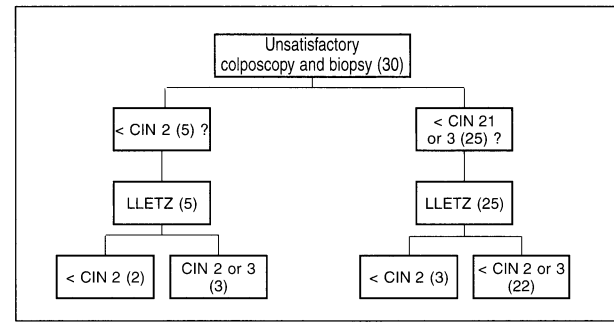

Figure 2. — Histological results of group B (patients with an unsatisfactory colposcopic evaluation, whose colposcopic evaluation included a cervical biopsy and endocervical curettage).
CIN = cervical intraepithelial neoplasia;
LLETZ = large loop electric excision for the transformation zone.

Table 1. — *Age, parity, menopausal status, and outcome of all groups*.*

	Group A (n = 40)	Group B (n = 30)	*p* Value
Age (yrs) Mean ± SD	46.9 ± 10.9	54.4 ± 10.9	0.031
Parity Mean ± SD	2.5 ± 1.5	3.5 ± 2.1	NS
Menopause (%)	14/40 (35%)	17/30 (56.7%)	0.023
Over-treatment rate (%)	4/40 (10%)	2/30 (6.7%)	
Under-treatment rate (%)	4/40 (12.5%)	3/30 (10%)	

Group A included patients with a satisfactory colposcopic evaluation, whose colposcopic evaluation included a cervical biopsy. Group B included patients with an unsatisfactory colposcopic evaluation whose colposcopic evaluation included a cervical biopsy and endocervical curettage.
NS = not significant.

Table 2. — *Sensitivity, specificity, positive predictive value, negative predictive value, and false-negative rate of colposcopic examination for high-grade squamous intraepithelial lesions (HGSIL)*.*

	Group A	Group B	*p* Value
Sensitivity	29/33 (87.9%)	22/25 (88.0%)	NS
Specificity	2/5 (40.0%)	2/5 (40.0%)	NS
Positive predictive value	29/32 (90.6%)	22/25 (88.0%)	NS
Negative predictive value	2/6 (33.2%)	2/5 (40.0%)	NS
False negative rate	4/6 (66.7%)	3/5 (60.0%)	NS

Group A included patients with a satisfactory colposcopic evaluation, whose colposcopic evaluation included a cervical biopsy. Group B included patients with an unsatisfactory colposcopic evaluation whose colposcopic evaluation included a cervical biopsy and endocervical curettage.
NS = not significant.

treated women were diagnosed with LGSIL and the other two women had invasive cancers. The rate of over-treatment in group A was 10.0% (4/40), based on satisfactory colposcopic evaluation. The rate of over-treatment in group B was 6.7% (2/30), based on unsatisfactory colposcopic evaluation. In contrast, 10% of the patients (7/70) were considered under-treated because they had HGSIL but colposcopic biopsy revealed the severity to be CIN 1. These patients would not have undergone LLETZ according to their colposcopic biopsy report. The rate of under-treatment in group A was 10% (4/40), based on satisfactory colposcopic evaluation. The rate of under-treatment in group B was 10% (3/30), based on unsatisfactory colposcopic evaluation.

The positive predictive values of group A and B were 90.6% and 88.0% respectively. The negative predictive values were 33.2% and 40.0%, respectively. Table 2 shows the sensitivity, specificity, positive predictive value, negative predictive value, and false-negative rate of colposcopic examination for HGSIL. There were no significant differences between the two groups.

Discussion

Women with a cytologic diagnosis of HSIL have approximately a 70% to 75% chance of having a biopsy-confirmed CIN II or III and a 1% to 2% chance of having invasive cervical cancer [4, 7, 8]. In this study, the risk of invasive cancer seemed to be high (4.3%), which caught our attention. First, cervical cancer is the most common disease among female malignancies in Taiwan [9-12], but the use of the Pap smear in sexually active or adult women in Taiwan is still low, at about 30% to 40% [9, 10]. The accurate rate of colposcopic diagnosis seemed to be acceptable in this study, but under-diagnosis should not be overlooked, especially for invasive cancer. Because under-diagnosis with colposcopic evaluation cannot be avoided, it provides a rationale to use a "look and treat" policy, i.e., the use of LLETZ instead of the initial colposcopic evaluation, because the requirement for conization is based on colposcopic diagnosis.

There are at leat seven surgical techniques available for managing HGSIL. However, there is no obviously superior surgical technique for treating CIN [14]. LLETZ appears to provide relatively reliable specimens for histologic examinhation and its morbidity is lower than that of laser or cold-knife conization [15]. There are not enough data to assess its effect on morbidity compared with laser ablation [15]. Therefore, LLETZ has become the treatment of choice for CIN 2 or 3 cervical lesions in our setting because it is associated with minimal complications. Furthermore, it allows us to diagnose and treat these cases in one simple procedure.

Other investigators have skipped the standard colposcopic evaluation and performed a direct LLETZ when investigating women with suspected cervical HGSIL [16-18]. Several trials that managed women with HGSIL by immediate LLETZ (i.e., "see and treat") have reported this method to be safe, efficacious, and cost-effective [19-22]. Histologic results from colposcopic-directed biopsy are not always accurate. A positive predictive rate of colposcopic evaluation has been found to be 29% for "absence of suspected CIN tissues", 16% for CIN 1, 32% for CIN 2, 86% for CIN 3, 59% for microinvasive disease, and 83% for invasive disease, respectively [6]. Diagnostic error of colposcopic evaluation could have resulted in suboptimal treatment in many cases [16]. Denny *et al.* showed that colposcopic punch biopsy does not reduce the occurence of negative histology after LLETZ [20]. In this study, we reconfirmed the fact that a consistent risk of under-treatment and over-treatment was present in directly applying LLETZ for the management of cytologic HGSIL [5, 20, 23]. We are more concerned about the risk of under-treatment because close follow-up for these patients cannot be predicted, especially in Taiwan. In our unpublished data, we found that approximately 16% of women were lost to follow-up. Although the effect of losing women to follow-up has not been carefully reviewed, it might help explain the high prevalence of cervical cancer in Taiwan. In addition, some authors highly recommend that CIN 2 or 3 lesions be treated with LLETZ or knife conization [14]. In our study, the risk of over-treatment seemed to be similar between the two groups. It suggests that direct LLETZ might be used as effectively as colposcopic evaluation for women with HGSIL.

So far, colposcopic evaluation seems to have many limitations. The whole transformation zone cannot always be visualized during colposcopic evaluation, so an accurate diagnosis may not be possible. In addition, an unsatisfactory colposcopic evaluation is often associated with advancing age, multiple gravidity, and parity [24]. This finding was also confirmed in ous study. Hopmann *et al.* also found the prevalence rate of unsatisfactory colposcopic examinations increases with more advanced lesions [16]. This finding supports our suggestion that direct LLETZ may be appropriate for elderly or postomenopausal women with HGSIL.

LLETZ has also been found to be more accurate than colposcopic evaluation in detecting invasive cervical lesions. Some studies found that colposcopic evaluation might fail to detect microinvasive diseases, but LLETZ could successfully overcome this limitation [17, 18, 14]. In this study, we would have missed one invasive cancer if we had not performed LLETZ. This missed identification of invasive disease would increase the possibility of inadequate treatment, if ablative therapy was applied. Thus, proponents of LLETZ emphasize the risk of ablating an undetected adenocarcinoma in-situ or microinvasive carcinoma lesions that have been found unexpectedly in up to 2% to 3% of specimens excised by LLETZ [16, 17]. With this consideration, direct diagnostic LLETZ is a better choice in managing women with HGSIL.

Recent reports on the "see and treat" mode of management have been proposed and have gained preliminary acceptance [26]. One study reported on the use of a one-stop colposcopy clinic and found this method to be feasible for the management of women with low-grade smear abnormalities [26]. In addition to delivering a quality service, it optimizes patient management, reduces anxiety, and is the patient's choice. Another study also revealed that LLETZ at the first colposcopic visit is a practical and fast method of treating most cervical lesions with limited complications and has the advantage of eliminating a second treatment session [27]. Decision making based on colposcopic examination should be undertaken carefully in managing patients with HGSIL.

Some studies on women undergoing immediate LLETZ for cytologic abnormalities have reported that a significant number of excised specimens lack histologically confirmed CIN [22]. This tecniques has the disadvantage of considerable "over-treatment" of low-grade lsions when integrated into the management of all patients with abnormal cytology [22, 23, 28], because their rate of over-treatment (30.3%) is higher. This high rate of over-treatment may be due to the inclusion of the women with low-grade cytologic abnormalities in their study [22, 23, 28]. In our opinion, direct LLETZ should be performed for selective high-risk cases with high-grade CIN such as HGSIL, and used especially in older women; the subsequent lower over-treatment rate will make this procedure more acceptable clinically.

Furthermore, cases of biopsy-proven LGSIL following a HGSIL smear represent a unique subset of lesions distinguished by their high incidence of high-risk types and greater risk of subsequent HGSIL on follow-up [7]. Treatment for these cases theoretically may not be considered over-treatment.

The main problem of direct diagnostic LLETZ is the possible complications that may follow after over-treatment. Clinically, the complications of LLETZ, such as postoperative hemorrhage, infection, and cervical stenosis, are minor and easily managed. Theoretically, LLETZ can also impair fertility in several ways, including leading to cervical stenosis, decreased volume of cervical mucus, cervical incompetence, or tubal scarring induced by post-treatment infection. However, some studies have shown that the destruction of the cervix after LLETZ is less than with other techniques, and that these other techniques have little or no adverse effect on fertility and pregnancy [20, 29, 30]. The low morbidity rate makes the use of LLETZ in treating women with HGSIL reasonable.

Conclusion

The use of direct diagnostic and therapeutic LLETZ for HGSIL shows advantages in terms of shortening the management course, minimal complications, and an acceptable over-treatment rate. It is possible that this procedure may be useful in reducing patient anxiety and may be especially helpful for older women, women who have completed their families, women who are in danger of being lost to follow-up, and women with a severe cancer-phobia.

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