

RESEARCH COMMUNICATION

Recurrent Rates with Cervical Intraepithelial Neoplasia having a Negative Surgical Margin after the Loop Electrosurgical Excision Procedure in Thailand

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Abstract

LEEP conization has become the treatment of choice in patients presenting with high grade intraepithelial lesions (HSILs) especially in cases with negative surgical margins. However, surveillance after such treatment is necessary due to the potential for recurrence. To evaluate the recurrent rate in patients with negative surgical margins after HSIL treatment with LEEP, the medical records of such patients treated between January 2000 and June 2007 were reviewed. All of them subsequently underwent Pap smears every 4-6 months to detect the recurrence of cervical intraepithelial neoplasia. There were 272 patients in the study period. Of these, 9 (3.3%) developed abnormal Pap smears with a median follow up of 12 months. The abnormal smears featured: atypical squamous cells of undetermined significance in 5 cases; atypical squamous cells where high grade squamous cell intraepithelial lesion cannot be excluded in 2 cases; and low grade squamous intraepithelial lesions in the 2 remaining cases. Further investigation with colposcopic directed biopsies were conducted in all who exhibited an abnormal Pap smear and only 3 of them (1.1%) showed cervical dysplasia at biopsy. In conclusion, the patients with HSIL who were treated with LEEP and have negative surgical margins have a very low recurrence rate.

Key Words: LEEP - HSIL - negative surgical margin

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Introduction

Since the loop electrosurgical excision procedure (LEEP) was introduced by Prendiville in 1989 for the evaluation and treatment of cervical intraepithelial neoplasia (Prendiville et al.,1989), it has rapidly gained acceptance among the gynecologists due to many advantage reasons such as the providing adequate cervical specimens for pathological examination, the convenience to perform in an outpatient setting, and the high success rate with low major surgical morbidity (Wright et al.,1992; Kietpeerakool et al., 2006).

Cervical intraepithelial neoplasia (CIN) 2, 3 or HSIL of the cervix is now generally accepted as a precancerous lesion of squamous cell carcinoma. With trend toward of conservative surgery, cervical conization particularly LEEP has become the treatment of choice. However, there is a certain proportion of such women will eventually have persistent or recurrent disease after LEEP. In previous studies, risk of persistent or recurrent disease has been consistently associated with large lesion, endocervical extension and incomplete LEEP excision (Felix et al.,1994; Suprasert et al.,1999; Dietrich et al.,2002; Brockmeyer et al., 2005; Kim et al.,2007). Interestingly,

although uncommon, women with negative surgical margins following LEEP are noted to have persistent or recurrent disease (Gardeil et al.,1997; Fadare et al.,2008). However, since studies of recurrent rates in these patients are limited, the present investigation was conducted to determine the incidence of recurrent disease in patients who had negative surgical margins after LEEP for CIN 2/3 in our institute.

Materials and Methods

After approval of the Research Ethics Committee, the medical records of women who had HSIL on LEEP with negative surgical margins treated at Chiang Mai University Hospital between January 2000 and June 2007 were reviewed. LEEP was performed in an outpatient setting by gynecologic oncologist trainee under direct staff supervision. The second LEEP was also performed subsequently at 4-6 weeks if the previous surgical margins were involved. The electrical power for the loop electrode was set to 60 W cut and 40 W coagulation in a blended mode. Endocervical curettage (ECC) after LEEP was routinely carried out.

The LEEP specimen diameters, including cone base

and length, were measured before fixation. All specimens were opened longitudinally and sectioned serially along the entire length of the endocervix to the ectocervix at intervals of 1-3 mm and they were then embedded in paraffin. The surgical margins of the cones were marked with indelible ink. All sections were then stained with hematoxylin and eosin. Negative margin was defined as the absence of dysplastic epithelium at all cone margins by histopathologic examination. The ECC specimens were histologically interpreted as negative, positive, or inadequate. The results were negative when normal endocervical cells were presented. Positive results were those in which neoplastic cells were noted. Inadequate results were those without cells for interpretation. Patients were instructed to return in every 4 - 6 months for follow-up cytologic evaluation. The physician performed Papanicolaou smears (Pap smears) using a wooden spatula and some cases performed an endocervical brush with direct application onto glass slide and subsequent fixation. Cytology was described using the Bethesda system 2001. Abnormal cytology was defined as atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H), atypical glandular cells of undetermined significance (AGUS), low-grade squamous intraepithelial lesion (LSIL), or high-grade squamous intraepithelial lesion (HSIL). Patients with abnormal cytology were referred for further colposcopic evaluation at our institution. Patients were excluded from the study

if no follow-up records could be located or not came to follow up in the appointment date. Patients were also excluded if marginal status could not be determined.

The statistical analysis was carried out using SPSS program for window (version 15.0) computer software (SPSS Inc, Chicago, Ill) for calculated means, median and the percentage of data

Results

There were 290 HSIL patients treated with LEEP conization and revealed negative surgical margins in the study period. Eighteen patients were excluded from the study due to subsequent hysterectomy in 12 patients and never attended the follow-up schedule in the rest. The remaining 272 patients were retrospective analysis for the incidence of recurrent rate. The clinical characteristic of these patients were noted in Table 1. The mean age of the patient was 43 years. About 90% of patients were multiparity and nearly one - third used oral contraceptive pill. Only 5% demonstrated positive anti HIV test. About 40% of patients had lesion in 4 quadrants of LEEP specimens.

With the median follow up time of 12 months (4-69 months), nine patients (3.3%) revealed subsequently positive cervical cytology at 4-45 months after LEEP. The details of these patients were showed in Table 2. The abnormal smear consisted of ASC-US in 5 patients, ASC-H in 2 patients and LSIL in the remaining patients. All of them were negative for HIV testing. Only 1 patient had underlying disease as chronic renal failure. Three patients received two times of LEEP. The endocervical curettage was done in 5 patients but adequate for interpreted as HSIL in 1 patient whereas the other showed normal histology. All of these patients received further colposcopic examination. Among the patients whose cervical cytology revealed ASC-US, all of them showed satisfactory colposcopic finding. Three patients revealed normal transformation zone and still no evidence of disease after follow-up for 6-45 months. One patient was diagnosed as LSIL from colposcopic finding but the colposcopic directed biopsy (CDB) revealed only atrophic squamous epithelium. Her further cervical smear was normal after follow-up for 6 months. The remaining patient with ASC-US had colposcopic finding consistent with flat

Table 1. Clinical Characteristics of the Patients

Mean age (range: year)		43 (20-74)
Parity	Nulliparity	20 (7.3)
	Multiparity	252 (92.6)
Positive anti HIV test		15 (5.5)
Contraception	Oral contraceptive pill	90 (33.1)
	DMPA*	31 (11.4)
	Tubal resection	61 (22.4)
	Other	22 (8.1)
None		68(25.0)
Lesion size	1 quadrant	55 (20.2)
	2 quadrants	67 (24.6)
	3 quadrants	39 (14.3)
	4 quadrants	111 (40.8)

*DMPA = Depo Medroxyprogesterone Acetate

Table 2. Details of Patients Presenting with Subsequent Positive Cervical Cytology

Age	Underlying disease	Anti HIV	Initial Pap	Initial colpo.	LEEP episode	ECC	Lesion size (quadrants)	Interval (mo)	Abnormal PAP	Subsequent colpo.	CDB	Re-treatment	FU *(mo)
53	CRF	-ve	HSIL	HSIL	First	Not done	3	35	ASC-US	LSIL	Atrophic	FU	6
39	None	-ve	CA	HSIL	Re -	Not done	4	45	ASC-US	Flat condyloma	HSIL	Re-LEEP	-
49	None	-ve	CA	HSIL	Re -	≥HSIL	4	6	ASC-US	No definite	Not done	FU	6
49	No	-ve	LSIL	LSIL	First	Inadequate	2	12	ASC-US	No definite	Not done	FU	45
44	None	-ve	LSIL ⁺	LSIL	First	Inadequate	2	5	ASC-US	No definite	Not done	FU	7
20	None	-veg	ASC	HSIL	First	Normal	4	7	LSIL	LSIL	LSIL	FU	0
44	None	-veg	HSIL	HSIL	First	Not done	1	14	LSIL	LSIL	HSIL	Re-LEEP	32
42	None	-ve	HSIL	HSIL	Re -	Normal	1	5	ASC-H	Unsat.: HSIL	CC	FU	3
48	None	-ve	HSIL	HSIL	First	Inadequate	4	25	ASC-H	Unsat.: HSIL	CI	FU	19

Colpo. = colposcopy diagnosis; CDB = Colposcopic directed biopsy; FU = follow up; unsat= unsatisfactory; CRF=chronic renal failure; HSIL = high grade squamous cell intraepithelial lesion; LSIL = low grade squamous cell intraepithelial lesion, LSIL⁺, plus human papilloma virus; ASC= atypical squamous cell suspected high grade lesion; ASC-US= atypical squamous cell of undetermined significance; CC, chronic cervicitis; CI, chronic inflammation

condyloma. However, the CDB showed HSIL. She was treated with LEEP again and the final histology revealed HSIL at 1-3 o'clock with uninvolved surgical margin. She was planned to follow up in the next 6 months.

For two patients whose cervical smear revealed LSIL, both had satisfactory colposcopic finding and were diagnosed as LSIL. Interestingly, the CDB of one patient showed HSIL whereas the other showed only LSIL. The patient with HSIL also treated with LEEP again and the final histology showed HSIL at 11-2 o'clock with a free surgical margin. Her further cervical smears remained negative for over 2 years.

In addition, 2 patients with ASC-H revealed unsatisfactory colposcopic finding and were impression as HSIL. CBD was performed and revealed only chronic cervicitis. Both patients were followed with cervical cytology and remained negative for 3 and 19 months, respectively.

Discussion

The present study showed abnormal cervical cytology in 3.3% of the HSIL patients who previous completely excised with LEEP and only 1.1% of them had final diagnosed as recurrent HSIL from cervical biopsy. This finding was corresponding to the study of Gardeil et al (Gardeil et al.,1997) . In their series, 5 of 107 patients (4.7%) who diagnosed as HSIL and were treated with complete LEEP excision revealed abnormal cervical smear. With further investigation, 2 of them (1.2%) underwent re-LEEP and the final histology confirmed persistent of cervical intraepithelial neoplasia (CIN). However, Fadare et al (2008) reported the recurrent rate in the same situation higher than this. They studied 87 CIN2,3 patients who had at least 1 follow-up cervical cytology smear and colposcopy and noted that 10 patients (8.7%) developed recurrence of HSIL (Fadare et al., 2008). The difference of recurrent rate probably from many aspects such as the sample size and the follow up time.

In the current study, 3 of 5 patients with subsequent abnormal cervical smear revealed cervical dysplasia from the biopsy at 7,14 and 45 months after initial LEEP. Some authors defined the abnormal cytology or histology that occurred within 1 year as the persistent disease and defined such abnormal that happened after that as the recurrent disease (Gold et al.,1996). With this definition, only 1 patient in our study demonstrated persistent disease.

The methods that were recommended for surveillance post CIN-treated with LEEP consisted of cervical cytology, colposcopy, endocervical curettage (ECC) and human papilloma virus testing (Bornstein et al., 2004). The guidelines for clinical practice using to follow-up patients treated for CIN 2, 3 according to British National Health System's Cervical cytology was followed with Pap smear at 6 months after treatment and then annually for 5 years. If all results are persistently negative, the patients should be followed up every 3 years (Bornstein et al., 2004). However, the American Society Colposcopy and Cervical Pathology (ASCCP) is recommended to follow-up with either cytology with or without colposcopy every 4-6 months until 3 consecutive negative smear, then

annually check up or using HPV testing and if it shows neagitive result, the patients could be yearly check up with Pap smear (Wright et al.,2007). In our center, the policy for surveillance the high grade lesion patients who previously completed resection with LEEP is follow – up with Pap smear every 4-6 months until 5 years and if the smear revealed abnormal, the colposcopic examination was done after that. In addition, some author suggested that the patietns with CIN 2,3 who treated with LEEP should be followed by performing Pap smear and colposcopy every 6 months for a peroid of 3 years(Bornstein et al.,2004). We did not use HPV testing as routine follow-up because of its high cost and did not routinely performing ECC or endocervical cytobrush in patients who revealed negative endocervical margin from LEEP specimens.

About the risk factors of persistent of recurrent disease in patients who diagnosed HSIL and were completely excised with LEEP, Paraskevaidis et al mentioned that the older age over 40 years, the glandular involvement and the satellite lesions were related to increase the reappearance of cervical dysplasia after loop excision with uninvolved margin (Paraskevaidis et al.,2000). In our study, among the 3 subsequent positive histology, the age of 2 patients who revealed recurrence HSIL were 39 and 40 years, respectively while the age of 1 recurrence LSIL was 20 years. None of them was revealed glandular involvement lesion. Two patients who occurred recurrent HSIL and LSIL in each had the lesion confined in 4 quadrants and the remaining 1 recurrent HSIL patient had initial involvement lesion in single quadrant of original LEEP specimen. We could not analyse the risk for development of recurrence disease in our data due to the small number of recurrent patients.

Gold et al (1996) noted that re-LEEP can be used as the treatment of recurrent high grade cervical dysplasia They revealed that 13 of 18 (72%) patients were successfully treated with LEEP again after re-development of HSIL. With the small number of patients, they also suggested that the larger study populations would be needed to clarify the proper treatment in these recurrence patients. In the present study, we performed re-LEEP in both patients with recurrence HSIL eventhrough 1 of them had previous twice times of LEEP. In our center, if no other indication for hysterectomy, we usually treated persistent or recurrence high grade lesion with re-LEEP except its could not be done due to the small remaining cervix.

The limitation of the present study was the short median time of follow- up as only 12 months and the majority of patients did not completely followed-up according to the surveillance programme. If we extend the followed up time or persued most of the lost follow-up patients, it probaple increases the number of recurrence patients.

In conclusion, the recurrence rate of cervical dysplasia in patients with high grade disease who treated with LEEP excision and revealed clear margins was as low as 1%. However, with the limitation of this study as mentioned above, we suggested that the closed surveillance of these patients is recommended.

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