RESEARCH COMMUNICATION

Clinicopathologic Predictors of Incomplete Excision after Loop Electrosurgical Excision for Cervical Preneoplasia

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Abstract

The aim of this study was to identify the factors affecting incomplete excision after the loop electrosurgical excision procedure (LEEP) for evaluation and treatment of cervical neoplasia. Patients with abnormal cervical cytology who underwent colposcopy and LEEP at Chiang Mai University Hospital between October 2004 and July 2005, were retrospectively evaluated. During the study period, 201 patients were eligible for analysis. All cone margin involvement was observed in 44% of the patients (95% CI, 37.3-51.4). Multivariate analysis revealed that invasive cancer on cytology (adjusted odds ratio [aOR] =3.05, 95% confidence interval [CI] =1.03 to 9.00; P=0.02), invasive cancer on LEEP histopathology (aOR=9.73, 95%CI =3.95 to 23.9; P<0.001), and a cone length of less than 10 mm (aOR =1.95, 95%CI =1.04 to 3.66; P =0.03) were significant predictors for any cone margin involvement. For endocervical margin involvement, postmenopausal status and a cone length of less than 10 mm were significant predictors of incomplete excision. In contrast to endocervical margin involvement, postmenopausal status was significantly associated with a decreased risk of ectocervical margin involvement. Invasive cancer on histopathology was a significant predictor of both ecto- and endocervical margin involvement. In conclusion, invasive cancer either on cytology or LEEP specimens and a cone length of less than 10 mm are significant predictors of incomplete excision.

Key Words: Loop electrosurgical excision procedure - cone margin - cervical neoplasia - multivariate analysis.

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Introduction

Cervical cancer is a major global health burden. Worldwide, an estimated 470,000 new cases occur annually, of which nearly half die. In addition, approximately 80% of these deaths occur in developing countries, where, resources are limited (Ferlay et al., 2000). Among Thai women, cervical cancer is the most common cancer with an age standardized incidence rate (ASR) of 19.5 per 100,000 person-years. The incidence is highest in Chiang Mai, a northern province of Thailand, with an ASR of 25.6 followed by Lampang (ASR=23.6), Bangkok (ASR=20.7), Songkhla (ASR=16.1), and Khon Kaen (ASR=15.0) (Pengsaa et al., 2003).

The comprehensive strategy for cervical cancer prevention must take into account the two critical processes that make up an effective program i.e. early detection and prompt treatment of its precursor disease. Although there are various methods being developed for detecting the precancerous lesions of the cervix, cervical cytology is still the principal technique. Once abnormal cytology is detected, these women then need proper investigation and treatment.

Since loop electrosurgical excision procedure (LEEP) was introduced by Prendiville in 1989 for the evaluation and treatment of cervical neoplasia (Prendiville et al., 1989), this procedure rapidly gained acceptance because it provided specimens of histopathologic examination, had a high success rate, and low surgical morbidity (Wright et al., 1993).However, the detection of histologic incomplete excision of cervical neoplastic epithelium has been reported in a considerable high proportion of cases. Several studies reported an incomplete excision as a significant risk factor for persistence, recurrence of cervical dysplasia after LEEP (Zaitoun et al., 2000, Fogle et al., 2004, Brochmeyer et al., 2005).Thus, it would be beneficial to know which patients are at higher risk for incomplete excision. The identification of predictive factors would provide the surgeon with guidelines for decision making on treatment strategies, including use of an appropriate surgical technique to minimize an incomplete excision rate, post-treatment surveillance and patient counseling before the operation. This study was undertaken accordingly to identify the factors affecting incomplete excision after LEEP for the diagnosis and treatment of cervical neoplasia.

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Materials and Methods

Selection of Patients

Patients with abnormal cervical cytology who underwent LEEP at Chiang Mai University Hospital were eligible for the study. Between October 2004 and July 2005, a total of 210 patients were identified. However, nine patients were excluded because of no abnormal cervical epithelium on LEEP specimens (7) and undetermined margin status from severe thermal artifact (2). Accordingly, 201 patients were analyzed. Abstracted data included patient characteristics, abnormal cervical cytology results, indications of the operation, colposcopic findings, histopathology of LEEP specimens, and cone margin status.

Operative and Histopathologic Technique

LEEP was performed in the outpatient department under local anesthesia by fellows and staffs of the Gynecologic Oncology Division. Colposcopy was performed prior to LEEP and Lugol iodine solution was used to delineate the area of neoplastic epithelium. The diameter of the loop was selected depending on the extent of the lesion, with the largest being 25 mm in diameter. The specimens were marked for correct orientation by their clock face position and were routinely cut in parallel slices at a maximum thickness of 2-3 mm. Additional sections were obtained from suspicious areas. LEEP histopathology was evaluated by the gynecologic pathologists at our institution. Cone margin involvement was defined as the presence of neoplastic epithelium of any grade at the margin by histopathologic examination. In our study, cone margin involvement was classified into four categories :(1) ectocervical margin involvement (2) endocervical margin involvement (3) both ecto- and endocervical margin involvement, and (4) any margin involvement.

Statistical Analysis

Nine clinical and pathological variables including age, parity, menopausal status, HIV status, invasive cancer on cervical cytology, colposcopic findings, maximum cone base diameter, cone length, and invasive cancer on LEEP histopathology were analyzed for predictive significance of each involved cone margin. The chi-square or Fisher's Exact test was used to univariately identify those factors which related to incomplete excision after LEEP. For significant factors in a univariate analysis, a multivariate analysis using a logistic regression model was further fitted to find independent risk factors. An odds ratio, with a 95% confidence interval that did not include unity, was considered statistically significant. All statistical tests were two sided and a P value of less than .05 was considered statistically significant.

Results

The median age of the 201 patients was 43 years with a range of 26-72 years. Fifty-five (26.9%) patients were menopausal. The majority of patients (93.5%) were multiparous. Thirteen (6.5%) patients had a positive screening for HIV status. During colposcopy, unsatisfactory findings and lesions involving ≥ 3 quadrants were noted in 98 (48.7%) and 36 (17.9%) patients, respectively. Of 201 LEEP specimens, 163 (81.1%) had a maximum cone base diameter more than 20 mm, 130 (64.7%) had a cone length more than 10 mm. Forty-two (20.9%) patients had invasive lesions on cone histopathology. The frequency of cone margin involvement was 44.3% (95% CI, 37.3-51.4). The distribution of abnormal cervical cytology, indications for LEEP, and frequency of cone margin involvement are summarized in Table 1.

For any cone margin involvement, univariate analysis revealed that invasive cancer on cytology, cone length less than 10 mm, and invasive cancer on LEEP histopathology were found to be significant factors as shown in Table 2. Postmenopausal status, invasive cancer on cytology, cone length of less than 10 mm, and invasive cancer on LEEP histopathology were significant predictors for positive endocervical margin. Postmenopausal status and invasive cancer on LEEP histopathology were significantly associated with ectocervical involvement and both margin involvement, respectively.

Multivariate analysis using a logistic regression model, which included all the above significant covariates, was performed and summarized in Table 3. For all cone margin involvement, invasive cancer on cytology, cone length of less than 10 mm, and invasive cancer on LEEP histopathology remained statistically significant predictors of incomplete excision. In the group of endocervical margin

Table 1. Clinical Characteristics of the 201 Patients

Characteristics	N (%)
Severity of abnormal cervical cytology	
HSIL	111 (55.2)
LSIL	25 (12.4)
SCCA	20 (10.0)
ASC H	17 (8.5)
Others	28 (13.9)
Indications for LEEP	
HSIL on cervical cytology	81 (40.3)
HSIL on colposcopic biopsy	67 (33.3)
Unsatisfactory colposcopy	35 (17.4)
Suspicion of MIC	14 (7.0)
Others	4 (2.0)
Cone margin involvement	
Absence	112 (55.7)
Endocervical margin	40 (19.9)
Ectocervical margin	23 (11.4)
Both margins	26 (12.9)

HSIL = High grade squamous intraepithelial lesion
LSIL = Low grade squamous intraepithelial lesion
SCCA = Squamous cell carcinoma
ASC H = Atypical squamous cells cannot rule out high grade squamous intraepithelial lesion
MIC = Microinvasive carcinoma
Both margins = Concurrent ectocervical and endocervical cone margin involvement

Table 2. Significant Variables Associated with Cone Margin Involvement from Univariate Analysis

Margin involvement	Variables	Category	N (%)	P-value
Any margin (N=89)	Invasive cancer cytology	Presence	15/21 (71.4)	0.01
		Absence	74/180 (41.1)	
	Cone length (mm)	<10	39/71 (54.9)	0.02
		≥10	50/130 (38.5)	
	Invasive cancer histology	Presence	35/42 (83.3)	<0.001
		Absence	54/159 (33.9)	
Endocervical only (N= 40)	Menopausal status	Postmenopausal	19/54 (35.2)	<0.001
		Premenopausal	21/147 (14.3)	
	Invasive cancer cytology	Presence	8/21 (38.1)	
		Absence	32/180 (17.7)	0.03
	Cone length (mm)	<10	23/71 (32.4)	
		≥10	17/130 (13.8)	<0.001
	Invasive cancer histology	Presence	14/42 (33.3)	
		Absence	26/159 (16.3)	0.02
Ectocervical only (N=23)	Menopausal status	Postmenopausal	2/54 (3.7)	
		Premenopausal	21/147 (14.3)	0.02
Both margins (N=26)	Invasive cancer histology	Presence	14/42 (33.3)	
		Absence	12/159 (7.5)	<0.001

Table 3. Logistic Regression Model of Significant Covariates Associated with Cone Margin Involvement

Margin involvement	Variables	Adjusted odds ratio	95% CI low-high	P-value
Any margin	Invasive cancer cytology	3.05	1.03-9.00	0.02
	Cone length < 10 mm	1.95	1.04-3.66	0.03
	Invasive cancer histology	9.73	3.95- 23.9	< 0.001
Endocervical only	Postmenopause	2.37	1.09-5.15	0.02
	Cone length < 10 mm	3.19	1.48-6.90	0.003
Ectocervical only	Postmenopause	0.23	0.05-0.91	0.02
Both margins	Invasive histopathology	6.13	2.36-16.0	<0.001

involvement, only the postmenopausal status and cone length of less than 10 mm were significant predictors of incomplete excision. Postmenopausal status and invasive cancer on LEEP histopathology were independent predictors for ectocervical involvement and both ecto/endocervical margin involvement, respectively.

Discussion

Although LEEP is widely accepted for the diagnosis and treatment of cervical neoplasia because of its simplicity and efficiency, incomplete excision of neoplastic epithelium is not uncommon and may cause problems in clinical management. Recently, several studies reported that an involvement of cone margin resulted in significantly higher risk of developing persistent and recurrent cervical dysplasia after LEEP (Zaitoun et al., 2000, Fogle et al., 2004, Brochmeyer et al., 2005).

Murdoch et al (1992) attempted to investigate an association between various clinical variables and cone margin involvement after cervical loop excision. They found that incomplete excision was more likely with more severe lesions, extensive lesions, and involvement of the endocervical canal from univariated observation. Costa et al (2000) used univariate and multivariate logistic regression analysis in a retrospective study of 718 patients to determine the factor that might predict cone margin involvement after LEEP. These authors concluded that histological diagnosis of cone specimens and surgical experience were strong predictors for cone margin involvement including both endocervical and all margins.

In this study, we systematically evaluated demographic, colposcopic, and histopathologic variables for determination of their relationship to cone margin involvement after LEEP. A multivariate analysis revealed that invasive cancer on cervical cytology, invasive cancer on LEEP histopathology and cone length of less than 10 mm were significant predictors for any cone margin involvement (P=0.02, P<0.001, and P=0.03 respectively). In postmenopausal status, an affected transformation zone tended to recede into the deep cervical os. Therefore, it was not surprising that the postmenopausal status, from our multivariate analysis, was an independent predictor of endocervical margin involvement (P=0.02), since patients were almost 2.5 times to have this positive site. In addition, cone length of less than 10 mm had 3.2 times increase in probability of incomplete excision for this margin. These findings indicated that an increasing value of cone depth, if possible, should be performed to reduce the incidence of endocervical margin involvement, especially in postmenopausal patients who carry a higher risk.

For ectocervical margin involvement, the postmenopausal status had an inverse association, with a 77% reduction of incomplete excision rate (P=0.02). This

finding may be secondary to the postmenopausal change of the cervical transformation zone, resulting in neoplastic lesions that are more likely to confine within the deep endocervical canal, thereby providing more chance to tailor the ectocervical lesions completely. Although an increasing diameter of cone base may be expected to reduce risk of ectocervical cone margin involvement, our study has failed to observe this association. However, this negative finding needs to be considered cautiously as almost all cone specimens (81%) in our series had a maximum cone base of at least 20 mm, which may result in no statistical impact on the status of ectocervical cone margin.

Because of its extensive and severe natural course, the presence of invasive cancer on LEEP histopathology was a strong predictor of positive either one or both margins. Patients with invasive lesions on their cone histopathology showed a 9 and 6 times increase in probability of positive either one or both margins, respectively.

In our series, the incidence of cone margin involvement was 44.3% which was similar to other reported incidence that ranged from 16-44% (Zaitoun et al., 2000, Murdoch et al., 1992., Costa et al., 2000, Lapaquette et al., 1993, Chan et al., 1997). However, it should be noted that 20.9% of the patients in our study had invasive cancer on LEEP histopathology, which was a higher than those previously reported at 0-6% (Zaitoun et al., 2000, Murdoch et al., 1992., Costa et al., 2000, Lapaquette et al., 1993, Chan et al., 1997, Prendiville, 1995). The observed frequent occurrence may be due to one-step or "see and treat" approach in our institute. This greater incidence of invasive cancer on LEEP histopathology, which was the strongest predictor from our multivariated observation, would inevitably pose an adverse impact on our cone margin involvement rate. Therefore, a direct comparison between case series with different histopathologic composition may be unwarranted.

In conclusions, this study revealed that invasive cancer either on cytology or LEEP specimens and cone length of less than 10 mm are significant predictors for histologic incomplete excision after LEEP.

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