RESEARCH COMMUNICATION

Factors Predicting Occult Invasive Carcinoma in Women Undergoing a "See and Treat" Approach

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Abstract

This study was undertaken to evaluate the incidence and independent predictors of unexpected invasive cancer of cervix in women with high-grade squamous intraepithelial lesions (HSIL) on Pap smear who had undergone "see and treat" approach. Women with HSIL on cervical cytology undergoing colposcopy, followed by loop electrosurgical excision procedure (LEEP) at Chiang Mai University Hospital between January 2001 and April 2006 were analyzed. During the study period, 446 women were identified. Mean age was 45.6 years (range, 25-78 years). One hundred and twenty-one (27.1%) women were postmenopausal. Unsatisfactory colposcopy was observed in 357 (80.0%) women. Of the 446 women, 76 (17.04%, 95% CI= 13.67 to 20.86) had invasive lesions on LEEP specimens. Multivariate analysis revealed that unsatisfactory colposcopy and premenopausal status were statistically significant independent predictors for invasive lesion on "see and treat" LEEP with an adjusted odds ratio of 4.68 (95%CI=1.82 to 12.03, P< 0.01) and 2.10 (95%CI=1.12 to 3.94, P=0.02), respectively. In conclusion, occult invasive lesion of the cervix was noted in 17% of women with HSIL Pap smear who underwent "see and treat" approach at our institute. Unsatisfactory colposcopy and premenopausal status were significant independent predictors of having such lesion.

Key Words: LEEP - HGSIL - cervical cancer - predictor - 'see and treat'

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Introduction

The "see and treat" approach is an immediate treatment of cervical intraepithelial neoplasia in which women with abnormal Pap smear undergo colposcopy followed by loop electrosurgical excision procedure (LEEP) without intervening tissue diagnosis. The most significant advantage of such approach is the dual role of both histological diagnosis and treatment in one step management resulting in reduction of both patient visits and time interval from diagnosis to definite treatment. Additionally, it also provides accurate histological diagnosis, decrease in cost, and greater patient convenience. The incidence of overtreatment which defines as negative LEEP histology is considerably low when this policy is strictly implemented in women with Pap smear suggesting high-grade squamous intraepithelial lesions (HSIL) at a range of only 0% to 8% (Irwin et al., 2002, Dunn et al., 2003, Charoenkwan et al., 2004, Numnum et al., 2005).

In our institute, the "see and treat" strategy for women with HSIL on Pap smear has almost entirely replaced the traditional two-step approach which requires the confirmed histological diagnosis with colposcopically-directed biopsy before LEEP. Recently, we reported our experience in the "see and treat" approach, the impressive results were that 96% of women had high-grade lesion or higher and none had negative histology on LEEP specimens (Charoenkwan et al., 2004). In such study, however, we observed an extraordinary high prevalence of invasive lesions (20%) on LEEP specimens. The application of LEEP in case of occult invasive cancer may cause problems in clinical management. Difficulty in orientation of LEEP specimens obtained by multiple passes and the high rate of transection of invasive foci may result in the inability to evaluate tumor depth and width accurately. Therefore, it would be beneficial to know which women are at higher risk of having occult invasive lesions. The identification of predictor would provide the surgeon with information to avoid the aforementioned dilemma. Accordingly, this study was undertaken to evaluate the predictors of unexpected invasive cancer discovered by LEEP in women with HSIL on Pap smear who underwent "see and treat" approach.

Materials and Methods

Selection of patients

The medical records of patients with HSIL on Pap smear who underwent colposcopy followed by LEEP

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without either a prior histological diagnosis of cervical neoplasia or suspicion of invasive cancer at the Department of Obstetrics and Gynecology, Chiang Mai University Hospital between January 2001 and April 2006 were reviewed. At our institute, Human immunodeficiency virus (HIV) infection was routinely screened before colposcopy. Abstracted information included general characteristics, the status of HIV infection, colposcopic findings, size and detailed histological results of LEEP specimens. Staging methods of invasive cervical cancer was clinically made according to the classification of the International Federation of Gynecology and Obstetrics (FIGO).

Operative and Pathologic Report

LEEP was performed at outpatient department under local anesthesia. The dimension of the loop was selected depending on the extent of the lesion. The largest is 25 mm in diameter. The electrical power was set to 60 watts cut and 40 watts coagulation in blended mode. We attempted to remove the entire lesions in a single pass. If the first pass failed to remove the entire lesion, the second or third pass would be carried out.

LEEP margin status was classified into three categories: (1) negative margin, (2) positive margin, (3) non-evaluable margin. Negative margin was defined as the absence of dysplastic epithelium at all cone margins by histopathologic examination. Positive margin was defined as the presence of dysplastic epithelium of any grade at any cone margin. Non-evaluable margin was defined as of at least one margin could not be evaluated margin status while other margins were negative.

Statistical Analysis

The chi-square or Fisher exact test were used to univariately identify factors related to the presence of residual disease. For those factors with a P value of less than .10 in univariate analysis, a multivariate analysis using logistic model was further used to find the independent factors. An odds ratio, with a 95% confidence interval that did not include unity, was considered statistically significant.

Results

During the study period, 446 women with HSIL on Pap smear who underwent "see and treat" approach were reviewed. Mean age of the study population was 45.6 years (range, 25-78 years). Twenty-five (5.61%) women were nulliparous. Mean parity among the remaining 421 multiparous women was 1.94 (range, 1-14). One hundred and twenty-one (27.1%) women were postmenopausal. Unsatisfactory colposcopy was observed in 357 (80.0%) women. Cone dimension measurement was not available in 21 women. Mean cone base and length among the remaining 425 LEEP specimens were 23.12 mm and 8.70 mm, respectively. Multiple passes was noted in 133 (29.8%) women with an average of 1.3 slices. LEEP margin involvement was observed in 239 (53.59%) women.

Of the 446 women, 76 (17.04%, 95% CI= 13.67-20.86) had invasive lesion, 330 (74.0%) had HSIL, 9 (2.0%) had LSIL, 5 (1.1%) had adenocarcinoma in situ (AIS), and 26 (5.8%) had no lesion on LEEP specimens. Among 76 women who had invasive lesion, 72 had squamous cell carcinoma (51 stage IA1, 6 stage IA2, and 15 stage IB1) and the remaining 4 had adenocarcinoma (2 stage IA1, 2 stage IA2).

The comparisons of baseline characteristics between women who had invasive lesion on LEEP specimens and

Table 1. Clinical Characteristics Stratified by the Presence of Cancer on LEEP Specimens

Characteristics	With cancer (N=76)	Without cancer (N=370)	P-value
Age (years)	44.87 ± 7.67	45.69 ± 9.25	0.47
Parity	1.83 ± 1.05	1.96 ± 1.31	0.41
Cone base (mm)	24.16 ± 5.86	22.91 ± 5.47	0.08
Cone length (mm)	9.10 ± 3.56	8.62 ± 3.46	0.29
Symptoms at screening			
Absence	64 (84.21)	330 (89.19)	0.44
Abnormal bleeding*	5 (6.58)	19 (5.14)	
Abnormal discharge*	5 (6.58)	11 (2.97)	
Other symptoms	2 (2.63)	10 (2.70)	
Colposcopic lesion size			
Unsatisfactory	71 (93.42)	286 (72.29)	0.003
1 – 2 quadrants	4 (5.26)	30 (8.11)	
3 – 4 quadrants	1 (1.32)	54 (19.60)	
Multiple LEEP passes	27 (35.53)	106 (28.65)	0.73
LEEP margin status			
Negative	15 (19.74)	176 (47.57)	<0.001
Positive	60 (78.95)	179 (48.38)	
Non – evaluable	1 (1.31)	15 (4.05)	

* Vaginal

Table 2. Univariate and Multivariate Analyses for Predictors of the Presence of an Invasive Lesion

Variables	Number (%)	Univariate P-value	Multivariate OR (95% CI)	Multivariate P-value
Colposcopic findings				
Unsatisfactory	71/357 (19.9)	<0.01	4.68 (1.82-12.0)	<0.01
Satisfactory	5/89 (5.62)		Reference	
Menopausal status				
Premenopausal	62/325 (19.1)	0.06	2.10 (1.12-3.94)	0.02
Postmenopausal	14/121 (11.6)		Reference	
Age (years)				
≥ 60	3/27 (11.1)	0.59	Variable removed	
< 60	73/419 (17.4)			
Parity				
Nulliparous	4/25 (16.0)	1.00	Variable removed	
Multiparous	72/421 (17.1)			
HIV infection				
Positive	1/16 (6.25)	0.33	Variable removed	
Negative	75/430 (17.4)			

Table 3. Probability of Invasive Lesions Stratified by Colposcopic Findings and Menopausal Status

Conditions	Number	Percentage
Unsatisfactory colposcopy (N=357)		
Premenopausal	57/248	23.0
Postmenopausal	14/109	12.8
Satisfactory colposcopy (N=89)		
Premenopausal	5/77	6.5
Postmenopausal	0/12	0.0

those without invasive lesion are displayed in Table 1. The incidence of unsatisfactory colposcopy and LEEP margin involvement were significantly higher in women with invasive lesions (P=0.003 and P<0.001, respectively).

Five clinical variables including age at LEEP, parity, menopausal status, status of HIV infection, and colposcopic finding were analyzed for predictive significance of the presence of invasive lesion on LEEP specimens. Univariate analysis revealed that unsatisfactory colposcopic finding and premenopausal status were found to have a P-value of less that 0.10. Multivariate analysis using a logistic regression model which included those 2 significant covariates was performed. Both unsatisfactory colposcopy and premenopausal status remained statistically significant predictors for invasive lesion on the "see and treat" LEEP (Table 2).

Table 3 displays the probability of having invasive lesions stratified by colposcopic finding and menopausal status.

Discussion

Because of its simplicity and efficiency, LEEP is the most preferred conization method in our institute. However, multiple passes of LEEP are frequently carried out to excise the entire suspected lesions. Tseng et al (1999) reported that the fragmentation of LEEP specimens was noted in 23% of women with an average of 1.3 slices. Naumann et al (1994) reported that cervical lesion was completely excised with a single pass LEEP in only 29% of the study population, with an average slice of 2.1. In the present study, multiple passes of LEEP was performed in approximately 30% of women. The multiple passes may raise the problem in women with occult cervical cancer if the invasive foci are transected. Tseng et al (1999) noted that the multiple passes of LEEP resulted in the pathological measurement of depth and width of invasive lesion was undetermined in 2 patients. Eddy et al (1994) reported 2 women whose dimension of invasive lesion on their conization specimens could not be assessed accurately due to the transection of invasive foci by LEEP. Several studies demonstrated that conization specimens obtained from cold-knife conization (CKC) technique were significantly larger in both cone base and length, had a lower incidence of either non-evaluable cone margin status or multiple slices than those obtained from LEEP (Giacalone et al., 1999, Huang and Hwang, 1999, Fanning and Padratzik, 2002). Thus, CKC may be a preferred conization procedure for women who possibly have occult invasive lesion of the cervix rather than LEEP. This suggestion was recently supported by the study of Tseng et al (2006) which found that 11.4% of LEEP specimens had specimen disorientation, had a limitation of stromal invasion evaluation due to transection of invasive foci as opposed to none in the CKC specimens.

In the present study, the incidence of occult invasive lesion on "see and treat" LEEP was 17% which was considerably higher than those reported which ranged from 0 % to 3 % (Irwin et al., 2002, Dunn et al., 2003, Numnum et al., 2005). This observation may reflect the high incidence of cervical cancer in the northern region of Thailand which is secondary to the limitation of national screening program.

In this study, unsatisfactory colposcopy (P<0.01) and premenopausal status (P=0.02) were significant independent predictors for having such lesions. Women with unsatisfactory colposcopy were approximately 4.7 times increase in the probability of harboring invasive lesion on the "see and treat" LEEP. The accuracy of colposcopic evaluation is utmost limited in women with unsatisfactory findings because the entire cervical lesion could not be seen. Consequently, there is a higher chance to have unexpected invasive lesions compared to those women with satisfactory colposcopy whose cervical lesions could be completely evaluated. If women with unsatisfactory colposcopy in the present study were eliminated from the analysis, the incidence of unexpected invasive lesion on the "see and treat" LEEP would be reduced to only 5.6%. Based on our finding, therefore, the "see and treat" LEEP may not be appropriate in women with HSIL Pap smear who had unsatisfactory colposcopy due to its high incidence of unexpected invasive lesions.

In this study, premenopausal women had 2 times increased in the chance of having invasive lesion on LEEP specimens after "see and treat" management compared to postmenopausal group. Ferenczy et al (1997) reported that the incidence of high-risk human papillomavirus (HPV) infection among postmenopausal women was rare, irrespective of the hormonal therapy status. Additionally, Sawaya et al (2000) noted that the majority of menopausal women with abnormal cervical smears had negative evaluation. These would theoretically put postmenopausal women at the lower risk of having severe cervical lesion such as invasive disease than that observed in the premenopasual group.

We recently reported that the presence of invasive lesions on LEEP specimens was a significant independent predictor for positive cone margin after LEEP. Women with such lesions on their cone specimens showed a 9 times greater in probability of having positive LEEP margin (Kietpeerakool et al., 2005). Unsurprisingly, women with occult invasive cancer in the present study had a significant higher incidence of LEEP margin involvement compared to those without cancer.

In conclusion, occult invasive lesion of the cervix was noted in 17% of women with HSIL Pap smear who underwent "see and treat" approach at our institute. Unsatisfactory colposcopy and postmenopausal status were significant independent predictors of having such lesion.

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