RESEARCH COMMUNICATION

Positive Margin Prevalence and Risk Factors with Cervical Specimens Obtained from Loop Electrosurgical Excision Procedures and Cold Knife Conization

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Abstract

Objectives: To determine the prevalence and predictive factors of residual disease in the specimens from cold knife conization (CKC) or the loop electrosurgical excision procedure (LEEP) and complication rates of these procedures. Design: Descriptive analytical study in Srinangarind Hospital, Khon Kaen, Thailand, of a total of 463 patients with abnormal Pap smears who underwent LEEP or CKC during 2002-2007. Methods: The medical records of 463 women were retrospectively reviewed to ascertain the prevalence, associated factors of positive surgical margin, and complications of LEEP and CKC. The patients' characteristics and pathologic parameters were collected and analyzed. Univariate analysis was based with the chi-square test and the Student's t-test. Multiple logistic regression models were employed to investigate factors associated with cone margin involvement. Results: Of the 463 patients, 124 cases had a positive cone margin (26.8%). 53 patients had complications (11.4%), such as bleeding (25) and infection (28). The margin involvement was significantly associated with type of conization, purpose of conization, skill of surgeon, and histological diagnosis. Conclusion: The prevalence of a positive cone margin is rather high. Physicians who perform conization should take into account risk factors in management of cases with abnormal cytological screening for cervical cancer.

Key Words: Cervical intraepithelial neoplasia - cold knife conization - LEEP - positive margin

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Introduction

Cervical cancer is a common disease worldwide. It is a leading cause of cancer-related death for women in developing countries.(Shanta et al., 2000) In Thailand, the prevalence of cervical cancer varies from 9.13 to 20.9 per 100,000.(Vatanasapt et al., 1995;Chichareon, 1993) The cervical cancer is considered as a preventable cancer because it has a long period of precancerous lesion. Cervical cancer screening strategy, for example cytology screening and visual inspection of the cervix with acetic acid (VIA) are effective method for detecting the premalignant lesions (Goldie et al., 2005; Deerasamee et al., 2007).

In recent years, an increased prevalence of precancerous lesion of cervix, so called cervical intraepithelial neoplasia (CIN), has been observed worldwide (Parkin et al., 1982; Armstrong et al., 1986; Mitchell and Medley, 1990; Cecchini et al., 1995; Miller et al., 1996; Giannopoulos et al., 2005; Reece, 2007). There are many treatment options for the precancerous lesions varying from ablative methods, i.e. cryotherapy, electrocautery and laser vaporization, to excisional methods, i.e. cold knife conization (CKC), laser conization and the loop electrosurgical excision procedure (LEEP) (Lindeque, 2005; Jordan et al., 2008), these being popular as both diagnostic and therapeutic procedures for the management of patients with CIN, in particular those young patients wishing to preserve reproductive function. However, there is evidence to suggest that patients with positive cone margins have significantly higher chances of having disease persistence and/or progression to squamous cell carcinoma than those with negative margins (Marana et al., 2001; Costa et al., 2009). Therefore, great attention has been focused on the possibility of complete excision of a CIN lesion by these procedures. Several studies have reported the prevalence of positive surgical margin, varying from 27 to 42.2% (Im et al., 1995; Denehy et al., 1997; Costa et al., 2000; Fan et al., 2001; Sun et al., 2009). The difference may be explained by the different place, histological type, and studied population. At Srinagarind Hospital, a referral center of the North-east part of Thailand, Khon Kaen University, there had been no information regarding the prevalence and risk factors of the positive surgical margin of cervix obtaining from LEEP or CKC. Therefore, the purposes of the present study were to ascertain the prevalence and risk factors of positive excisional margin of CKC and LEEP specimens, and prevalence of complications related to these procedures.

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Materials and Methods

Medical records of women who underwent either LEEP or CKC at the Department of Obstetrics and Gynecology, Srinangarind Hospital during January 2002 to December 2007 were retrospectively reviewed under permission of Ethic Committee of Faculty of Medicine, Khon Kaen University. All included patients had either abnormal cervical cytology or positive endocervical curettage, and subsequently underwent colposcopic examination before performing the conization. Patient who had insufficient information in her medical recorded was excluded. The types of the conization including in the study were LEEP and CKC. Indications for the CKC included unsatisfactory colposcopic findings, positive endocervical curettage, suspicion of microinvasive disease, and discrepancies of greater than two levels between results of Papaniculaou smear (Pap smear) and colposcopic directed biopsy. Data on patients' characteristics, previous cytological report, colposcopic finding and complication were extracted from the medical records.

As our routine practice, all conization and LEEP specimens were measured and fixed in formalin and processed in a standard fashion. The specimens were submitted for histopathologic examination including maximal neoplastic severity and extension to margins. All histological slides were reviewed by an experienced pathologist at the Department of Pathology, Faculty of Medicine, Khon Kaen University.

A positive surgical margin was defined as the presence of cervical intraepithelial neoplasia or invasive cancer at edges of the specimens. Continuous variables are presented as mean ± SD. Categorical variables are presented as numbers of cases or percentages. Univariate analysis was based on either the chi-square test or student t- test where appropriate. To evaluate the risk factors associated with the positive surgical margin, multiple logistic regression analysis was used. The decision about which variables to include in the logistic regression models involved consideration of results from our own univariate analyses. For all statistical tests, p-value less than 0.05 were considered significant.

Table 1. Surgical Margin Status (N=463)

Status	LEEP & CKC	LEEP	CKC
Free margin	339 (73.2)	178 (66.2)	161 (83.0)
Positive margin	124 (26.8)	25 (9.3)	33 (17.0)
Ectocervical	42 (9.1)	39 (14.5)	17 (8.8)
Endocervical	50 (10.8)	91 (33.8)	11 (5.7)
Deep or stromal	2 (0.4)	2 (0.7)	0 (0.0)
Multiple	30 (6.5)	25 (9.3)	5 (2.5)

Table 2. Factors Associated with a Positive Margin

Parameter	LEEP & CKC		LEEP		CKC	
Age	0.313	NA	0.502	NA	0.062	NA
Parity	0.015	0.442	0.122	NA	0.401	NA
Menopausal status	0.222	NA	0.926	NA	0.170	NA
Pap smear result	0.047	0.873	0.207	NA	0.105	NA
Satisfactory level of colposcopic findings	0.250	NA	0.229	NA	0.007	0.490
Conization purpose	0.001	<0.001	0.279	NA	<0.001	0.015
Skill of surgeon	0.004	0.014	0.739	NA	0.162	NA
Histodiagnosis	<0.001	<0.001	<0.001	0.001	<0.001	<0.001
Type of procedure	<0.001	<0.001	NA	NA	NA	NA

Table 3. Complications of Conization (N=463)

Status	LEEP & CKC	LEEP	CKC
Bleeding	25	11	14
Infection	28	11	17
Total	53	22	31

Results

From January 2002 to December 2007, data of 463 patients were available for analysis. Mean age (+SD) of the patients was 43.8(+9.0) years. The majority of the patients were multiparity (94.8%) and premenopausal (78.8%). The most common preoperative cervical cytology was high-grade squamous intra-epithelial lesion (HSIL) up to 263 cases (56.8%). 189 (40.8%) of cases had unsatisfied colposcopic findings. 194 patients (41.9%) underwent CKC while 269 patients (58.1%) underwent LEEP. The procedures were performed for diagnosis in 285 patients, for treatment in 55 patients, and for both diagnostic and therapeutic purposes in 123 patients.

Table 1 shows margin status of cone specimens. 124 of 463 the specimens had positive margin for either CIN or invasive cancer. Therefore, the prevalence was 26.8%. The most common site of involved margins was ectocervix (50/124 or 40.3%). The prevalence of margin involvement was significantly higher in LEEP than that in CKC.

Table 2 shows the associated factors for the positive surgical margins. Univariate analysis showed that the margin involvement in the conization procedures was significantly associated with parity, Pap smear result, purpose of conization, surgeon skill, type of conization, and histological diagnosis. However, parity and Pap smear result were no longer associated with the margin involvement by multiple regression analysis. As LEEP and CKC were different in clinical perspective, subgroup analysis was performed. Positive cone margin obtained from LEEP was significantly associated with histological diagnosis. For CKC, the associated factors were surgeon skill, and histological diagnosis.

Table 3 shows complication rate of conization. Complications of the conization procedures were reported in 53 patients (11.4%). Bleeding and infection were found in 25 (5.4%) and 28 (6%) cases, respectively. The rates of bleeding and infection were significantly higher in CKC than those in LEEP.

Discussion

The positive surgical margin in this study was common. More than one fourth of cone specimens obtained from CKC and LEEP had margin involvement. When combined the data of CKC and LEEP, purpose of conization, surgeon skill, type of conization, and histological diagnosis were significantly associated with the margin involvement. In subgroup analyses,

histological diagnosis was the only associated factor for positive cone margin obtained from either LEEP or CKC while satisfactory of colposcopic findings and surgeon skill were found to be associated with cone margin involvement from CKC.

The prevalence of the positive cone margin reported in other studies was not less than that in the present study. Costa et al and Sun et al reported the prevalence of 27% while Im et al reported 33% (Im et al., 1995; Costa et al., 2000; Sun et al., 2009) The prevalence was similar to ours. The Costa and the Sun's studies were conducted in CIN patients who undergoing conization while the Im's study was conducted in patients with adenocarcinoma in situ of cervix (AIS). Fan et al (2001) reported that unclear margins were noted in 42.2% including 15.6% of resection margin positive and 26.7% of resection margin undetermined. According to these consistent findings, the positive cone margin is the common problem.

There were differences in the factors related to the positive cone margin across studies. In Costa's study (2000), histology diagnosis and time period were the strongest determinants of cone margin involvement (Costa et al., The effect of lesion size was of borderline significance. The endocervical location emerged as a multivariate determinant of margin positivity and effects of cone width and depth were not confirmed. In Fan's study (2001), HSIL accounted for the majority of the positive cases(94.7%). Univariate analysis in Sun's study showed that the parity, cytological grade, multi-quadrants of CIN III by punch biopsy, gland involvement, as well as the depth of conization were significant factors correlated with a positive cone margin ($P < 0.05$) (Sun et al., 2009). However, the age, gravidity, grade of dysplasia in punch biopsy, as well as the cone methods were not significantly correlated ($P > 0.05$). Multivariate analysis in Sun's study revealed that the cytological grade, depth of conization, parity, and multi-quadrants of CIN III were significant predictors with increased risk for positive margin.(Sun et al., 2009). In multivariate analyses of our study, the purpose of conization, surgeon skill, type of conization, and histological diagnosis were related to the positive cone margin. According to these findings, no factors have consistently been reported as a risk of the positive cone margin. This may from the differences in study design, sample size, factors of interest, setting, and studied population. A multicenter, prospective cohort or randomized controlled trial which take all potential factors into account for analysis would be beneficial and clearly identified risk factors of positive cone

The rate of postoperative bleeding in this study was 5.4% which is slightly higher than that reported by Alberico's study (1989), where the rate of early post-operative hemorrhage was 3% of the cases. Larsson et al (1983) compared intraoperative and postoperative complications of laser conization and cold knife conization. In 428 women hospitalized for CKC, 23.6% had one or more complications; 14.3% had postoperative hemorrhages, 6.8% had infections, and 4.7% suffered from stenosis.(Larsson et al., 1983) Of 260 women who were hospitalized for laser conization; 5.1% of them had complications. Postoperative hemorrhage occurred in 2.8% and infections in 2.3% (Larsson et al., 1983). These complication rates were higher in CKC which was similar to our study. Since CKC removes larger specimen, this may be responsiblefor the higher rate of complications.

In Thailand, based on our search, this is the first study regarding the prevalence and the associated factors of cone margin involvement. However, as the nature of retrospective study, some information may be unable to find or inaccurately measured. Although subgroup analysis demonstrated that LEEP and CKC had the different associated factors of margin involvement, the strength of evidence is weakened as the analysis is post-hoc.

Based on our findings, more than one forth of patients with abnormal cervical cytology who undergo conization would have the cone margin involvement. For clinical perspective, physician should be aware that the marginal involvement is rather common. Identification of the associated factors is, therefore, important in management of CIN. As the significance and further management of the margin involvement are still controversial, a research on the prognosis of the patients with the positive cone margin would be valuable.

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