Significance of Margin and Extent of Dysplasia in Loop Electrosurgery Excision Procedure Biopsies Performed for High-Grade Squamous Intraepithelial Lesion in Predicting Persistent Disease

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Context.—High-grade squamous intraepithelial lesions (cervical intraepithelial neoplasia 2 and 3) are commonly treated with loop electrosurgery excision procedure (LEEP) biopsies.

Objective.—To highlight the significance of positive margins and extent of positive margins of the cervical LEEP biopsies in predicting the persistence of high-grade squamous intraepithelial lesion and to provide suggestions for reporting margins in cervical LEEP biopsies.

Design.—The pathology files at the University of Arkansas for Medical Sciences were searched for cervical intraepithelial neoplasia 2 and 3 treated by LEEP biopsy from 1990 to 2001.

Results.—A total of 489 LEEP biopsy specimens were retrieved and reviewed; 270 patients had follow-up within 1 year. The biopsy specimens of 110 patients showed positive endocervical margins. One hundred sixty specimens had negative ectocervical-endocervical margins. Follow-up of 54% of the cases with initial positive margins showed residual high-grade squamous intraepithelial lesions. This association was even greater when multiple blocks showed positive endocervical margins and in cases with positive deep margins. On the other hand, a negative margin predicted ability to completely remove the lesion in 95% of patients.

Conclusion.—This study reiterates the significance of the evaluation of the margin, even in samples that were received as multiple fragments. Reporting of LEEP biopsy findings should include the extent of the dysplasia, the status of the ectocervical-endocervical margin, and the status of the deep margin.

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A cervical biopsy specimen obtained by loop electrosurgery excision procedure (LEEP) is used to diagnose and treat high-grade squamous intraepithelial lesions (HSILs) (cervical intraepithelial neoplasia [CIN] 2 and 3). LEEP is a safe method for treating HSILs. LEEP biopsy was introduced in 1989 by Prendiville et al to treat cervical dysplastic lesions that could be completely visualized at the time of colposcopy. During recent years, indications have extended beyond cases that involved the ectocervix to include lesions with margins not defined at colposcopy. Cervical LEEP biopsies are also used for the diagnosis and possible treatment of cases in which abnormal Papanicolaou smears show CIN 2 and 3 that could not be visualized at the time of colposcopy.

The major advantages of LEEP over cold-knife coneization are a shorter operation time, less blood loss, and fewer long-term complications. The importance of positive margins and the presence of residual disease have been reviewed in the past. We investigated the significance of positive margins and the extent of dysplasia at the endocervical or ectocervical margins and the deep margin of the LEEP biopsy specimens in predicting the presence of residual disease.

MATERIALS AND METHODS

The pathology files at the University of Arkansas for Medical Sciences, Little Rock, were searched for cases of CIN 2 and 3 that were treated by LEEP biopsy from 1990 to 2001. We identified 489 patients with HSIL whose lesions were diagnosed or treated by cervical LEEP biopsy. A total of 201 patients were lost to follow-up; 96 (48%) of them had positive endocervical margins, and 105 (52%) had negative endocervical margins. The final sample size was 270; patients with follow-up longer than 1 year (n = 18) were excluded from the study. Gross descriptions of 50 cases seen from July 1997 to 2001 were available for review. Because of a change in the computer program used in the department, we did not have access to the gross description of the remaining cases. Thirty-one of these cases (62%) were received as 2 or more fragments; 19 (38%) of these specimens were a single fragment. Although this represents a fraction of the study material, it can be assumed that these are representative of all cases. We reviewed the original surgical pathology reports available in the computer system, the follow-up reports, and glass slides. Ectocervical-endocervical margins and deep margins were reevaluated.

A margin was considered positive if HSIL was present at the
ink or cauterized endocervical margin. LEEP biopsy specimens were considered to have extensive involvement if multiple fragments or multiple blocks showed HSIL clearly extending to the endocervical margin (Figure 1). Deep margin involvement was also assessed. Follow-up material consisted of repeated Papanicolaou smears, repeated cervical biopsies, endocervical curetting, repeated LEEP biopsy, or hysterectomy. A positive deep margin is illustrated in Figure 2. We reviewed the follow-up surgical specimens by using the same criteria as listed above.

The extent of involvement of the ectocervical and endocervical margins and the status of the deep margin were evaluated and correlated with the results of subsequent follow-up. The crude odds ratio and corresponding confidence interval were used to examine the association between margin status (and deep margin status) and follow-up status. Adjusted odds ratios were calculated after adjustment for age in logistic regression models.

**RESULTS**

The median patient age was 32.5 years (range, 17–73 years). A total of 110 patients (41%) had positive endocervical margins; 160 LEEP specimens (59%) had negative endocervical margins on LEEP, and none of the patients had positive ectocervical margins. Fifty-nine (54%) of the 110 patients who initially had positive endocervical margins continued to have HSIL on follow-up. Only 7 (4%) of 160 patients with negative endocervical margins still had HSIL on follow-up. In comparison, 35 (87.5%) of 40 patients who initially presented with extensive positive margins (as previously described in the ‘Materials and Methods’) had HSIL on follow-up.

Women whose LEEP biopsy specimen had positive margins were significantly more likely to have residual HSIL on follow-up than women whose specimens had negative margins (Table 1). In addition to positive endocervical margins, 15 patients also had positive deep margins. Of these, 13 (87%) women had positive findings on follow-up, and 2 (13%) women had negative findings. Patients with cervical LEEP biopsy specimens that had both positive endocervical margins and positive deep margins were at greater risk for HSIL on follow-up (Table 2). This association was weaker for women who had negative deep margins (Table 2).

The LEEP biopsy specimens of 40 women showed extensive involvement of the endocervical margin. Thirty-five (87.5%) of these patients had HSIL on follow-up. Five (12.5%) patients had negative findings on follow-up ($P = .01$). Endocervical curettage performed at the time of initial LEEP showed HSIL in 18 women. Subsequent high-grade dysplasia on follow-up was seen in 14 (78%) of these 18 women, and 4 women (22%) had no residual disease.

**COMMENT**

High-grade squamous intraepithelial lesion is a common preneoplastic condition of the cervix that encompasses moderate (CIN 2) or severe (CIN 3) dysplasia. LEEP biopsies were introduced in 1989 by Prendiville et al to treat lesions that could be visualized by colposcopy. LEEP has been proven to be a safe method for treating lesions that involve the endocervix. LEEP has several advantages over cold-knife conization, including shorter operating times, less blood loss, and fewer complications.
Since no general anesthesia is necessary to perform a LEEP biopsy, the procedure can be done in the office setting.\textsuperscript{1,2} Pathology reports of LEEP biopsy specimens typically include the grade of dysplasia, status of the ectocervical and endocervical margins, and involvement of the endocervical glands. On the basis of our personal experience, many pathologists have traditionally been hesitant to assess the margin of multiple LEEP biopsy fragments if they were received in 1 container.

Our study investigated whether the assessment of the margins, including margins of the multiple LEEP biopsy specimens submitted in one container, can accurately predict the presence of residual HSIL in the cervix. Other authors have previously reported that surgical margins could be effectively evaluated with thermal artifact but that fragmentation limited the interpretation of margins.\textsuperscript{11} Therefore, they limited their studies to oriented, intact LEEP biopsy specimens. In our study, 62% of cases for which a gross description was retrievable were multiple fragments. We found that fragmentation did not affect the interpretation of the margins. Many of these samples are likely to be taken from separate grossly abnormal lesions that were visualized at the time of colposcopy. Therefore, each fragment may indeed represent a clinically defined lesion. Although we reviewed the gross description of only a portion of the study material, we can assume that they are representative of material received in our department. Ninety-five percent of women with negative endocervical margins remained negative at follow-up, and 59% of women with positive endocervical margins had positive findings at follow-up. Women with a extensive positive endocervical margin, a positive margin seen in more than 1 section or more than 1 block, or a positive deep margin were more likely to have residual disease than women with a negative margin. Eighty-seven percent of patients with extensive involvement of the endocervical margin had residual disease at follow-up.

The rate of residual or recurrent HSIL was higher in our study than in other reports in the literature. Other studies identified a 27.5% and 37% rate of residual disease compared with 53% in our study. This increased rate of residual disease might reflect a difference in the populations served at various institutions.

On the basis of our criteria, a positive margin resulted in positive findings at follow-up in 53% of our patients, and a negative margin resulted in negative findings at follow-up in 93% of our patients. Our study shows that the extent of involvement of the endocervical margins and deep margin are significant predictors of the residual disease in patients with HSIL, and this information should be part of the surgical report, even in cases for which multiple fragments are submitted in 1 container.

Adjustment for the effect of age showed that women older than 50 years of age had a 5.1 times increased likelihood of residual HSIL compared with women younger than 30 years of age (95% confidence interval, 1.6–16.0 times).

Of interest is a 50-year-old patient who developed metastatic squamous cell carcinoma following diagnosis of HSIL with extensive involvement of the endocervical margin. We excluded this case from the study because follow-up occurred 2 years after the initial LEEP biopsy. This case illustrates the importance of reporting the extent of the margin involvement by the disease. It also highlights the necessity of close follow-up in patients with extensive disease, especially in older women.

In our study, 77% of patients with positive findings on endocervical curettage had dysplasia on follow-up. Husseinzadeh et al\textsuperscript{12} found that 80% of their patients with positive findings on endocervical curettage at LEEP had residual disease at hysterectomy. Therefore, endocervical curettage at the time of LEEP may improve assessment of the endocervical margin.

In conclusion, the authors believe that the histopathology reports of cervical LEEP biopsy specimens should include extent of the HSIL and endocervical gland involvement, as well as the assessment of ectocervical and endocervical and deep margins. This assessment can be performed on specimens that are received as multiple fragments.

References