


Management of high-grade squamous intraepithelial lesion patients with positive margin after LEEP conization

A retrospective study

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Abstract

To explore the optimal way to manage patients with high-grade squamous intraepithelial lesion (HSIL) and positive margin by identifying the risk factors for its recurrence and residue.

A retrospective study was conducted on 267 cases of a pathologically confirmed HSIL with positive margin following conization by loop electrosurgical excisional procedure (LEEP) between January 2010 and December 2015. One hundred two cases were selected for regular follow-up every 6 months, and 165 cases were selected for a second surgery (repeat cervical conization or hysterectomy) within 3 months of initial LEEP. We analyzed the association between recurrent or residual diseases and these factors: age, menopausal status, ThinPrep cytologic test (TCT) results, high-risk human papillomavirus (HR-HPV) infection, pathological grades of the margin, number of involved margins, and glandular involvement.

The recurrence rate among 102 cases who underwent follow-up was 17.6% (18/102). The factors: atypical squamous cells of undetermined significance cannot exclude HSIL (ASC-H) or higher lesions in the pre-LEEP TCT ($P=.038$), persistent HR-HPV infection at the 6th month post-LEEP ($P=.03$), HSIL-positive margin ($P=.003$), and multifocal-involved margin ($P=.002$) were significantly associated with recurrent disease, while age, menopause, and pre-LEEP HR-HPV infection were not associated with recurrent disease ($P>.05$). The residual rate among 165 patients who underwent a second surgery was 45.5% (75/165), of which 15 cases were residual cervical cancer. The factors: menopause ($P=.02$), \geq ASC-H in pre-LEEP TCT ($P=.04$), pre-LEEP HR-HPV infection ($P=.04$), \geq HSIL-positive margin ($P<.001$), and multifocal-involved margin ($P<.001$) significantly increased the risk of residual disease. No correlation existed between residual disease and age or glandular involvement ($P>.05$).

For patients with a positive margin after LEEP, regular follow-up or second surgery should be selected according to fertility requirement and pathological characteristics of the positive margin, as well as TCT and HR-HPV infection condition.

Abbreviations: ASC-H = atypical squamous cells of undetermined significance cannot exclude HSIL, CIN = cervical intraepithelial neoplasia, HR-HPV = high-risk human papillomavirus, HSIL = high-grade squamous intraepithelial lesion, LEEP = loop electrosurgical excisional procedure, LSIL = low-grade squamous intraepithelial lesion, TCT = ThinPrep cytologic test.

Keywords: high-grade squamous intraepithelial lesion, loop electrosurgical excisional procedure, positive margin, recurrent diseases, residual diseases

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AMAA and HL contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Cervical cancer is one of the most common malignant tumors that affects the female genital tract worldwide.^[1] The majority of cervical cancer cases occur in less-developed countries. With the world's largest population, China accounts for 14% of the global burden of new cervical cancer cases annually.^[2] Cervical intraepithelial neoplasia (CIN) is a precursor of cervical cancer. Untreated high-grade CIN significantly increases the risk of invasive cervical cancer. Therefore, accurate and standardized treatment of high-grade CIN is considered to be an effective method to prevent cervical cancer.^[3,4] As a minimally invasive surgery, loop electrosurgical excision procedure (LEEP) is a common strategy of cervical conization and has been widely performed to treat high-grade CIN in recent years, as it is usually carried out under local anesthesia in a short time with fewer complications in an outpatient clinic.^[3,5] However, LEEP is more associated with positive margin than some other treatment procedures.^[6–8] Positive margin is associated with an increased risk for recurrent and residual diseases.^[5,9,10] However, nearly half of the cases with positive margin did not develop recurrent or residual disease,^[4] which has led to controversy regarding the management of positive margin among gynecologists. Generally, positive margin is managed either by a regular follow-up or by a second surgical intervention, including repeat conization or hysterectomy. The decision is usually made according to the patient's age, fertility requirement, and compliance with follow-up.^[11] The American Society for Colposcopy and Cervical Pathology (ASCCP) has given its recommendations for managing these patients: "If CIN II, CIN III, or CIN II~III is identified at the margins of a diagnostic excisional procedure or in an endocervical sample obtained immediately by endocervical curettage after the procedure, reassessment using cytology with endocervical sampling at 4–6 months after treatment is preferred. Performing a repeat diagnostic excisional procedure is acceptable. Hysterectomy is acceptable if a repeat diagnostic procedure is not feasible."^[12] However, the most appropriate treatment remains unclear. Accordingly, many researchers are studying to identify the risk factors of recurrent and residual diseases in patients with positive margins, including the clinical, pathological, and demographic factors.^[4,6,11] These studies about risk factors may enable gynecologists to choose the most appropriate treatment for each individual. In this present study, we aimed to find the optimal way for managing patients with positive margin after initial LEEP conization through identifying the clinicopathological risk factors of residual and recurrent diseases in patients with positive margin after initial LEEP conization.

2. Material and methods

2.1. Ethics statement

The study procedures were approved by the Human Ethics Committee of the Qilu Hospital of Shandong University. Written informed consent was obtained from all subjects (KTLL-2017-560).

2.2. Study design and case selection

A retrospective study from January 2010 to December 2015 was conducted, in which 3860 cases underwent LEEP cervical conization in the Department of Obstetrics and Gynecology, Qilu Hospital of Shandong University due to a biopsy-confirmed

HSIL. Consequently, a total of 267 cases with pathological HSIL were reported to display positive margins in their initial LEEP specimens, which accounted for 6.9%. This group of patients with positive margin was selected as the subjects of our study. We collected the clinical and pathological data of these patients, including age, menopausal status, ThinPrep cytologic test (TCT), high-risk human papilloma virus (HR-HPV), pathological grades of the margin, number of involved margin, and glandular involvement in the initial LEEP specimens from the computerized medical records.

2.3. Initial LEEP

Firstly, the patient was sterilized for the area in a lithotomy position. Then, an insulated speculum was inserted into the vagina to expose the uterine cervix. After that, a Lugol iodine smear was applied to visualize the boundary of the cervical lesion, and 5 mL of local anesthesia were injected into the 4 quadrants of the cervix. Then cervical cone resection was done by gently passing the electric circle through the tissue once without dragging or stopping. The electric circle was inserted vertically from the outside of the transformation zone (3–5 mm away from the unstained area) at 3 o'clock, moved horizontally to the outside of 9 o'clock, and slid out vertically. The length of the excised cone was 10 to 20 mm, and the depth of gland destruction was ≥ 5 mm. Finally, the site of the resected cone was coagulated by a ball electrode to prevent bleeding. The size of the electric circle was selected based on the size and site of the lesion. The specimens were fixed with 4% neutral formalin and embedded in paraffin for the pathological examination.

2.4. Sequential management

According to the pathological lesion of the patient's postoperative resection margin, the patient's willingness to retain fertility, and the level of patient compliance, our patients had the following 3 options:

2.4.1. Regular follow-up in an outpatient clinic. A total of 102 cases with positive margins were selected for a regular follow-up after initial LEEP. Follow-up was performed every 6 months for the first 3 years after the initial LEEP conization and once a year thereafter. The follow-up period in our study ranged between 6 to 72 months. In each postoperative visit, patients were subjected to a combination of HR-HPV test (using Hybrid Capture 2 assay; the results were described as positive or negative for the HR-HPV test), cervical cytology (using an Ayre spatula for the collection of ectocervical sample and a cytobrush for the collection of the endocervical sample; the results were evaluated according to the Bethesda 2001 criteria),^[13] and colposcopies (carried out using a colposcope after outfitting the uterine cervix with 5% acetic acid). In patients with abnormal cytological results or positive HR-HPV test results and abnormality in the transformation zone in a colposcopy, a colposcopy-directed punch biopsy was performed. If the abnormality was absent under colposcopy or the transformation zone was invisible, multipoint cervical biopsy or endocervical curettage would be performed.

2.4.2. Repeat cervical conization. A total of 87 cases with positive margin were selected for a repeat cervical conization within 3 months after initial LEEP conization, 26 cases of which underwent repeat LEEP (the procedure was similar to that of initial LEEP). The remaining 61 cases underwent cold knife conization.

2.4.3. Hysterectomy. A total of 78 cases with positive margins were selected for a hysterectomy within 3 months after initial LEEP conization, 64 of which underwent a total hysterectomy due to positive margin in their initial LEEP specimens. The remaining 14 cases underwent a radical hysterectomy with lymphadenectomy due to invasive cervical cancer at the margin of the initial LEEP specimens.

2.5. Important definitions

A positive margin in our study was defined as a cervical resection margin of cervical conization that had cervical intraepithelial neoplasia (CIN I-III) or invasive cancer. The postoperative pathological results of cervical conization were described as follows: the lesion was involved within the resection margin, the resection margin showed the lesion, or the lesion was close to the resection margin. CIN I is classified as a low grade squamous intraepithelial lesion (LSIL), and CIN II-III is classified as HSIL. A recurrent cervical lesion was defined as the presence of cervical intraepithelial neoplasia of any grade (CIN I-III) in the specimens obtained by biopsy during follow-up after the initial conization by 6 months or more. A residual cervical lesion was defined as the presence of \geq CIN II in the specimens obtained from the second surgery that had performed within the first 3 months after the initial conization.

2.6. Statistical analysis

Statistical analysis was performed using IBM SPSS for Windows (v21.0). χ^2 was applied to estimate the association of age and number of involved margins to the recurrent disease and age, menopausal status, TCT, glandular involvement, and number of involved margins to residual disease. The remaining factors were analyzed by using Fisher test (for sample size <5). When P value was $<.05$, the differences were deemed statistically significant.

3. Results

3.1. Characteristics of the patients

A total of 3860 cases were diagnosed with HSIL by biopsy and thereafter underwent LEEP conization from January 2010 to December 2015 in Qilu Hospital, 267 (6.9%) cases of which displayed a positive cone margin after initial LEEP conization and were selected as the study population. The general characteristics of these 267 patients are shown in Table 1. The mean age of these subjects was 38.52 ± 6.0 years old and ranged between 20 and 70 years. Among the 267 cases with positive margin, 219 (82%) cases were non-menopausal, and 242 (90.6%) cases were HR-HPV infected before initial LEEP. The pathological grades of the margins in the initial LEEP specimens of the overall 267 cases were: CIN I in 77 (28.2%) cases, CIN II-III in 132 (49.4%) cases, gland-involved CIN II-III in 44 (16.5%) cases, and invasive cervical cancer in 14 (5.2%) cases. Among the 267 cases with positive margin, 102 (38.2%) cases were selected for regular follow-up in an outpatient clinic: 56 (54.9%) cases had LSIL-positive margins and 46 (45.1%) cases had HSIL-positive margins in the initial LEEP specimens. During the follow-up period, 18 cases had recurred in the form of CIN I in 4 cases and CIN II-III in 14 cases, and no subjects progressed to cervical cancer. All cases with recurrence were subjected to reoperation. The remaining 165 (61.8%) cases with positive margins were

Table 1

Characteristics of the 267 cases with positive margin after cervical conization.

Factors	Group	Cases (n, %)
Age	≤ 50	230 (86.1%)
	>50	37 (13.9%)
Menopausal status	Menopausal	48 (18.0%)
	Nonmenopausal	219 (82.0%)
Pre-LEEP HR-HPV	Positive	242 (90.6%)
	Negative	25 (9.4%)
Pathological grade of the margin	CIN I	77 (28.2%)
	CIN II-III	132 (49.4%)
	CIN II-III involved glands	44 (16.5%)
	Invasive cancer	14 (5.2%)

CIN = cervical intraepithelial neoplasia, HR-HPV = high risk human papilloma virus, LEEP = loop electrosurgical excisional procedure.

selected for a second surgery: 87 (52.7%) cases underwent a repeat conization (16 cases had LSIL-positive margins, and 71 cases had HSIL-positive margins in the initial LEEP specimens), 64 (38.8%) cases underwent a total hysterectomy (5 cases had LSIL-positive margins, and 59 cases had HSIL-positive margins in the initial LEEP specimens) and 14 (8.5%) cases underwent radical hysterectomy with lymphadenectomy for invasive cancer in the margin of the initial LEEP specimens. The pathological reports of the second surgery revealed the following: 46 (29.1%) cases had chronic cervicitis, 44 (26.7%) cases had CIN I, 60 (36.4%) cases had CIN II-III, and 15 (9.1%) cases had cervical cancer. The sequential management of the 267 patients with positive margin is illustrated in Figure 1.

3.2. Rate and risk factors of recurrent disease

A total recurrence rate among the 102 cases who underwent follow-up in the outpatient clinic was 17.6% (18/102), which included 4 cases of recurrent LSIL and 14 cases of recurrent HSIL. The first relapse occurred in the 9th month after surgery, and the average recurrence period was 10.5 months. Before initial LEEP, 88.2% (90/102) of the patients were HR-HPV infected. At the 6th month after initial LEEP, the percentage of the HR-HPV infected patients reduced to 66.7%. As shown in Table 2, pre-LEEP TCT results of atypical squamous cells of undetermined significance cannot exclude HSIL (ASC-H) or higher lesions ($P=.04$), post-LEEP HR-HPV positivity ($P=.03$), HSIL-positive margins in the initial LEEP specimens ($P=.003$), and multifocal-involved margins ($P=.002$) were associated with a higher rate of recurrence and considered to be significant risk factors for recurrent disease, while age ($P=.152$), menopausal status ($P=.238$), and pre-LEEP HR-HPV infection ($P=.687$) were not correlated with recurrence of disease.

3.3. Rate and risk factors of residual disease

Among the 165 cases that received a second operation, 75 (45.5%) cases were reported with residual disease, 15 (20%) cases of which were residual cervical cancer (8 cases were microinvasive cervical cancer, and 7 cases were invasive cervical cancer). As shown in Table 3, we found that the residual rate was significantly higher in: menopausal women compared to non-menopausal (62.9% vs 26.9%, $P=.02$), \geq ASC-H cases compared to \leq LSIL cases in the pre-LEEP TCT (52.7% vs 36.5%,

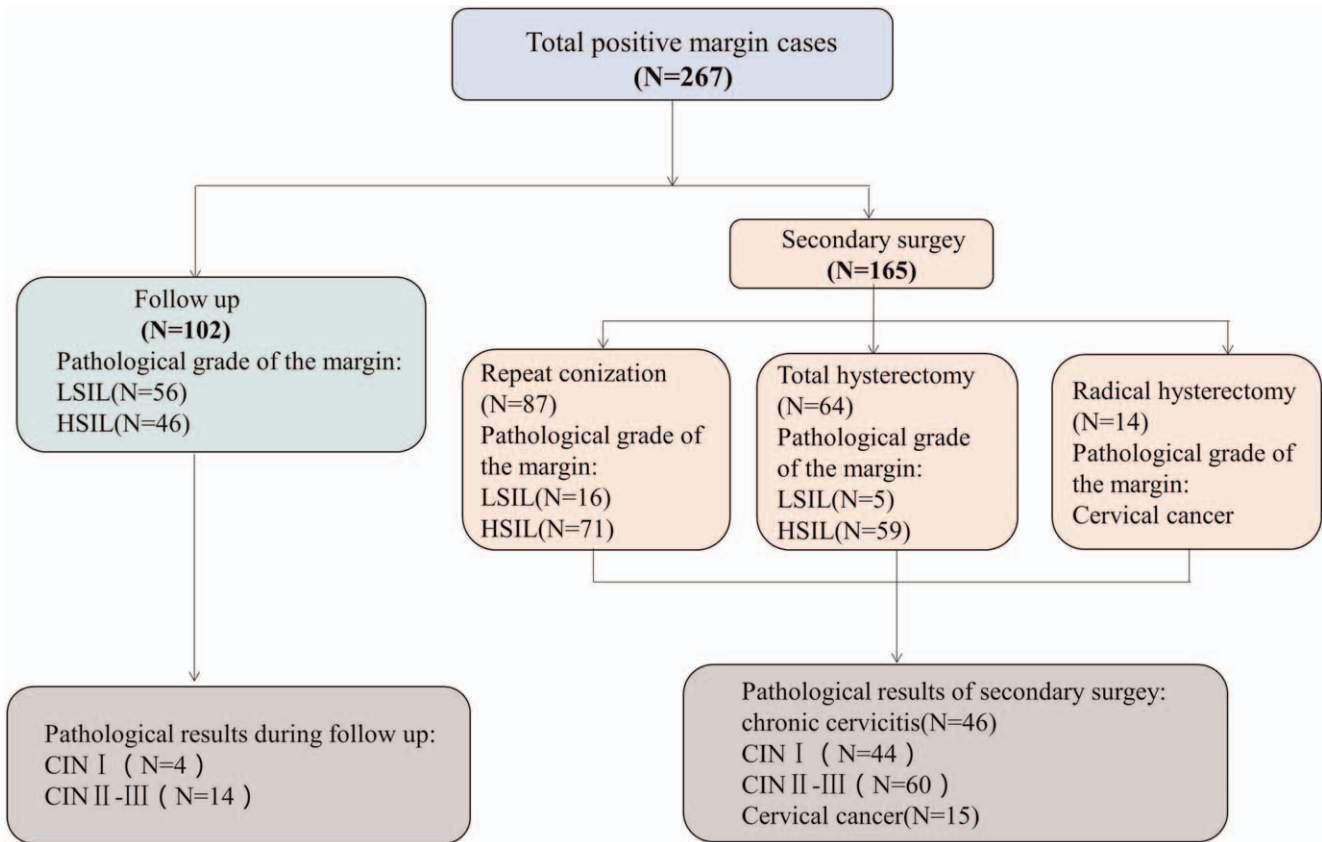


Figure 1. The sequential management of the 267 patients with positive margin.

$P = .04$), women with pre-LEEP HR-HPV positive tests compared to those with HR-HPV negative tests (48.0% vs 15.4%, $P = .04$), women with \geq HSIL-positive margins in the first conization compared to those with LSIL-positive margins (50.7% vs 9.5%, $P < .001$), and women with multifocal-involved margins com-

pared to those with focal-involved margins (82.9% vs 35.4%, $P < .001$); all of these factors were considered to be risk factors for residual disease. However, there were no significant differences between age and residual disease ($P = .06$) or between glandular involvement and residual disease ($P = .381$).

Table 2

Analysis of risk factors for recurrent disease in the 102 cases with positive margin who underwent regular follow-up.

Factors	Group (n)	Recurrent disease		χ^2	P value
		yes	no		
Total		18	84		
Age	≤ 50 (86)	13	73	2.416	.152
	> 50 (16)	5	11		
Menopausal status	Menopause (13)	4	9		.238
	Non-menopause (89)	14	75		
TCT	\leq LSIL (46)	4	42		.038
	\geq ASC-H (56)	14	42		
Pre-LEEP HR-HPV	Positive (90)	17	73		.687
	Negative (12)	1	11		
Post-LEEP HR-HPV	Positive (68)	16	52		.03
	Negative (34)	2	32		
Pathological grade of the margin	LSIL (56)	4	52		.003
	\geq HSIL (46)	14	32		
Number of involved-margin	Multifocal (39)	13	26	10.69	.002
	Focal (63)	5	58		

ASC-H = atypical squamous cell highly indicates the existence of high-grade cervical lesions, HR-HPV = high-risk human papilloma virus, HSIL = high grade squamous intraepithelial lesion, LEEP = loop electrosurgical excisional procedure, LSIL = low grade squamous intraepithelial lesion, TCT = ThinPrep cytological test; Focal-involved margin means the lesion affect < 2 quadrants, multifocal-involved margin means the lesion affect ≥ 2 quadrants.

Table 3**Analysis of risk factors for residual disease in the 165 cases with positive margin who underwent second surgery.**

Factors	Group	Residual disease		χ^2	P value
		yes	no		
Total	165	75	90		
Age	≤50 (144)	61	83	4.37	.06
	>50 (21)	14	7		
Menopausal status	Menopause (35)	22	13	5.43	.02
	Non-menopause (130)	53	77		
TCT	≤LSIL (74)	27	47	4.35	.04
	≥ASC-H (91)	48	43		
Pre-LEEP HR-HPV	Positive (152)	73	79		.04
	Negative (13)	2	11		
Pathological grade of the margin	LSIL (21)	2	19		<.001
	≥HSIL (144)	73	71		
Glandular involvement	Yes (44)	21	23	0.13	.73
	No (121)	54	67		
Number of involved-margin	Multifocal (35)	29	6	25.1	<.001
	Focal (130)	46	84		

ASC-H = atypical squamous cell highly indicates the existence of high-grade cervical lesions, HR-HPV = high-risk human papilloma virus, HSIL = high grade squamous intraepithelial lesion, LEEP = loop electro-surgical excisional procedure, LSIL = low grade squamous intraepithelial lesion, TCT = ThinPrep cytological test. Focal-involved margin means the lesion affect <2 quadrants, multifocal-involved margin means the lesion affect ≥2 quadrants.

4. Discussion

As a standard strategy for the treatment of cervical intraepithelial neoplasia in recent years, LEEP has demonstrated superiority in its effectiveness and minimal invasiveness. However, positive margin after LEEP conization have been reported in some cases, which may increase the possibility of recurrent and residual disease.^[5,7,9] In our study, cases of positive margin accounted for a rate of 6.9%, which was situated in the lower limits of the range reported in a recent large systematic review and meta-analysis of 97 studies, which was 2.8% to 59.5%.^[7] The low percentage of positive margin in our study is possibly due to the relatively young age of the enrolled participants (38.52 ± 6 years old). The management of positive margins has been controversial among researchers. Some assume that follow-up protocol is the ideal way for management of positive margin,^[14] while others prefer a second surgical intervention such as repeat conization or hysterectomy.^[3,11,15–17] As for the management of positive margins, both over-treatment and insufficient treatment should be avoided.^[18] Accordingly, many studies have focused on identifying the risk factors for residual and recurrent disease in patients with positive margin, such as age, menopausal status, TCT results, HPV infection, and the pathological characteristics of the conization specimens. These studies may guide gynecologists to choose the most appropriate treatment for each individual and, further, to decrease the risk of recurrent and residual disease.

4.1. Rate and risk factors of recurrent disease

In this study, the rate of recurrent disease in patients with positive margin who underwent regular follow-up after initial LEEP was 17.6%, which was consistent with previous studies with a rate of 9.3% to 21.7%.^[6,8,17] The difference in the recurrence rates with the literature is possibly due to the diversity in the definitions of recurrent disease and the various durations of follow-up. In our research, we divided the pre-LEEP TCT results into 2 groups: ≤ LSIL and ≥ASC-H, and by the statistical analysis we found that ≥ASC-H in the pre-LEEP TCT was a significant predictive risk

factor for recurrent disease. Similarly, Chen et al^[6] reported that TCT grade is a significant risk factor for recurrent disease. In previously reported studies, preconization and postconization HR-HPV infections in positive margins were significant predictors for treatment failure.^[19–21] Likewise, we confirmed that post-LEEP HR-HPV-infected women had significantly higher recurrence rates than non-infected women, indicating that persistent post-LEEP HR-HPV infections are a significant predictor for recurrent disease. However, we did not find a correlation between pre-LEEP HR-HPV infections and recurrent disease. There have been several studies about the association of pathological characteristics of positive margin with recurrent and residual diseases, such as the location and number of involved margins. In the current study, we studied the correlation between the pathological grades of the margin and recurrent disease and observed that the recurrence rate in patients who had HSIL-positive margins was significantly higher than those who had LSIL-positive margins. In addition, multifocal-involved margin was also a significant risk factor for recurrent disease. Consistently, Shaco-Levy et al reported that the extent of margin involvement was a predictive factor for residual/recurrent disease.^[22] However, neither age nor menopausal status was a predictor for recurrent disease in our study, which is similar to previously reported studies.^[6,21,23]

4.2. Rate and risk factors of residual disease

In this study, the residual rate of cervical lesions in patients with positive margins who underwent a second surgery after initial LEEP was 45.5% (75/165), which is consistent with previously reported residual rates (7.6%–53.7%).^[5,8,11,14,24] In our data, more than half of the patients did not develop residual disease. This may be explained by: thermal destruction of the residual lesions during cauterization of the loop base, eradication of the remaining lesions by the inflammatory process that occurs after LEEP, or a falsely positive margin caused by insufficient cone resection.^[14,22,25] In this study, residual lesions were significantly affected by the menopausal status of the patients, since residual

lesions in menopausal women occurred more frequently higher than in nonmenopausal women. In agreement with this finding, Bilibio et al.^[11] confirmed that menopausal status is a risk factor of residual disease. The increased rate of residual disease in menopausal women may be explained by the upward retraction of the transformation zone during menopausal age, which may lead to inadequate visibility of the lesion during conization and, therefore, inadequate resection of the lesion.^[5,11] In our study, an \geq ASC-H result in a pre-LEEP TCT significantly increased the risk of residual disease after initial conization in patients with positive margins, which is compatible with the findings of another report.^[18] Moreover, we found that pre-LEEP HR-HPV infections were a significant predictor for residual disease, which is similar to findings in previous studies.^[6,18,20,23] Subsequently, we compared the rate of residual disease between the patients with LSIL-positive margins and those with \geq HASIL-positive margins and found a significant difference between the 2 groups. In several articles, the number of involved margins has been identified as a significant risk factor for residual disease.^[3,4,22,24] Similarly, we observed that multifocal-involved margins were a strong predictor for residual disease. In our study, neither age nor glandular involvement were identified as risk factors for residual disease in patients with positive margins, which is similar to results in previously reported studies.^[15,16,18]

Through this research, we provided guidance for clinicians to manage patients with positive margins after cervical conization. However, it still has limitations such as insufficient sample size, relatively short follow-up time, and insufficient detailed patient's characteristics. Therefore, further large-scale studies are necessary to confirm our findings.

In conclusion, our study indicated that patients with positive margins after LEEP cervical conization should be strictly and closely managed. Regular outpatient follow-up, secondary cervical conization, or hysterectomy should be selected according to the patient's fertility requirement and clinico-pathological characteristics, including TCT, HR-HPV infection, grade, and extent of involved margin.

Author contributions

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