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Predictors of recurrence in patients with high-grade cervical intraepithelial neoplasia after cervical conization

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Abstract

This study was to identify the predictors of recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN) after cervical conization.

Totally 415 patients with CIN≥II who underwent loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC) were included in this retrospective study. Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) regarding the association between postoperative recurrence and clinicopathological data.

After the mean follow-up of (21.48±5.82) months, 90 (21.69%) out of 415 cases were subjected to recurrence after cervical conization. The influencing factors for postoperative recurrence included times of full-term birth, history of preterm birth, history of abortion, positive margin, cone length, width, depth, smoking, and history of complicating diseases ($P < .05$). Multivariate Cox model indicated the positive margin (HR=2.144, 95% CI: 1.317–3.492, $P < .05$), history of preterm birth (HR=4.515, 95% CI: 1.598–12.754, $P < .05$), history of complicating diseases (HR=3.552, 95% CI: 1.952–6.462, $P < .05$) were independent risk factors for recurrence after cervical conization. The restricted cubic diagram showed that the cone depth >0.5 cm was a protective factor for postoperative recurrence.

For the patients with high-grade CIN after cervical conization, positive margins, histories of preterm birth, and complicating diseases were associated with increased risk of recurrence, but cone depth (>0.5 cm) with lower risk of recurrence.

Abbreviations: BMI = body mass index, CI = confidence interval, CIN = cervical intraepithelial neoplasia, CKC = cold knife conization, HPV = human papillomavirus, HR = hazard ratio, ICC = invasive cervical cancer, LEEP = loop electrosurgical excision procedure.

Keywords: cervical intraepithelial neoplasia, cold knife conization, loop electrosurgical excision procedure, predictor, recurrence

1. Introduction

The incidence and mortality of cervical cancer rank the fourth in all cancers.[1] In 2018, 569,847 new cervical cancer cases and 311,365 deaths were estimated globally, in which the incidence in developing countries was higher, approximately accounting for 85% of all cervical cancer cases.[1,2] Most cervical cancers are preventable via the organized screening programmer, which is conducive to detecting precancerous lesions and treating them timely before invasive disease occurs. Cervical intraepithelial neoplasia (CIN), a precancerous lesion of cervical cancer, serves as a precursor to invasive cervical cancer (ICC) and exhibits one of the most frequent gynecologic diseases of reproductive-age women.[3] A small proportion of CIN cases, especially high-grade CIN cases, will progress into ICC eventually if left untreated.[4]

It is mainly unpredictable for the natural history of high-grade CIN, and the current histopathological examination is difficult to distinguish between the lesions that will regress and those that will not.[5] Accordingly, surgical excision is the most common treatment modality for most high-grade CINs. Cervical conization, a crucial method for diagnosing and treating CIN, primarily includes the 2 most frequent techniques of loop electrosurgical excision procedure (LEEP) and cold knife conization (CKC).[6,7] It is highly effective for CIN, but there are still 5% to 25% of patients suffering from recurrent or persistent high-grade lesions after treatment.[8–10] There was a piece of evidence suggesting that the risk of developing ICC in women with residual lesions or recurrence after treatment was about 5 times higher than the

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general population.[11] Meanwhile, incomplete follow-up was also associated with an increased risk of cervical cancer.[8,12] Consequently, the long-term follow-up after cervical conization is essential for accurately identifying the patients at high risk of recurrence.

In this study, we analyzed the clinical outcomes of patients with high-grade CIN 2 years after cervical conization and investigated the predictors of postoperative recurrence, aiming at providing some evidence for the suitable formulation of surgeries and postoperative follow-up regimens.

2. Materials and methods

2.1. Participants

The clinicopathologic data of 415 patients with CIN≥II who underwent LEEP or CKC in Xuzhou No.1 People's Hospital between January 2013 and January 2018 were retrospectively analyzed in this study. All the patients voluntarily participated in the study approved by the Institutional Review Board of Xuzhou No.1 People's Hospital (approval No.: xyykk[2020]26).

Inclusion criteria: CIN≥II diagnosed by cervical multi-site biopsy under the colposcope; patients undergoing LEEP or CKC; patients willing to cooperate with the follow-up. Exclusion criteria: patients complicated with other reproductive tract diseases, severe respiratory and circulation system diseases, as well as hepatic and renal dysfunction; patients receiving total hysterectomy, and those postoperatively diagnosed as ICC; patients with coagulation disorders or low-dose heparin treatment; patients with the previous history of cervical lesions, hormone replacement therapy, or acute infectious disease; pregnant women; patients who had taken other trial drugs 1 month before enrollment or were participating in other trials, and those unsuitable for this study according to clinician's assessment.

2.2. Methods

2.2.1. Collection of clinicopathological data. Through a detailed analysis of medical records, the clinicopathological data of patients were collected, including the age, body height, body weight, times of full-term birth and miscarriage, menopause status, smoking condition, history of premature labor, and complication with diseases (including diabetes, hypertension, and cerebral infarction), lesion degree, human papillomavirus (HPV) classification, as well as the margin status and range.

2.2.2. Surgical techniques. HPV detection was preoperatively performed in all patients, and intraoperatively LEEP or CKC was conducted after regular implementation of endocervical curettage. LEEP: cervical conization was performed under local anesthesia using a super high-frequency electric knife. Before excision, the cervix was stained with iodine solution, and the lesion location and range were confirmed in combination with colposcope images. The excision width was more than 0.3 to 0.5 cm of lesions, and the excision sample was sent to pathological examination after being marked. CKC: cervical conization was conducted under general anesthesia. The excision range was determined based on the lesion-involved range and presence or absence of fertility demands. Postoperatively, the suturing label was done at 12 points of cone bottom, and then the sample was sent to pathological examination.

2.2.3. Measurement of cervical conization samples. The cervical conization sample was placed in a 10% formalin solution for fixing 24 to 48 hours, and it was split across a vertical plane. Ronco et al found that fresh cervical tissues could shrink after fixation with formaldehyde, dehydration, and paraffin embedding, and its shrinking proportion was 15.3% of the fresh tissues. Accordingly, in our study, shrinking factors were taken into consideration. The corresponding cone range was calculated by the measuring results/0.847 × 2, namely the cone depth = sample width/0.847 × 2; the cone width = sample thickness/0.847 × 2; the cone length = sample length/0.847 × 2. Two pathologists were responsible for reviewing the pathological sample and rechecking the final lesion degree and margin status. The incisal margin is defined as positive based on the presence of high-grade CIN in any incisal margin or the distance from high-grade CIN to the incisal margin <1 mm.

2.3. Follow-up

Postoperatively, the patients were follow-up 2 years, and were rechecked respectively at 3, 6, 12, 18, and 24 months through the outpatient HPV examination and thin-prep cytology test. The diagnostic criteria for recurrence: CIN or cervical cancer at any degree was confirmed by cervical multi-site biopsy under the colposcope and/or endocervical curettage during the follow-up.

2.4. Statistical analysis

Statistical analysis was done using SAS software (version 9.4, SAS Institute Inc., NC). Normally distributed data presented as the mean ± standard deviation ($\overline{x} \pm s$) by *t* test, with abnormally distributed data as the median and quartile [$M(Q_{25}, Q_{75})$] by Mann–Whitney *U* rank-sum test. Chi-squared test or Fisher exact test was used to compare enumeration data manifesting as n (%). Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) regarding the association between postoperative recurrence and clinicopathological data. The variables with the *P*-value < .05 in the univariate analysis were included in a multivariate model, and those not significantly associated with postoperative recurrence were eliminated from the final model, unless a 10% or greater change was caused in the HR estimate for another variable or variables in the model.[13] The proportional hazards assumption was validated for each variable enrolled in the final model. For the continuous variable in the model, a restricted cubic diagram was drawn to reflect the variation tendency of the HR and 95% CI. The *P*-value exhibited 2-side, and that ≤.05 was considered statistically significant.

3. Results

3.1. Baseline information of participants

A total of 415 patients were eligible for the study according to inclusion and exclusion criteria, with the mean age of (43.45 ± 10.29) years. Among them, 14 (4.40%) cases had body mass index (BMI) <18.5 kg/m^2, 179 (56.29%) cases had BMI of 18.5 to 23.9 kg/m^2, and 125 (39.31%) cases had BMI ≥24 kg/m^2. There were 283 (68.19%) participants with a history of abortion, 259 (62.17%) with severe atypical hyperplasia, and 351 (86.67%) with high-risk HPV. After the mean follow-up of (21.48 ± 5.82) months, 90 cases (21.69%) were subjected to recurrence after cervical conization, while 325 (78.31) did not. The baseline information of participants was summarized in Table 1.

Table 1

Baseline characteristics of participants [n (%)/($\bar{x} \pm s$)/M (Q_{25}, Q_{75})].

Characteristics	Description (n = 415)
Age, yrs	43.45 ± 10.29
BMI, kg/m^2	
<18.5	14 (4.40)
18.5–23.9	179 (56.29)
≥24	125 (39.31)
Times of full-term birth	1 (1, 2)
History of preterm birth	5 (1.20)
History of abortion	283 (68.19)
Menopause	102 (24.58)
Lesion grading	
CIN II	156 (37.59)
Severe atypical hyperplasia	259 (62.17)
Carcinoma in situ	1 (0.24)
History of complicating diseases	33 (7.95)
HPV types	
High-risk	351 (86.67)
Intermediate-risk	31 (7.65)
Low-risk	23 (5.68)
Incisal margin status (positive)	86 (20.72)
Involvement of neck glands	221 (53.25)
Cone length, cm	2.00 (1.80, 4.00)
Cone width, cm	2.00 (1.50, 3.00)
Cone depth, cm	1.43 ± 0.83
Smoking	42 (10.37)
Follow-up time, month	21.48 ± 5.82
Outcomes	
Recurrence	90 (21.69)
No recurrence	325 (78.31)

BMI = body mass index, CIN = cervical intraepithelial neoplasia, HPV = human papillomavirus.

3.2. Univariate Cox analysis of recurrence after cervical conization

As shown in Table 2, univariate Cox analysis showed that the influencing factors for recurrence after cervical conization included times of full-term birth (HR = 1.512, 95% CI: 1.191–1.920, $P < .05$), history of preterm birth (HR = 7.255, 95% CI: 2.645–19.900, $P < .05$), history of abortion (HR = 2.158, 95% CI: 1.273–3.660, $P < .05$), positive margin (HR = 1.724, 95% CI: 1.092–2.720, $P < .05$), cone length (HR = 0.953, 95% CI: 0.918–0.989, $P < .05$), width (HR = 0.924, 95% CI: 0.8–0.975, $P < .05$), depth (HR = 0.390, 95% CI: 0.285–.535, $P < .05$), smoking (HR = 2.143, 95% CI: 1.264–3.634, $P = .05$), and history of complicating diseases (HR = 3.392, 95% CI: 2.022–5.691, $P < .05$), but not age, BMI, menopause, lesion grading, HPV types, and involvement of neck glands (all $P > .05$).

3.3. Multivariate Cox model of recurrence after cervical conization

The factors with statistically different in univariate analysis (times of full-term birth, history of preterm birth, history of abortion, incisal margin status, conization length, width, thickness, smoking, and history of complicating diseases) were included in the multivariate Cox model.

The finally established multivariate Cox model indicated that the positive margin (HR = 2.144, 95% CI: 1.317–3.492, $P < .05$), history of preterm birth (HR = 4.515, 95% CI: 1.598–12.754, $P < .05$), history of complicating diseases (HR = 3.552, 95% CI: 1.952–6.462, $P < .05$) were independent risk factors for recurrence after cervical conization (Table 3). Based on the cone depth, the risk of postoperative recurrence was drawn in Fig. 1. It could be observed that the cone depth >0.5 cm was a protective factor for postoperative recurrence.

Table 2

Univariate Cox analysis of recurrence after cervical conization.

Characteristics	β	S.E.	χ^2	P	HR	95% CI
Age, yr	–0.015	0.010	1.966	.161	0.986	0.966–1.006
Body mass index, kg/m^2						
<18.5	Ref					
18.5–23.9	0.057	0.519	0.012	.913	1.059	0.382–2.933
>23.9	0.017	0.221	0.006	.938	1.017	0.659–1.570
Times of full-term birth	0.414	0.122	11.536	<.001	1.512	1.191–1.920
History of preterm birth	1.982	0.515	14.816	.001	7.255	2.645–19.900
History of abortion	0.769	0.269	8.158	.004	2.158	1.273–3.660
Menopause	–0.367	0.269	1.861	.173	0.693	0.409–1.174
Lesion grading						
CIN II	Ref					
Severe atypical hyperplasia	0.218	0.223	0.955	.328	1.244	0.803–1.925
HPV types						
Low-risk	Ref					
Intermediate-risk	0.595	0.588	1.024	.312	1.813	0.573–5.739
High-risk	0.445	0.707	0.396	.529	1.560	0.390–6.239
Incisal margin status (positive)	0.544	0.233	5.476	.015	1.724	1.092–2.720
Involvement of neck glands	0.169	0.213	0.629	.428	1.184	0.780–1.796
Cone length, cm	–0.048	0.019	6.575	.010	0.953	0.918–0.989
Cone width, cm	-0.079	0.028	8.355	.004	0.924	0.875–0.975
Cone depth, cm	–0.940	0.161	34.210	<.001	0.390	0.285–0.535
Smoking	0.762	0.269	8.008	.005	2.143	1.264–3.634
History of complicating diseases	1.221	0.264	21.405	<.001	3.392	2.022–5.691

CI = confidence interval, HR = hazard ratio, S.E. = standard error.

Table 3

Multivariate Cox model of recurrence after cervical conization.

Characteristics	β	S.E.	χ^2	*P*	HR	95% CI
Age, yr	–0.016	0.013	1.479	.224	0.984	0.959–1.010
Times of full-term birth	0.280	0.152	3.423	.064	1.324	0.983–1.782
History of preterm birth	1.507	0.530	8.095	.004	4.515	1.598–12.754
History of abortion	0.067	0.304	0.049	.824	1.070	0.590–1.940
Incisal margin status (positive)	0.763	0.249	9.397	.002	2.144	1.317–3.492
Smoking	0.156	0.299	0.273	.601	1.169	0.651–2.101
History of complicating diseases	1.267	0.305	17.223	<.001	3.552	1.952–6.462
Cone width, cm	0.065	0.067	0.926	.336	1.067	0.935–1.217
Cone depth, cm	–0.036	0.094	0.146	.703	0.965	0.802–1.161
Cone width, cm	–1.021	0.249	16.804	<.001	0.360	0.221–0.587

CI = confidence interval, HR = hazard ratio, S.E. = standard error.

4. Discussion

It is well-known that positive treatment of high-grade CIN is critical to control the development and progression of cervical cancer. As one of the mainstays of high-grade CIN treatment, cervical conization allows the histological confirmation of lesions, assessment of resection margins, exclusion of invasive neoplasia, and uterine preservation.[14] The studies have demonstrated that for CIN, LEEP is associated with a significantly higher overall curative rate and a lower risk of cervical neoplasia recurrence than cryotherapy.[15–17] However, there still exists the risk of residual disease and recurrence after cervical conization. By identifying the predictors of recurrence in patients with high-grade CIN after cervical conization, we found that positive margins were associated with an increased risk of

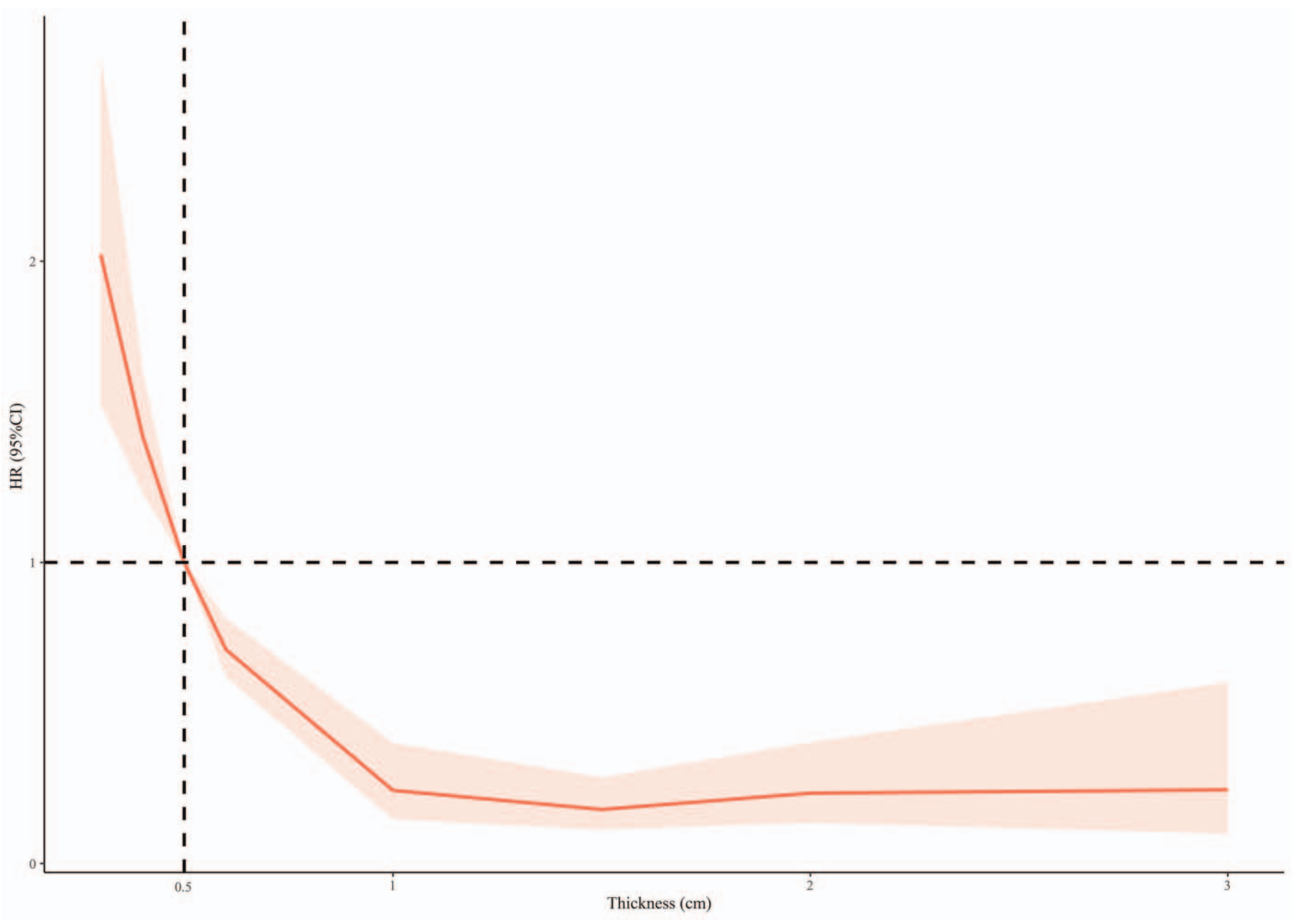

Figure 1. The risk of postoperative recurrence based on the cone depth. With 0.5 as the reference, the cone depth <0.5 cm is a risk factor for postoperative recurrence (HR >1), while the cone depth >0.5 cm had a protective effect on postoperative recurrence (HR <1). All significant differences are presented when 1 is excluded in 95% confidence interval.

recurrence, while the cone depth >0.5 cm with a reduced risk of recurrence.

Positive margins after cervical conization are usually thought to be incomplete excision, which is easy to cause the lesions remaining in the margins to progress into invasive carcinoma.[18] In a retrospective study of women over 50 years after large loop excision of the transformation zone, an association was observed between involved margins and disease recurrence.[19] A meta-analysis involving 35,109 women who received an excisional procedure for CIN showed that women with positive margins were more likely to be at a higher risk of posttreatment recurrence than those with clear or uncertain margins.[20] In addition, the probability of residual disease may also be increased if positive endocervical and ectocervical margins were concurrent. There was a piece of evidence suggesting that in 390 cases of positive margins after CKC for CIN III, the persistent or recurrent disease was more common in patients with positive endocervical and ectocervical margins than in those with only endocervical or ectocervical margin.[21] Our results further affirmed that positive margins were a significant risk factor for recurrence after cervical conization, supported by the results of Serati et al.[22]

Costa et al[23] reported that multiple factors, such as cone width, cone depth, lesion site, and lesion size, had no influence on the residual disease in CIN patients undergoing electrosurgical conization. In our study, however, it was found that the cone depth >0.5 cm was a protective factor for recurrence after cervical conization. The difference may be associated with the inclusion of diverse risk factors and high-risk HPV infection in our study. Based on the cone depth, a recent meta-analysis on adverse obstetric outcomes following local treatment for cervical preinvasive and early invasive diseases exhibited that the probability of preterm birth was gradually increased with increasing cone depth. This risk was respectively increased almost 2 folds, 3 folds, and almost 5 folds for excisions depth <1 cm when compared with excisions depth >1 cm, 1.5 to 1.7 cm, and >2 cm.[24] Therefore, the operators should flexibly control the cone depth according to the feasibility of excisions and patients' demands. For young women with demands for fertility, the conization should not be too deep, which not only can reduce the cervical deformation and stenosis induced by excessive excision of cervical tissue, consequently leading to a low risk of adverse pregnancy outcomes, but also can decrease the recurrent rate of CIN to a certain extent. For the women hoping to preserve the uterus but no demands for fertility, deep conization should be performed to decrease the recurrent rate as more as possible.

In this study, we found that preterm birth history was associated with the recurrence in patients with high-grade CIN after cervical conization. To our knowledge, the current study reported, for the first time, the association of preterm birth history with postoperative recurrence. However, the mechanisms underlying the independent associations between preterm birth history and recurrence are uncertain. It has been reported that patients with preterm deliveries are proved to exert a pro-inflammatory phenotype,[25] and inflammation is a strong predictor of CIN.[26] Besides, the previous study has shown that CIN is closely related to low socioeconomic status,[27] which has been confirmed to be associated with preterm birth.[28] Those studies might explain our finding of the unique association between postoperative recurrence and preterm birth history. Despite these limited data, our results suggest that it is necessary for patients with a history of preterm birth to undergo postoperation screening.

In addition, we found that the history of complicating diseases significantly predicted the recurrence after adjustment covariates. A large body of literature has reported associations between the CIN progression and/or HPV-infection and the complicating diseases. Of note, literature concerning the association of complicating diseases with CIN recurrence after treatment primarily focused on areas with a high prevalence of HIV.[29–31] There was no obvious relationship between positive margins during loop excision and HIV-infection in a piece of research conducted in the region with low HIV-infection prevalence.[32] A meta-analysis conducted by Arbyn et al[33] to explore the association of incomplete excision with treatment failure did not discuss these complicating diseases. Only in a Sweden cohort followed by 16 years, Aldex et al[34] found that comorbidity was a significant independent predictor of postoperative recurrence, which was basically consistent with our findings.

Emerging studies have highlighted the value of HPV persistency as a risk factor for CIN recurrence.[35–37] Nevertheless, in our study, HPV infection was not shown a risk factor for postoperative recurrence, supported by the results of Serati et al[22] and Lodi et al.[29] It may be attributed to the fact that most cervical lesions are transient and can regress spontaneously.[38] Accordingly, a close follow-up should be performed for women with high-risk HPV because of an increased risk of invasive carcinoma, while a shorter follow-up for those with consecutive negative HPV testing after cervical conization.

The superiority of this study was that the influencing factors of recurrence were assessed by the Cox proportional hazards model, which was not only appropriate for multivariate analysis but also for the assessment of influencing factors throughout the follow-up period. The use of proper statistical analysis was conductive to shunning the misleading results and confusing clinical information. In addition, a relatively long-term follow-up was performed since most recurrences were detected within 2 years after intervention. However, this study also had some limitations. For example, small sample size may affect the statistical power; clinical data were not completely collected due to the limitation of a retrospective study, such as HPV types and causes of premature birth.

5. Conclusions

For the patients with high-grade CIN after cervical conization, positive margins, histories of preterm birth and complicating diseases were associated with increased risk of recurrence, but cone depth (>0.5 cm) with a lower risk of recurrence. Thus, incisal margin status and cone depth should be controlled strictly during cervical conization to prevent a postoperative recurrence, and closer follow-up evaluation and more stringent cancer screening are required for patients with a history of preterm birth or complicating diseases.

Author contributions

Data curation: Yongli Liu, Yanbo Liu.
Methodology: Yun Cheng.
Project administration: Yun Cheng.
Software: Yanbo Liu.
Supervision: Yun Cheng.
Writing – original draft: Yan Ge, Yongli Liu.
Writing – review & editing: Yan Ge, Yun Cheng.

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