

Comparison of the safety between conization and hysterectomy for patients with cervical adenocarcinoma in situ

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Abstract

Objective: To compare the safety between conization alone and hysterectomy for patients with adenocarcinoma in situ (AIS) of the cervix. **Design:** A cohort study of AIS patients during 2007-2021. **Setting:** Women's Hospital of Zhejiang University School of Medicine. **Population:** A total of 453 AIS patients diagnosed by conization who underwent cervical conizations only (n=153) or conization followed by hysterectomy(n=300). **Methods:** The clinicopathological and follow-up data were reviewed. Univariate analysis was examined by chi-square test and multivariate analysis was performed by logistic regression analysis. **Main outcome measure:** The rates of residual disease in specimens of hysterectomy and repeated conization were compared between positive and negative margin of conization. And the rates of recurrence were compared between patients treated by conization(s) alone and hysterectomy. The factors influencing residual disease and recurrence were assessed, respectively. **Results:** Among 310 specimens of hysterectomy or repeated conization, the rates of residual disease were 50.56% (45/89) for positive margin and 2.26% (5/221) for negative margin, with a significant difference (p=0.000). Totally 4 patients recurred as vaginal intraepithelial neoplasia(VAIN)in those treated by hysterectomy and 1 recurred as cervical squamous intraepithelial neoplasia (CIN) in those treated by conization(s) alone. The rates of recurrence were 0.65% (1/153) for conization(s) alone and 1.33 % (4/300) for hysterectomy, with no significant difference (p=0.431). Hysterectomy was a factor influencing neither residual disease nor recurrence. **Conclusions:** Conization is an effective and safe option for patients with AIS of the cervix, provided the margin is negative. **Keywords:** adenocarcinoma in situ, conization, hysterectomy, margins.

Introduction

Adenocarcinoma in situ (AIS) of the uterine cervix is a precursor lesion for invasive cervical adenocarcinoma¹. The incidence of cervical AIS is increased over past few decades compared with high-grade cervical squamous intraepithelial neoplasia (CIN), especially among women aged 30–39 years, the average age at cervical AIS diagnosis is 36.9 years². Unlike CIN, AIS of the cervix is recommended to hysterectomy. For women who wish to maintain fertility, cervical conization is feasible, but total hysterectomy is preferred after completing the childbearing^{3, 4}. This type of treatment mode affects the quality of life in young patients even without reproductive requirements. The reason for concern about the safety of conservative treatment for cervical AIS is that it has long been considered as “jumping lesions with multifocal distribution-foci” of adenocarcinoma cells that are not contiguous², even if the margin status of conization is negative, there still is a high risk of residual AIS or invasive cancer in unresected tissues. However, there is insufficient evidence to demonstrate a skip lesion in cervical AIS up to now. It has been reported that cervical conization with negative margin may be safe for cervical AIS, but more evidence is needed.

We retrospectively collected 453 patients with cervical AIS, of those, 153 underwent conization(s) alone and 300 underwent conization followed by hysterectomy. The aim of this study was to evaluate the effect and safety of the conization alone in cervical AIS patients; and to investigate the factors for recurrence or progression that may guide optimal management and follow-up.

Patients and methods

Collection of patients

All patients, who were pathologically diagnosed as cervical AIS on cervical conization specimens and underwent repeated conization, hysterectomy or followed up respectively in Women's Hospital of Zhejiang University School of Medicine between January 2007 and May 2021, were collected using computerized databases from the Departments of Gynecologic Oncology and Pathology. Those were excluded if: i) a history of previous high-grade CIN, AIS or invasive cervical carcinoma; ii) previous surgery in cervix; iii) directly treated with hysterectomy; and iv) incomplete clinical and follow-up data. In 920 collected patients with cervical AIS, 453 eligible patients were included in this study, of those, 153 underwent conization(s) alone and 300 underwent conization followed by hysterectomy.

Medical records were reviewed, including demographic data, HPV status, cytology, colposcopy, pathologic findings, and treatment procedure and outcomes. HPV was detected by Hybrid Capture 2 (HC-II) HPV Test and [?]1 RLU/CO was defined as positive result. Cervical cytology was detected by Thinprep cytologic test (TCT) and results were classified according to the Bethesda System 2001, which classified as negative for intraepithelial lesions or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells-cannot exclude HSIL (ASC-H), squamous cell carcinoma (SCC), atypical glandular cells (AGC), adenocarcinoma in situ (AIS), and adenocarcinoma (AC). The cytology result [?] ASC-US or AGC was defined as abnormal.

The colposcopy adopted a photoelectric integrated system, (manufactured in Leisegang, Germany), and both acetic acid and lugol's iodine solution were used during the examination. The cervical transformation zone was classified as type I, II or III according to the International Federation for Cervical Pathology and Colposcopy in 2011⁵.

Conization was performed by cold knife (CKC) or loop electrosurgical excision procedure (LEEP). A positive margin was defined as lesion within 1 mm from the epithelial lesion to the surgical margins. Residual disease was defined as CIN, AIS or invasive cervical cancer was pathologically found in specimens of hysterectomy or repeated conization. The indications of hysterectomy were no child-bearing desire, older age, and/or conization with positive margin. The flowchart of patient collection was shown in Figure 1.

All pathologic diagnoses were thoroughly re-evaluated by two pathologists blindly. Recurrence was defined as the reappearance of cervical or vaginal intraepithelial neoplasia after hysterectomy or last cervical conization 3 months or later.

The study was approved by Women's Hospital Human Research Ethics Committee.

Follow-up

All patients were followed up by cytology and HPV testing, according to the procedures, scheduled every 3 months within two years, and every 6 months for three-five years, once a year thereafter. Patients with cytology abnormal and/or HPV positive were referred to colposcopy with or without biopsy. The mean follow-up period was 50.09 months (range12~170 months) from the time of first conization to August 31, 2021.

Statistical analysis

The SPSS version of 26 was adopted for statistical analysis in the study. Descriptive statistics were used to analyze the characteristics of the patients; univariate and multivariate analysis were performed with chi-square test and logistic regression for factors related to the residual and recurrence. P-value < 0.05 was considered statistically significant.

RESULTS

The patients' characteristics

The clinicopathological characteristics of 453 AIS patients, including 153 underwent cervical conization(s) alone and 300 underwent cervical conization followed by hysterectomy, were summarized in Table 1. There were 97.93% of HPV positive and 67.39% of abnormal cytology, respectively. The transformation zone was type III in 60.88% of the patients and type I~II in 39.12% of the patients. The initial conization margin was positive in 19.65% of the patients. Pathologically, 145 patients were AIS only, 308 patients were cervical AIS coexisting with CIN. The mean age was 34.54 ± 5.59 years in patients with cervical conization alone and 45.10 ± 7.77 years in patients with hysterectomy respectively. The flowchart of the study design was show in Figure 1.

Residual disease and its related factors

In 153 patients undergoing cervical conization alone, 143 had negative margins and 10 had positive margins who received repeated conization. In addition, 300 underwent further hysterectomy after conization, of those, 79 had positive margins and 221 had negative margins of conization. Thus, the overall rate of residual diseases was 16.13% in 310 specimens of hysterectomy and repeated conization. The rate of residual disease was 50.56% (45/89) for positive margins and 2.26% (5/221) for negative margins, respectively, with a significantly difference ($p=0.000$). In specimens with positive margins, 45 cases had residual diseases including 31 AIS, 9 CIN 2/3, and 5 (5/89, 5.62%) invasive adenocarcinoma. In specimens with negative margins, 5 cases had residual diseases including 4 AIS, 1 CIN 1, and 0 (0/221, 0%) invasive adenocarcinoma. The difference in the residual invasive carcinoma rate between patients with positive and negative conization margins was statistically significant (5.62% vs 0%, $p=0.000$).

The risk factors influencing residual disease were further analyzed by univariate (Table 2) and multivariate analysis. The results showed that pre-operative cytology ($p=0.012$), conization method ($p=0.011$), cone length ($p=0.008$), and positive margin ($p=0.000$) were significantly associated with residual disease, but only conization margin was the independent factor influencing residual disease (OR=0.018, 95% CI 0.006-0.060).

Recurrence and its related factors

Totally 5 patients recurred during follow-up period, and the recurrence rate was 1.33% in patients treated by hysterectomy and 0.65% in patients treated by cervical conization(s) alone, with no significant difference ($p=0.431$). In patients treated by hysterectomy, 3 recurred as VAIN1 and 1 recurred as VAIN3. While in patients treated by conization(s) alone, only 1 recurred as CIN1. VAIN patients were treated by electrocautery or vaginal diseases excision and CIN patient was treated by repeated conization.

Univariate and multivariate analysis were performed to evaluate the factors influencing recurrence in AIS patients. Univariate analysis showed that post-operative cytology and hrHPV-DNA status (both $p=0.000$) were significantly associated with recurrence (Table 3). Further, multivariate analysis revealed that post-operative cytology (OR=10.784, 95% CI 1.333-87.246) and HPV status (OR=23.413, 95% CI 2.097-261.453) were independent factors influencing recurrence. Both univariate and multivariate analysis did not demonstrate that surgery method was associated with recurrence.

DISCUSSION

The residual lesions in unresected tissue after cervical conization are the source of disease recurrence. For high-grade CIN after cervical conization, the overall risk of residual or recurrent CIN2+ was 6.6% (95% CI 4.9-8.4) and was increased with positive compared with negative resection margins (relative risk 4.8, 95% CI 3.2-7.2)⁶. Therefore, conization is considered to be safe and the preferred treatment for high-grade CIN. However, previous literature reports, the overall risk of residual after AIS conization was between 14.1-52.8%^{2, 7}, which was significantly higher than that of CIN. Therefore, hysterectomy is preferred for AIS. Further studies found that positive conization margin was associated with a significant increase in the risk of residual disease. A meta-analysis of 1278 AIS patients indicates that achieving negative margins after a surgical excision is associated with a significantly lower rate of residual and recurrent disease (20.3% and 2.6%, respectively) compared with patients with positive margins (52.8% and 19.4%, respectively)². Baalbergen⁸

reviewed 965 AIS patients in 35 studies, showed that the residual rate was 16.5% in negative margins versus 49.3% in positive margins. In this study, the overall rate of residual diseases was 16.13% in 310 specimens of hysterectomy and repeated conization. The rates of residual disease were 50.56% (45/89) for positive margin and 2.26% (5/221) for negative margin, respectively, with a significant difference ($p=0.000$). On the other hand, residual invasive cancer is the greatest risk for the safety of conization. Retrospective studies reported that the rate of residual invasive cancer was less than 6%², even lower in the negative margin patient. In our study the rates of residual invasive cancer were 5.26% (5/89) for positive margin and 0 % (0/221) for negative margin, respectively. Our and previously reported data suggest that the risk of residual lesion and residual invasive cancer was low after conical resection, provided the margin was negative.

Recurrence of the disease is the "golden standard" for determining the safety of cervical conization for AIS. As the literature reported, the recurrent rate was about 0-5% in AIS patients underwent conization, and 0-3% in those with negative margins⁷⁻¹¹. Baalbergen⁸ reviewed 36 studies involving 1277 AIS patients who were diagnosed by conization and underwent conservative treatment, 64 (5%) patients relapsed, of whom 3% had negative margins. Hanegem et al¹² performed a retrospective study including 112 young (age [?]30 years) patients with AIS treated conservatively, but no recurrence was found. In this study, totally 5 patients recurred during mean 50.09 months follow-up period, and the recurrent rates were 1.33% in patients treated by hysterectomy and 0.65% in patients treated by cervical conization(s) alone, with no significant difference ($p=0.431$). Moreover, no invasive adenocarcinoma recurrence was identified in patients with negative conization margins. Both univariate and multivariate analysis did not demonstrate that surgery method was associated with recurrence. Our results suggested that the recurrent rate was extremely low for AIS patients with negative conization margin. Hysterectomy eliminates recurrence of CIN, but can not reduce the recurrence of vaginal lesions.

"Long-term follow-up with a combination of co-testing and colposcopy with endocervical sampling" is a recommended strategy for AIS patients treated with conization, according to the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines¹³. The recommendation by ASCCP guidelines was supported by previous studies, in which cytology, HPV testing, and colposcopy evaluation was regarded as irreplaceable in monitoring recurrence of AIS with conservative treatment^{14, 15}. In this study, we found that both cytology and HPV status were independent factors influencing recurrence of AIS. All recurrent patients were diagnosed by combined cytology and HPV testing followed by colposcopy at the precancerous stage, and no patient progressed to invasive cancer.

In summary, the rates of residual disease in specimens of hysterectomy and repeated conization were 50.56 % for positive margin and 2.26 % for negative margin, among 310 cervical AIS patients undergoing conization. During mean 50.09 months follow-up period, 1 patient recurred as CIN in those treated by conization alone and 4 recurred as VAIN in those treated by hysterectomy, and no invasive cancer recurrence was found. Surgery method was not an independent factor influencing residual and recurrence. Our results suggest that conization is an effective and safe option for patients with AIS of the cervix, provided the margin is negative.

Declarations section

Declaration of Conflict of Interest: None.

All authors of this research paper have directly participated in the planning, execution, or analysis of the study and have read and approved the final version submitted. This paper is new and has been seen and approved by all listed authors. These authors contributed equally: Jingjing Liu, Yu Wang.

The study was approved by the Human Research Ethics Committee of the Women's Hospital Zhejiang University School of Medicine on June 28, 2021, and the reference number is PRO2020-656.

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Tables and figure legend

Table1 The clinicopathological characteristics of 453 AIS patients.

Table2 Risk factors of residual lesion by univariate analysis.

Table3Factors of recurrence by univariate analysis.

Figure 1. Flowchart of the study design. Of the 453 patients with AIS on conization, 300 women underwent hysterectomy followed cervical conization, 153 underwent cervical conization(s) alone (including 10 accepted second conization because of positive margins).

*The margin means initial conization margin.

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