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The Proportion and Predicting Factors of Residual Disease after Conization of Women Diagnosed with Adenocarcinoma in Situ (AIS) in a Tertiary Center

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ABSTRACT

Objectives: To investigate the proportion of residual disease after conization and the factors that significantly predict residual disease in patients diagnosed with adenocarcinoma in situ (AIS) on conization who underwent subsequent hysterectomy.

Materials and Methods: Medical records of patients who were diagnosed with AIS on conization during 2007-2019 were retrospectively reviewed, and the data were followed until December 2020. Demographic/clinical data, method of conization, pathology results, follow-up data, and oncologic outcomes were analyzed using descriptive statistics. Logistic regression for univariate and multivariate analyses in a stepwise model was used to identify factors that predict residual disease in hysterectomy tissue.

Results: A total of 149 AIS patients were evaluated for eligibility. Of those, 57 patients were excluded due to having coexisting adenocarcinoma. The remaining 92 patients were recruited. The mean age of patients was 43.4 ± 10.8 years. The most common preceding cytology was high-grade squamous intraepithelial lesion (HSIL). Subsequent hysterectomy was performed in 68 patients, and 20 (29.4%) of those were found to have residual disease. Age ≥ 50 and absence of coexisting HSIL were significant in univariate analysis, but only age ≥ 50 years [adjusted odds ratios (aOR): 3.667, 95% confidence interval (CI) 1.224-10.980, p = 0.017] was identified as an independent predictor of residual disease in multivariate analysis. The median follow-up time was 58.4 months, and all 92 patients were alive without disease.

Conclusion: The proportion of residual disease in patients diagnosed AIS was 29.4%. Age ≥ 50 years was identified as the only independent predictor of residual disease.

Keywords: cervix, adenocarcinoma in situ, conization, hysterectomy, residual diseases.

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สัดส่วนและปัจจัยทำนายรอยโรคที่เหลือภายหลังการตัดปากมดลูกเป็นรูปกรวย ในสตรีที่ได้รับการวินิจฉัยรอยโรคภายในเยื่อบุปากมดลูกชนิดอะดีโนคาร์ซิโนมา ในสถานพยาบาลตติยภูมิ

ยืนยง ปราชญาพิทักษ์, ไอรีน เรืองขจร, สุชานัน หาญอมรรุ่งเรือง, สุทธิพล อุดมพันธุรัก, ภควดี จันทรอำพร

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาสัดส่วนของการมีรอยโรคที่เหลืออยู่จากผลพยาธิวิทยาของการตัดมดลูก ในสตรีที่ได้รับการวินิจฉัยรอยโรคภายในเยื่อบุปากมดลูกชนิดอะดีโนคาร์ซิโนมาจากการตัดปากมดลูกเป็นรูปกรวย และเพื่อประเมินปัจจัยทำนายการมีรอยโรคที่เหลืออยู่ดังกล่าว*

วัสดุและวิธีการ: *ทำการเก็บข้อมูลย้อนหลังของสตรีที่ได้รับการวินิจฉัยรอยโรคภายในเยื่อบุปากมดลูกชนิดอะดีโนคาร์ซิโนมาจากการตัดปากมดลูกเป็นรูปกรวย ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2550 ถึง 31 ธันวาคม พ.ศ. 2562 และข้อมูลของการตรวจติดตามจนถึงวันที่ 31 ธันวาคม พ.ศ. 2563 นำข้อมูลต่างๆ ได้แก่ ข้อมูลทั่วไป วิธีการตัดปากมดลูกเป็นรูปกรวย ผลทางพยาธิวิทยา ผลการตรวจติดตาม และผลลัพธ์ทางมะเร็งวิทยานรีเวช มาวิเคราะห์ด้วยสถิติเชิงพรรณนา และสำหรับปัจจัยทำนายการมีรอยโรคที่เหลืออยู่ใช้การวิเคราะห์การถดถอย*

ผลการศึกษา: *จากสตรีทั้งหมด 149 คน ที่ได้รับการวินิจฉัยรอยโรคภายในเยื่อบุปากมดลูกชนิดอะดีโนคาร์ซิโนมาในช่วงระยะเวลาดังกล่าว สตรี 57 คน ถูกคัดออกเนื่องจากมีมะเร็งปากมดลูกชนิดอะดีโนคาร์ซิโนมาร่วมด้วย ดังนั้นได้สตรีที่เข้าเกณฑ์งานวิจัยจำนวน 92 คน พบว่ามีค่าเฉลี่ยของอายุของสตรี เท่ากับ 43.4 ± 10.8 ปี ในสตรีที่มีผลเซลล์วิทยาปากมดลูกนำมาก่อนส่วนใหญ่พบเป็นชนิด high-grade squamous intraepithelial lesion (HSIL) มีสตรีได้รับการตัดมดลูกภายหลังการตัดปากมดลูกเป็นรูปกรวย จำนวน 68 คน ในจำนวนนี้มีสตรี 20 คน ตรวจพบรอยโรคที่เหลืออยู่ คิดเป็นร้อยละ 29.4 จากการวิเคราะห์ตัวแปรเดี่ยว (univariate analysis) พบว่า อายุมากกว่าหรือเท่ากับ 50 ปี และรอยโรคภายในเยื่อบุปากมดลูกชนิดสแควมัสขั้นสูงที่พบจากการตัดปากมดลูกเป็นรูปกรวยมีความสัมพันธ์กับการตรวจพบรอยโรคที่เหลืออยู่อย่างมีนัยสำคัญทางสถิติ และเมื่อทำการวิเคราะห์ตัวแปรพหุ (multivariate analysis) พบว่า ปัจจัยทำนายรอยโรคที่เหลืออยู่ คือ อายุมากกว่าหรือเท่ากับ 50 ปี จะเพิ่มโอกาสการมีรอยโรคที่เหลืออยู่ถึง 3.667 เท่า (95% CI 1.224-10.980, p = 0.017]) ระยะเวลาการตรวจติดตามที่ค่ามัธยฐาน 58.4 เดือน [interquartile range 26.3-100.7] พบว่า สตรีทั้ง 92 คน มีชีวิตอยู่โดยปราศจากโรค*

สรุป: *สตรีที่ได้รับการวินิจฉัยรอยโรคภายในเยื่อบุปากมดลูกชนิดอะดีโนคาร์ซิโนจากการตัดปากมดลูกเป็นรูปกรวย เมื่อรับการตัดมดลูกพบรอยโรคที่เหลืออยู่ คิดเป็นสัดส่วนร้อยละ 29.4 และอายุมากกว่าหรือเท่ากับ 50 ปี เป็นปัจจัยทำนายการมีรอยโรคที่เหลืออยู่*

คำสำคัญ: *ปากมดลูก, รอยโรคภายในเยื่อบุปากมดลูกชนิดอะดีโนคาร์ซิโนมา, การตัดปากมดลูกเป็นรูปกรวย, การตัดมดลูก, การมีรอยโรคที่เหลืออยู่*

Introduction

Cervical adenocarcinoma in situ (AIS) is a pathology diagnosis on conization procedure that attempts to excise the whole transformation zone in a single piece of conization specimen with a length of ≥ 10 mm to ensure no coexisting invasive adenocarcinoma. Either cold knife conization (CKC) or loop electrical excision procedure (LEEP) can be used[1-3]. AIS is recognized as a precancerous lesion of cervical adenocarcinoma. Since they are similar in morphology and oncogenic human papillomavirus types, coexisting AIS was found in most cervical adenocarcinoma cases, and patients with AIS were younger than those with adenocarcinoma by at least 5 years[2,4]. AIS normally hides in endocervical crypts, and 10-15% present as "skip lesion", which is condition in which AIS is separated by normal mucosa ≥ 2 mm[3]. This phenomenon is the cause of residual disease being found in up to 50% of post-conization hysterectomy specimens[5-7]. In addition, the recurrence rate in conservative treatment after free margin conization was 2.6-3%, and the rate increased to 17-19.4% in positive margins cases[2,4]. For this reason, the American Society for Colposcopy and Cervical Pathology (ASCCP) 2019 and the Society of Gynecologic Oncology (SGO) 2020 recommend hysterectomy as the standard of treatment for women who do not need to remain fertile. However, in cases where fertility must be preserved, free margin conization and negative disease on endocervical curettage must be combined with close surveillance until the completion of childbearing[1,2].

The emergence of cervical cancer screening programs has led to a decrease in the incidence of cervical squamous precancerous lesion. On the contrary, the incidence of AIS has increased, and the mean age of patients at diagnosis was reported to be 35-37 years[2]. A current lifestyles trend in many countries is delayed childbearing, which increases the need for fertility-sparing surgical treatments. Accordingly, the primary aim of this study was to investigate the proportion of residual diseases after conization, and the secondary aim was to determine factors that independently predict residual disease in patients diagnosed with AIS on conization who underwent subsequent hysterectomy. Along with, to assess the oncologic outcomes of both definite hysterectomy and fertility conserved patients.

Materials and Methods

After receiving study approval from the Siriraj Institutional Review Broad of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (COA Si 009/2020), medical data of patients diagnosed with AIS on conization from January 2007 to December 2019 were retrospectively reviewed, and the data were followed until December 2020. Demographic and clinical data, preceding cervical cytology results, conization methods, pathological description of conization and hysterectomy specimens, post-surgical management, and follow-up data were collected, recorded, and analyzed. Written informed consent was not obtained due to the anonymous retrospective nature of this study.

Cervical cytology results were reclassified according to the Bethesda 2014 system. Conization tissue was inked prior to serial section and entirely submitted for microscopic evaluation. Histopathology diagnosis was made by gynecologic pathologists. Cone margins were divided into ectocervical and endocervical margins. Positive margin was defined as presence of squamous intra-epithelial lesions (SIL) or AIS at cone margins or ≤ 1 mm margin distance. According to histopathology criteria of the World Health Organization (WHO) 2014 classification, precancerous lesions was classified as either SIL and AIS. SIL was then further subclassified into low-grade SIL (LSIL) or high-grade

SIL (HSIL). In subsequent hysterectomy specimens, the "residual diseases" was defined as the presence of SIL, AIS, or invasive cervical cancer. In follow-up period, women were evaluated by pelvic examination together with cytology with/without high-risk human papillomavirus (HPV) testing every 6 months for 5 years and then every 1 year. Threshold for colposcopy was positive high-risk HPV or abnormal cytology at index atypical squamous cells of undetermined significance (ASC-US) or worse. Recurrent disease was defined as the histopathologic finding of SIL, AIS, or invasive cervical cancer at least 6 months after hysterectomy or conization.

Data were analyzed using SPSS Statistics software version 18.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to summarize baseline characteristics, such as demographic and clinical information, preceding cytology results, conization methods, subsequent management procedures, histopathology, residual diseases, and recurrent disease. Results were given as number and percentage. Continuous data was presented as median and interquartile range (IQR). Logistic regression analysis was used to identify independent predictors of residual disease in post-hysterectomy tissue. Univariate analysis was presented as odds ratio (OR) with 95% confidence intervals (CI) and multivariate analysis was presented as stepwise logistic regression. A p value (two-sided) less than 0.05 was considered to be statistically significant.

Results

A total of 2,093 women underwent conization at the Division of Gynecologic Oncology of the Department of Obstetrics and Gynecology during the study period. Of these, 149 medical records of patients with AIS on conization specimen were reviewed. The AIS patients with AIS on conization specimen were reviewed. The AIS patient recruitment process, including conization, subsequent management, and pathology results, is shown by flow diagram in Fig. 1. After excluding 57 patients for histopathologic diagnosis of AIS with concurrent adenocarcinoma, the remaining 92 patients were included for analysis. Thirty-two patients (34.8%) had positive cone margins. Of those, 2/13 of CKC (15.4%), and 30/79 of LEEP (37.9%) had positive margins. In 26 patients who positive cone margins had proportion of residual AIS and adenocarcinoma was 23.1% and 7.7%, respectively. But in 42 patients who negative cone margins were 16.7% and 4.8%, respectively.

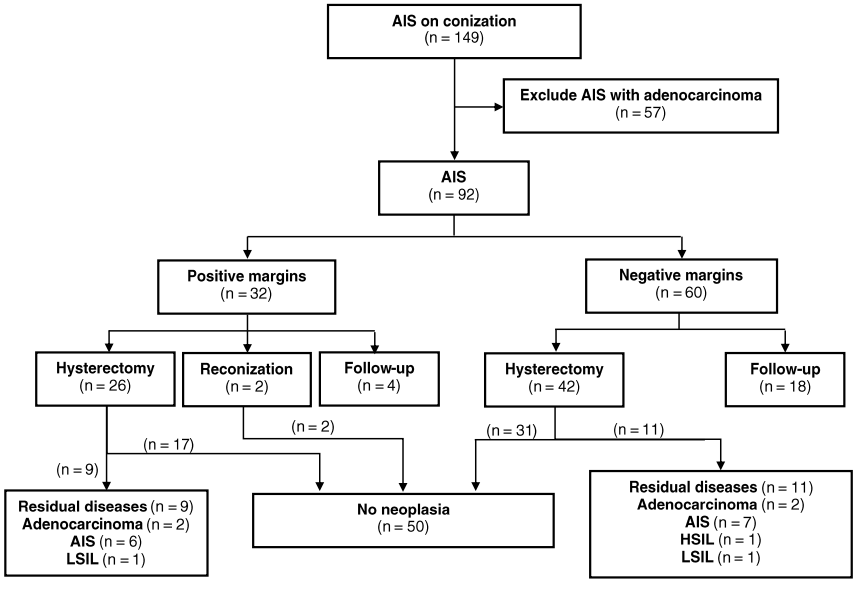

Fig. 1. Flow diagram demonstrating the recruitment process of patients with adenocarcinoma in situ on conization, and subsequent management with pathology results. AIS: adenocarcinoma in situ, HSIL: high-grade squamous intraepithelial lesion, LSIL: low-grade squamous intraepithelial lesion.

Demographic and clinical characteristics, pathologic findings, treatment outcomes, and laboratory investigations of 92 patients diagnosed with AIS on conization are shown in Table 1. The mean age of patients was 43.4 ± 10.8 years. The median parity was 2 (IQR 1-2). The median body mass index was 22.4 kg/m^2 (IQR 20.4-24.7). Seventy-one women (77.2%) were premenopausal. Eighty-seven patients had preceding cervical cytologies. The most common preceding cervical cytology was HSIL. Median time from conization to subsequent hysterectomy in 68 women was 10 weeks (IQR 8-12). Of these, 20 of 68 patients (29.4%) had residual diseases.

Table 1. Demographic and clinical characteristics, pathologic findings, treatment outcomes, and laboratory investigations of 92 patients diagnosed with adenocarcinoma in situ on conization.

Characteristics/ finding/ outcomes	Values
Preceding cytology	
NILM	2 (2.2%)
ASC-US	5 (5.4%)
LSIL	6 (6.5%)
ASC-H	5 (5.4%)
HSIL	35 (38.0%)
AGC-NOS	5 (5.4%)
AGC-FN	6 (6.5%)
AIS	13 (14.1%)
Adenocarcinoma	10 (10.9%)
Punch biopsies without cytology	1 (1.1%)
No data	4 (4.3%)
Conization method	
Cold knife conization	13 (14.1%)
Loop electrosurgical excision procedure	79 (85.9%)
Conization depth (mm)	10.3 (7.0-14.0)
Lesion size (quadrants)	
1	14 (15.2%)
2	19 (20.7%)
3	6 (6.5%)
4	18 (19.6%)
No data	35 (38.0%)
Coexisting squamous intraepithelial lesion	
None	35 (38.0%)
LSIL	3 (3.3%)
HSIL	54 (58.7%)
Conization margin	
Free margins	60 (65.2%)
Positive ectocervical margin	8 (8.7%)
Positive endocervical margin	24 (26.1%)
Disease at margins (n=32)	
LSIL	1 (3.1%)
HSIL	7 (21.9%)
AIS	15 (46.9%)
AIS and HSIL	9 (28.1%)

Table 1. Demographic and clinical characteristics, pathologic findings, treatment outcomes, and laboratory investigations of 92 patients diagnosed with adenocarcinoma in situ on conization. (Cont.)

Characteristics/ finding/ outcomes	Values
Pathology of subsequent hysterectomy (n = 68)	
No residual disease	48 (70.6%)
Residual LSIL	2 (2.9%)
Residual HSIL	1 (1.5%)
Residual AIS	13 (19.2%)
Adenocarcinoma	4 (5.9%)
Hemoglobin (g/dL)	12.7 (12.0-13.5)
Hematocrit (%)	38.9 (36.8-41.2)
Platelet count (/μL)	267,500 (227,000-301,750)
White blood cell count (/μL)	6,805 (5,680-8,368)
Neutrophil count (/μL)	4,002 (3,046-4,844)
Lymphocyte count (/μL)	2,154 (1,716-2,604)
Neutrophil/lymphocyte ratio	1.8 (1.5-2.4)

Data are presented as number (percentage) or median (interquartile range). AIS: adenocarcinoma in situ, AGC-FN: atypical glandular cells, favor neoplasia, AGC-NOS: atypical glandular cells, not otherwise specified, ASC-H: atypical squamous cell, cannot exclude HSIL, ASC-US: atypical squamous cells of undetermined significance, HSIL: high-grade squamous intraepithelial lesion, LSIL: low-grade squamous intraepithelial lesion, NILM: negative for intraepithelial lesions or malignancy

Univariate and multivariate analysis for predictive factors independently associated with residual disease in subsequent hysterectomy specimens is shown in Table 2. Conization methods, length of conization of ≥ 10 mm, and positive cone margins were not found to be significantly associated with residual diseases. Multivariate analysis showed that age of ≥ 50 years was to be the only one independent predictor of residual diseases with an adjusted OR of 3.667 (95%CI 1.224-10.980, p = 0.017) with a statistical power of 65%.

Table 2. Analysis for factors that significantly predict residual disease in 68 patients diagnosed adenocarcinoma in situ on conization who underwent subsequent hysterectomy.

Variables	Residual disease n (%)	Univariate	Multivariate
		OR [95%CI], p value	OR [95%CI], p value
Age (years)			
< 50 (n = 45)	9 (20.0%)	Reference	Reference
≥ 50 (n = 23)	11 (47.8%)	3.667 [1.224-10.980], 0.017	3.667 [1.224-10.980], 0.017
Coexisting HSIL			
No (n = 33)	14 (42.4%)	Reference	
Yes (n = 35)	6 (17.1%)	0.281 [0.092-0.859], 0.022	-
Conization method			
LEEP (n = 58)	17 (29.3%)	Reference	-
CKC (n = 10)	3 (30.0%)	0.967 [0.223-4.191], 1.000	
Conization length (mm)			
<10 (n = 29)	8 (27.6%)	Reference	-
≥10 (n = 39)	12 (30.8%)	0.857 [0.297-2.476], 0.776	
Disease at conization margins			
Negative (n = 42)	11 (26.2%)	Reference	-
Positive (n = 26)	9 (34.6%)	1.492 [0.516-4.311], 0.459	

OR: odds ratio, CI: confidence interval, CKC: cold knife conization, HSIL: high-grade squamous intraepithelial lesion, LEEP: loop electrosurgical excision procedure

Median follow-up time was 58.4 months (IQR 26.3-100.7). Recurrent vaginal HSIL was found in one patient at 20 months after laparoscopic total hysterectomy. The recurrent lesion was successfully treated by laser ablation. No disease recurrence was observed in 24 patients who did not undergo hysterectomy. All 92 patients were alive and disease-free at the end of the follow-up in December 2020.

Discussion

The current study showed the proportion of residual SIL/AIS/adenocarcinoma in patients who diagnosed with AIS on conization and who underwent postconization hysterectomy to be 29.4%. Negative cone margins demonstrated residual invasive disease in 4.8%. Age of ≥ 50 years and absence of co-existing HSIL were the factors significantly associated with increased risk of residual disease in univariate analysis, but age of ≥ 50 was found to be the only independent predictor of residual disease in multivariate analysis.

The proportion of positive cone margins in AIS patients was reported to be 27.5-45%, which was consistent with the findings of the present study[4-13]. The proportion of positive cone margins depends on various factors, such as definition of positive cone margins, methods of conization, and length of cone specimens. In this study, we used the same definition of positive cone margins as used by Kietpeerakool et al; however, most studies defined positive cone margins as the presence of AIS at the cone margins or AIS close to < 1 mm from the cone margins[7, 9, 12]. Alternatively, the other authors did not clearly describe how they defined positive cone margins[6, 8, 10].

In the present study, we found more positive cone margins in women treated with LEEP compared to those treated by CKC (37.9% vs. 15.4%, respectively) that consistent with other studies[4, 5, 9, 12, 13, 14]. A study from the University of Texas MD Anderson Cancer Center reported the proportion of positive cone margin AIS to be 37.8%, of which 30 were from 62 LEEP (48.4%) and 35 were from 110 CKC procedure (31.8%) (p = 0.017); however, they did not mention the length of cone specimens[9]. In contrast, Munro et al reported positive cone margin in 27.5% of patients, and the proportions in the LEEP and CKC procedures were 31.8% and 25%, respectively (p = 0.432). The length of conization specimens was reported to be significantly longer in the CKC group than in the LEEP group (16.1 mm vs. 10.7 mm, p < 0.001)[12]. Keitpeerakool et al found the average cone length from LEEP and CKC to be 9.5 mm and 16.3 mm, respectively, and LEEP had a significant higher proportion of positive cone margins compared to CKC (56.8% vs. 26.1%, respectively, p = 0.02)[5]. Young et al reported proportions of AIS positive cone margins of 50% for other conization methods, and 31% for CKC (p = 0.013). In contrast, another study found no significant difference in the length of cone specimens between the other conization methods and CKC methods (14.1 mm vs. 14.2 mm, respectively)[13]. A meta-analysis reported the proportion of positive cone margins to be 38.1%, and the proportions from the LEEP and CKC procedures were 51% and 30%, respectively[4]. A recent meta-analysis of 18 studies showed the proportion of positive cone margins after LEEP to be higher than after CKC (44% and 29%, respectively) (OR 1.55; 95%CI 1.34-1.80)[14]. That group also found the proportion of residual AIS/adenocarcinoma in subsequent reconization to be 9.1%, and in hysterectomy to be 11% (p > 0.05), and there was no significant difference in the recurrence rate between these two methods[14]. The current study and previous studies failed to address association of conization methods and proportion of residual or recurrent diseases[4,12,14]. Thus, all conization methods were not preferred in AIS and the length of cone was accepted to be more important than methods of conization[1-3].

The SGO reported the proportion of residual AIS and adenocarcinoma in postconization and received second excision specimens in cases with negative cone margins to be 20% and 2%, respectively. This proportion increase to 53% and 6%, respectively, in case with positive cone margins[2]. In 2014, a meta-analysis of 35 studies was conducted, with the enrollment of 2,125 patients diagnosed with AIS by conization. Subsequent repeat conization or hysterectomy was performed in 965 of those patients. Regarding cone margin status, residual AIS and adenocarcinoma in negative cone margins cases was found in 16.5% and 0.6% of patients,

respectively. In positive cone margin cases, residual AIS and adenocarcinoma was found in 49.3% and 5.9% of cases, respectively[4]. Keitpeerakool et al revealed a prevalence of residual AIS/HSIL in second excision specimens of 33%, and there was no case of carcinoma. They advocated positive neoplastic epithelium at the cone margin to be a strong predictor of residual AIS/HSIL ($p < 0.001$)[5]. Similarly, a study of 298 AIS patients undergoing second excision procedures found that patients who had positive cone margins had residual AIS in 56% of cases, and had adenocarcinoma in 12% of cases, whereas patients with negative cone margins had residual AIS in 20% of cases and had adenocarcinoma in 2% of cases (both comparisons $p < 0.001$)[15]. In contrast, the present study found the proportion of residual AIS/SIL/adenocarcinoma in postconization hysterectomy specimens to be as high as one-third (29.4%), and cone margins were not found to be associated with residual disease. This may be because of small number of participants for determining significant difference of margin status. Moreover, the proportion of residual carcinoma in postconization hysterectomy specimens was as high as 4.8%, even with negative cone margins.

The rate of coexisting SIL and AIS in the current study was consistent with the findings reported from previous studies (37.2-78.2%)[5, 8, 10, 12, 13, 15-18]. Furthermore, we found the absence of coexisting HSIL to be a significant predictor of residual diseases in univariate analysis. In contrary to the study of Tierny et al, they found coexisting SIL in 37.2% of AIS patients, and found no significant correlation with residual AIS/adenocarcinoma in re-excision specimens[15]. Compared with data from studies in conservative treatment, the author found that conization methods, positive cone margins, cone length more than 10 mm were not statistically correlated with persistent/recurrent of diseases[17, 18]. They found the age of > 30 years and absence of coexisting SIL to be risk factors for persistent/recurrent diseases with OR of 2.16 (95%CI 1.09-4.27), and 3.21 (95%CI 1.48-6.90), respectively[17]. Another study in 71 patients that receiving conservative treatment reported a proportion of coexisting SIL of 57.7%, and higher recurrent AIS in patients without coexisting SIL compared to those with coexisting SIL (17% vs. 2%, respectively, $p = 0.043$)[18]. The reasons that may explain the favorable effects of coexisting SIL include the fact that SIL lesions can easily be detected with screening program, and colposcopic criteria has been established to improve the detection of AIS before more aggressive pattern or migration of AIS into upper endocervical canal or beyond. Another reason is because SIL lesions are typically located mainly at the ectocervical area and might guide clinicians to perform large cone specimens.

Previous studies reported a median or mean age of AIS patients of 29-45 years[2,4]. The mean age at diagnosis in the current study was 43.4 years, which was consistent with previous findings from Thailand (45.1 years) and Korea (42 years)[5,10]. Age at diagnosis was reported to be younger in Western countries. Possible explanations for this difference include: (i) sexual activity is initiated later in Asians, and (ii) high-risk HPV genotypes in Asian patients, such as HPV 52, 58, and 66, may be less virulent than high-risk genotypes in Western countries. Unfortunately, the preservative treatment for fertility desire is not an issue because the mean age at diagnosis and the age associated with the increased residual AIS/SIL/adenocarcinoma in postconization hysterectomy are both out of reproductive period.

The strengths of this study used clearly definition of positive margin diseases, and recurrent disease types. Moreover, this study included only the participants undergoing hysterectomy for analyzing residual diseases to ensure diagnosis of all skip lesions. The limitations of this study included its retrospective design, quit not large sample size, and the lack of HPV genotyping data.

HPV genotyping or methylation profiles simultaneous at the time of conization should be further study. This information would help to predict residual diseases, which would facilitate triage of patient to undergo hysterectomy or safe uterine preservation. Furthermore, the virulence of the HPV types could help to estimate the time to recurrence in patients with

conservative treatment, which may have an influence on time of conception or time of definite radical surgery.

Conclusion

In conclusion, one-third of study patients had residual diseases. Age ≥ 50 years and absence of co-existing HSIL were factors significantly associated with increased risk of residual disease, but age ≥ 50 was the only independent predictor of residual disease. Negative cone margin was found not to ensure the absence of invasive disease. As such, women with AIS who have a strong desire to preserve their fertility and agree to accept the risk of residual disease can be conservatively treated by cervical conization and continuous monitoring. Hysterectomy can then be performed when these women complete childbearing.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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