

Original Article

Predictive value of clinicopathological characteristics for residual disease in subsequent hysterectomy specimens following cervical conization

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Abstract: Objectives: A hysterectomy is a pre-emptive treatment procedure for some cervical diseases. The goal of this study was to identify predictors for development of residual disease in hysterectomy specimens following cervical conization. Methods: This study retrospectively analyzed 408 patients, admitted to Fudan University Shanghai Cancer Center, between June 2010 and April 2018. They underwent hysterectomy procedures within 6 months of conization. Descriptive analysis and logistic regression were used with indicators, including age, margins/ECC (endocervical curettage) status, pathology types, and menopause state. Results: A percentage of 43.14% (176/408) of patients had residual disease after the hysterectomy procedure. PPV (positive predictive value) and NPV (negative predictive value) values of the margin status to residual disease were 47.78% and 61.46%, respectively. Regarding ECC status, values were 55.81% and 62.20%, respectively. For both positive, the PPV was 57.14% (positive likelihood ratio: 26.20). For both negative, the NPV was 71.28% (negative likelihood ratio: 0.6) and 27/94 (28.72%) had residual disease in the hysterectomy specimen. Multivariate regression analysis showed that both margin status (OR, 2.066; 95% CI: 1.213-3.518) and ECC status (OR: 2.075; 95% CI: 1.196-3.600) provided predictive value. According to univariate regression analysis, only ECC status (OR 2.078; 95% CI: 1.223-3.530) did show predictive value. However, age, menopause state, and pathology types did not. Conclusion: Margin status and ECC status may predict the presence of residual disease after conization. For patients negative with both variables, a hysterectomy is acceptable, as they may have residual disease after conization.

Keywords: Pre-invasive cervical cancer, electrode conization/LEEP, positive margin, positive endocervical curettage, residual disease, hysterectomy

Introduction

Cervical intraepithelial neoplasia is in a pre-carcinoma state. It is critical in identifying and preventing the development of invasive cancer. Conization [including the LEEP (loop electrosurgical excision procedure)] is most widely accepted method for treatment of pre-invasive cancer. In most cases, conservative surgery is curative for pre-invasive cancer. However, Kolstad et al. [1] reported a follow-up of 795 women that had undergone therapeutic conization for CIS (carcinoma *in situ*) for 5-25 years. Of these women, 19 (2.3%) had recurrent CIS, while 7 patients (0.9%) developed invasive cancer. After this initial finding, several other reports showed that women that had undergone therapeutic conization could still have residual

disease in a hysterectomy specimen. The rate was approximately 31.6%-53.25% [2-5]. According to some predictors, women with residual disease usually undergo secondary conization or hysterectomy procedures.

Several reports have shown that margin involvement [2, 6], AIS (adenocarcinoma *in situ*) [3], history of ECC [7], and age [4, 8] could partially predict the development of residual disease after conization/LEEP. However, these studies are still considered to be controversial [8-10]. Some articles have reported either recurrent or residual disease during follow-ups after conization [1, 11]. However, the only method to confirm whether a patient had residual disease present is analysis of hysterectomy specimens directly after conization.

Characteristics predict residual disease after subsequent hysterectomy specimens

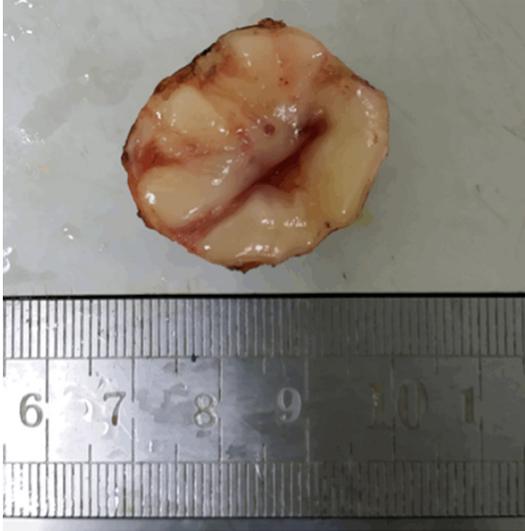


Figure 1. Conization specimen.

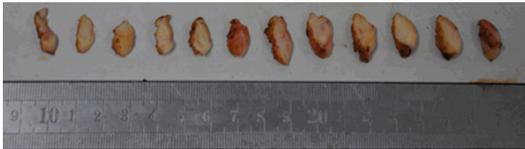


Figure 2. The 12 sections of a single conization specimen.

The current study hypothesized that pathological features presented in the conization/LEEP specimen and demographic characteristics of patients could predict the presence of residual disease in a hysterectomy specimen. These could be used to as guidelines for further therapy. The aim of the current study was to validate these predictive factors and to identify a group of women that would most benefit from having definitive treatment following conization for pre-invasive cancer.

Materials and methods

Patients and specimens

Medical records of 3,450 patients diagnosed with CIN II-III (cervical intraepithelial neoplasia II-III)/AIS, between June 2010 and April 2018, were reviewed at Fudan University Shanghai Cancer Center. Patients that underwent either electrode conization or LEEP, then had a hysterectomy within 6 months after conization, were included. Patients that had a hysterectomy more than 6 months and were not diagnosed with CIN/AIS by a pathologist after conization were excluded. Based on these criteria, 408 patients qualified for analysis. The Ethics Co-

mmittee of Fudan University Shanghai Cancer Center approved the current study. The 12 o'clock position in the excised specimen was marked by either a suture or an incision (**Figure 1**). Twelve sections from each cone or LEEP specimen were submitted for microscopic examination (**Figures 2** and **3**). All slides were reviewed by a pathologist at the Department of Pathology at Fudan University Shanghai Cancer Center. Pathology reports were obtained from the Fudan University Shanghai Cancer Center medical information computer system.

Data collection and statistical analysis

Collected data included age, menopause state, type of procedure (electrode conization or LEEP), pathological categories, ECC, and margin status. The highest degree of abnormality on the conization specimen was recorded. Pathological categories of the conization specimen were as follows: CIN II/III, AIS, and CIN II-III+AIS. Margins and ECC were classified as either positive or negative. Pathological reports of subsequent hysterectomies of included patients were identified as either having residual disease (pre-invasive cancer) or no residual disease (lack of invasive cancer).

Descriptive study methods were used to determine the association between variables (age, pathological status, margin status, ECC status, and menopause state) and the presence of residual disease in hysterectomy specimens, using specificity and sensitivity indicators, such as PPV, NPV, and LR (likelihood ratio). Univariate logistic regression was used to estimate the relationship between predictors and occurrence of residual disease in hysterectomy specimens. Odds ratios (an estimate of the relative risk of residual disease, OR) and 95% confidence intervals (CI) were calculated for each variable. Variables (ECC specimen findings, margin status, age, menopause state, and histopathological types) were then combined in multivariate logistic regression, estimating the incremental risk of residual disease for each factor adjusted for other factors. *P*-values less than or equal to 0.05 indicate statistical significance for all analyses.

Results

Baseline characteristics shows margin status could predict residual disease

According to pathological reports from Fudan University Shanghai Cancer Center and the

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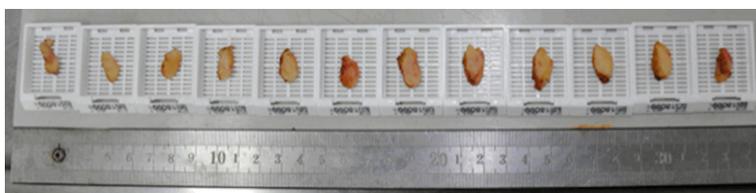


Figure 3. Making paraffin-embedded sections.

Table 1. Baseline characteristics of the patients

	Total	Residual disease (+)	Residual disease (-)	P
Age				
Median (range)	44 (29-72)	44.89 (29-44)	44.88 (31-72)	0.9885
First treatment				
LEEP	79	31	48	< 0.01
Conization	329	145	184	
Pathologic Subtype				
AIS	11	6	5	0.960
AIS+CIN	7	3	4	
CIN II	29	12	17	
CIN II-III	100	43	57	
CIN III	261	112	149	
Margin				
Margin+	204	98	106	0.046
Margin-	204	78	126	
ECC				
ECC +	86	48	38	0.838
ECC -	50	27	23	

ECC: endocervical curettage, LEEP: loop electrosurgical excision procedure, AIS: adenocarcinoma in situ, CIN: cervical intraepithelial neoplasia.

Table 2. Predictive value of the conization margin status to residual disease in hysterectomy specimens

	< 40 years	≥ 40, < 50 years	≥ 50 years	Total
Sensitivity	52.63%	51.64%	65.91%	55.11%
Specificity	37.74%	55.20%	68.52%	54.31%
PPV	37.74%	46.15%	63.04%	47.78%
NPV	52.63%	60.00%	71.15%	61.46%

PPV: positive predictive value, NPV: negative predictive value.

inclusion criteria, 408 patients were included. Of these, 43.14% (176/408) of patients had residual disease (pre-invasive cancer) in their hysterectomy specimen. All included patients had a margin status report, but only 250 patients had an ECC status report. Seventy-nine (19.36%) of the 408 patients underwent

LEEP, while the other 329 (80.64%) patients underwent electrode conization before hysterectomies. The conization report revealed that 391 (95.83%) patients were positive for CIN II-III, 10 (2.45%) patients had AIS, and 7 (1.71%) patients were diagnosed with both AIS and CIN.

The median age was 44 years (range of 29-72.) Ninety-one patients were under the age of 40. Of these, 41.76% (38/91) had residual disease present in the hysterectomy specimen (**Table 1**). There were 219 patients between the ages of 40 and 50 years old and 42.92% (94/219) of these patients had residual disease detected in their specimen tissue after hysterectomies. Finally, 98 patients were over the age of 50 years old and 44.90% (44/98) of them had residual disease.

Of the 408 patients, residual disease was present in 48.53% (99/204) of patients with a positive conization margin, while 38.24% (78/204) of patients showed a negative conization margin. Of the 250 patients that had an ECC report, residual disease was present in 55.81% (48/86) of patients with a positive ECC and 37.80% (62/164) of patients with a negative ECC after cervical conization.

Sensitivity, specificity, PPV, and NPV were increased when margin was positive and were decreased when ECC was positive with age increased in descriptive analysis

Tables 2-4 present descriptive study summaries of either the presence or absence of residual disease in patients regarding margin status and/or ECC status.

The PPV of the margin status to detect residual disease was 47.78%. The NPV was 61.46% (**Table 2**). For the 250 patients with ECC reports, the PPV was 55.81% and the NPV was 62.20% (**Table 3**). When margin and ECC statuses were

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Table 3. Predictive value of the conization ECC status to residual disease in hysterectomy specimens

	< 40 years old	≥ 40, < 50 years	≥ 50 years	Total
Sensitivity	50.00%	45.00%	31.81%	43.64%
Specificity	83.33%	69.51%	71.43%	72.86%
PPV	73.68%	51.92%	46.67%	55.81%
NPV	64.10%	63.33%	57.14%	62.20%

PPV: positive predictive value, NPV: negative predictive value, ECC: endocervical curettage.

Table 4. Predictive value of the conization margin and ECC status to residual disease of hysterectomy specimens

	Margin (+) and ECC (+)	Margin (+) and ECC (-) or margin and (-) ECC (+)	Margin (-) and ECC (-)
Sensitivity	18.18%	75.45%	71.82%
Specificity	89.29%	47.86%	46.84%
PPV	57.14%	53.21%	53.21%
NPV	58.14%	71.28%	71.28%
LR	+26.20	+1.35	-0.60

PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio, ECC: endocervical curettage.

analyzed together, the PPV was 57.14% and the NPV was 71.28%, regarding the presence of residual disease in the hysterectomy specimen. However, the positive likelihood ratio (LR+) was 26.20. The negative likelihood ratio (LR-) was 0.60 (Table 4).

This study observed 27 of 94 (28.72%) patients whose margin and ECC statuses were both negative and that had residual disease detected in hysterectomy specimens. Of these “false negatives”, 22 (81.48%) of them were older than 40.

ECC and margin status could predict residual disease in regression analysis

Using univariate logistic regression, only positive ECC specimens (odds ratio [OR], 2.078; 95% CI: 1.223-3.530; P = 0.007) were significantly associated with the presence of residual disease. Positive margin (OR, 1.460; 95% CI: 0.985-2.164; P = 0.60), age (≥ 40, < 50 years OR: 0.880, 95% CI 0.495-1.556; P = 0.663; ≥ 50 years OR: 0.923, 95% CI 0.570-1.491; P = 0.743), and pathological types (OR: 1.509, 95% CI 0.573-3.993; P = 0.407) were unable to predict residual disease in hysterectomy specimens with statistical significance (Table 5).

According to multivariate logistic regression analysis, margin involved (OR, 2.066; 95% CI: 1.213-3.518; P = 0.008) and positive ECC specimen findings (OR, 2.242; 95% CI: 1.196-3.600; P = 0.009) were significant predictors of the presence of residual disease in a hysterectomy specimen (Table 5).

Discussion

The current study discovered that approximately half of the hysterectomy specimens from the patient cohort had residual disease. Thus, it necessary to classify possible predictors of residual disease in hysterectomy specimens after conization.

Some reports have combined the detection of residual and recurrent disease for their analyses [1, 4]. However, the current study only included patients that had a hysterectomy within 6 months after conization, without any subsequent recurrence. This was to ensure the disease was residual but not recurrent. Additionally, the number of patients included in this study bolstered its reliability.

Results showed that margin status and a history of ECC could predict the presence of residual disease in a hysterectomy specimen. Meta-analysis was performed by Sadaf and his colleagues in 2007, showing that a positive margin had an RR (relative risk) of 5.47 (95% CI 4.37-6.83) to either residual or recurrent disease of any grade. The RR of high-grade disease was 6.09 (3.87-9.60), compared to the reference group, showing a negative margin. High-grade residual disease occurred in 597 of 3,335 (18%) women that had a positive margin versus 318 of 12,493 (3%) women that had a negative margin [12].

With regard to ECC status, Husseinzadeh et al. [7] and Kobak [8] et al. considered it to be a necessary predictive factor for the presence of residual disease, in accord with current results. Husseinzadeh and colleagues also observed that, when the inner margins of the cone were involved with CIN

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Table 5. The prediction values of the conization margin and ECC status, age, pathological types and menopause state to the residual disease in hysterectomy specimens

Variables	Univariate regression analysis			Multivariate regression analysis		
	OR	95% CI	P	OR	95% CI	P
Margin status	1.460	0.985, 2.164	0.60	2.066	1.213, 3.518	0.008
ECC specimens	2.078	1.223, 3.530	0.007	2.075	1.196, 3.600	0.009
Age						
<40 years*	1.000	1.000	1.000	1.000	1.000	1.000
≥40, <50 years	0.880	0.495, 1.566	0.663	0.992	0.449, 2.192	0.984
≥50 years	0.923	0.570, 1.491	0.743	0.848	0.433, 1.663	0.632
Pathological types	1.509	0.573, 3.993	0.407	2.807	0.426, 18.504	0.283
Menopause	1.123	0.688, 1.834	0.641	1.318	0.611, 2.840	0.481

*The age group analysis is based on the patient group <40 years. ECC: endocervical curettage. CI: confidence interval. OR: odds ratio.

III and the post-cone ECC was negative, 36% of hysterectomy specimens contained residual disease, compared to 88% of specimens when the post-cone ECC was positive. The 104 patients in the Kobak WH. study were divided into ECC-positive and ECC-negative groups. Invasive cancer was not presented in any of the patients in the benign ECC group but was presented in nine (22%) patients in the dysplasia group ($P < .0001$). A comparison of patients with involved endocervical margins revealed that none of the 37 patients in the benign ECC group had invasive cancer, compared to eight of 27 patients in the dysplasia group ($P < .0005$). Although ECC is a well-established predictor, its status remains under debate. Vierhout ME [13] and Spann CO Jr. [14] doubted ECC's predictive value because there was no significant increase when combined with margin status. The predictive value of the ECC status was less than that of the margin status. Since this might be because of the analysis method, present researchers viewed other articles. Lin H. et al. used multivariate logistic regression to determine if ECC status, margin status, menopause, and severity of disease could predict disease invasiveness. This group observed the postmenopausal state and found that a positive ECC, positive margin, and micro-invasive carcinoma could predict residual dysplasia. The probabilities of having residual dysplasia were approximately 0.99, 0.84, 0.4, 0.07, and 0.01 in patients with a presence of all four, any three, any two, any one, and no risk factors, respectively [2]. However, using the same analysis method, Ramchandani, S. M. [6] suggested that ECC did not have predictive value for residual disease.

According to the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines published in 2013 [15], if a margin of conization specimen is clear and follow-ups are sufficient, co-testing (HPV and cytology tests) at 12 months and 24 months is recommended. If both co-tests are negative, retesting in 3 years is recommended. Neither a repeat treatment nor a hysterectomy based on a positive HPV test are acceptable. However, in the current study, 38.24% (78/204) of patients whose margin was negative had residual disease, while 28.72% (27/94) of patients whose margin and ECC were both negative had the residual disease in their hysterectomy specimen. This suggests that, despite a negative margin and ECC status, there may be residual disease present. In this context, a hysterectomy is acceptable for conservatively treated patients that are unavailable for close follow-ups.

In this study, 94 patients had a hysterectomy, even though their margin and ECC statuses were both negative after conization. Because most of these patients had no desire to become pregnant, the median age of this group was 45 years old. It was speculated this might account for the HPV pathology in different locations, as the CIN/AIS pathologies were multifocal [16]. Conversely, during the collection of materials by pathologists, random errors existed. Pathologists viewed only a small section (3-4 μ m) from a paraffin-block of tissue, approximately 4-5 mm in size. These 3 reasons explain how negative margin and ECC statuses from the conization specimen could still result in residual disease.

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Increasing age has been shown to be a predictor for development of residual disease in hysterectomy specimens. Park et al. observed that age ≥ 50 years (RR: 2.74; 95% CI: 1.0-7.4) and a positive resection margin (RR: 4.35; 95% CI: 1.5-12.3; $P = 0.004$) were significant factors associated with residual disease [5]. Barbara et al. compared 25-year-old women with 40-year-old women. They found that the odds ratio of residual disease in the hysterectomy specimen was 2.7 (95% CI: 1.6-4.4) and 4.9 (95% CI: 2.2 to 10.8), respectively [4]. Lin [2] agreed that a postmenopausal status could predict residual disease. In conjunction with a positive ECC, positive margin, and micro invasive cancer, the probability of having residual dysplasia was approximately 0.99. The current study analyzed the association between age and menopause with the detection of residual disease in a hysterectomy specimen. However, there was no predictive power for either variable.

There was no association between pathological subtypes and presence of residual disease in the hysterectomy specimens because there were more CIN II-III patients (391) than AIS patients (17). However, Elena S. Diaz and colleagues [3] performed a retrospective study of 83 women with pre-invasive cancer, diagnosed by means of conization. They found that patients with squamous histology may not require repeat conization prior to definitive therapy. None of the factors explored here were able to predict residual disease with adenocarcinoma. In women with AIS, it is reasonable to proceed with a simple hysterectomy, even if the margins and ECC were negative and there was no evidence of microinvasion.

In summary, positive margin and positive ECC statuses after conization could predict the presence of residual disease in hysterectomy specimens. However, even if the margins and ECC are both clear, there could still be residual disease. Thus, these parameters are not recommended for replacement of conventional screening after conization, in accordance with the current guidelines [15]. However, a hysterectomy is acceptable following the conization if patient follow-ups are not feasible and the patient no longer wishes to become pregnant.

Disclosure of conflict of interest

None.

Abbreviations

ECC, endocervical curettage; PPV, positive predictive value; NPV, negative predictive value; LEEP, loop electrosurgical excision procedure; CIS, carcinoma in situ; AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; LR, likelihood ratio; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; OR, odds ratio; RR, relative risk; ASCCP, American Society for Colposcopy and Cervical Pathology.

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