International Journal of General Medicine

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ORIGINAL RESEARCH

Risk Factors for Residual Disease in Hysterectomy Specimens After Conization in Post-Menopausal Patients with Cervical Intraepithelial Neoplasia Grade 3

This article was published in the following Dove Press journal:
International Journal of General Medicine

International Journal of General Medicine downloaded from https://www.dovepress.com/
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Background: Post-menopausal patients with cervical intraepithelial neoplasia (CIN) have a high rate of residual or recurrent lesions after treatment, and their risk for cervical cancer later in life is higher than the general population. Hence, management for this specific group of post-menopausal patients needs more attention.

Objective: The study aimed to identify risk factors associated with the presence of residual disease in hysterectomy specimens in post-menopausal patients with cervical intraepithelial neoplasia grade 3 (CIN 3).

Methods: This study was a retrospective analysis of data from post-menopausal women who had undergone hysterectomy following conization for CIN 3 from 2012 to 2018 at Fujian Maternity and Child Health Hospital. Factors extracted from the database included age, parity, Thinprep cytology results, human papillomavirus (HPV) genotype, biopsy results, pre-cone endocervical curettage (ECC) results, conization method, operating surgeon, cone dimension, margin status and glandular involvement. Univariate and multivariate analyses were performed to identify risk factors associated with residual disease in hysterectomy specimens.

Results: Analysis of data from 129 women was performed. The proportion of residual disease was 43.41% overall. A higher grade according to colposcopy biopsy, abnormal pre-cone ECC results, the cone method (LEEP vs CKC), a cone volume >1.57 cm^3, and positive margins in conization specimens were found to be significantly associated with residual lesions on univariable analysis. After multivariate analysis, only an abnormal pre-cone ECC result (odds ratio 3.99; 95% confidence interval (CI) 1.41–11.33; p = 0.009) remained significant.

Conclusion: The rate of residual lesions in uterine specimens was high regardless of the cone margin status in post-menopausal women with CIN 3. Risk-based strategies are needed to identify patients who have abnormal pre-cone ECC results, and definitive treatment with hysterectomy should be considered in post-menopausal patients with an elevated risk for residual lesions.

Keywords: cervical intraepithelial lesion, menopause, margin status, endocervical curettage

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Introduction

To effectively reduce morbidity and mortality from cervical cancer, the most commonly used treatment modality for high-grade intraepithelial lesions (HSILs), or cervical intraepithelial neoplasia (CIN) grades 2–3, is excisional procedures, including the loop electrosurgical excision procedure (LEEP) and cold-knife conization (CKC).[1] However, excisional treatments pose problems

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such as incomplete eradication with significantly higher risks of residual or recurrent lesions.[2] Studies have reported that residual disease or recurrence of CIN 2+ after treatment ranges from 1.1% to 17.7%.[3–11] In addition, the risk for cervical cancer in patients treated for CIN 2–3 can be fivefold higher than that in the general population.[12] Therefore, to make more appropriate management decisions in clinical practice, many researchers have investigated risk factors that may predict residual disease after treatment for CIN 2–3.[3,5–10,13–17] Some have found that menopausal status[17] and older age (>45 years)[15] are associated with a higher risk for residual disease after cervical conization. This specific group of post-menopausal or older patients needs more attention during treatment.

For post-menopausal patients, fertility requirements are not a concern. However, residual and recurrent disease or the potential of progression to cancer may cause substantial panic for these patients. Hence, researchers have proposed that definitive treatment with hysterectomy should be considered in post-menopausal patients with additional risk factors for recurrence after conization for HSILs.

To date, few previous studies have focused on post-menopausal patients with CIN 3, and few studies have examined the whole uterus after hysterectomy for the identification of residual lesions. This retrospective study was therefore designed to identify the risk factors for residual lesions in hysterectomy specimens after conization in post-menopausal patients with pathologically confirmed CIN 3.

Patients and Methods

Patients

Patients who underwent total hysterectomy after an excisional procedure for CIN 3 in the Department of Gynecology at Fujian Provincial Maternity and Child Health Hospital between October 2012 and December 2018 were included. Patients who were pre-menopausal, whose pathology reports after conization showed normal results, with CIN 1–2, with invasive cervical cancer, and adeno lesions were excluded (Figure 1). A detailed medical chart review was then performed to obtain information regarding clinical parameters from the database.

Clinical Data

The following parameters in medical records were abstracted: age, parity, menopausal status, cytology results, human papillomavirus (HPV) genotype, pre-cone endocervical curettage (ECC) results, cone method, operating surgeon (junior: worked in gynaecology ≤ 5 years; senior: worked in gynaecology >5 years), cone dimension (the cone volume was calculated using the formula (1/3) × π × (length/2) × (width/2) ×depth; the volumes were added when there were several pieces), and the pathological findings of conization and hysterectomy specimens.

Colposcopy and biopsy were performed by expert colposcopists in our centre. An abnormal pre-cone ECC result was considered to identify CIN in an endocervical sample obtained during colposcopy examination. The known pathologic diagnosis of the patients who were referred from other centres was verified by expert pathologists in our centre.

The LEEP or CKC was used for all conizations. Procedures were performed under colposcopic guidance and under general anaesthesia. First, all cervical transformations and cervical lesions were distinguished by the application of 5% acetic acid and Lugol's iodine solution, and then a conical tissue sample extending to the endocervical area was excised using CKC or LEEP. When doing LEEP procedure, a rotary cut was performed to remove the entire transformation zone. As the squamocolumnar junction could not be observed, a portion of the endocervical canal from the cervix were removed from the endocervix additionally. The pathology results were classified as normal, CIN 1, CIN 2, CIN 3, or invasive cervical cancer. The resection margins of the excision specimen were not graded but were categorized as positive if precancer was present at the resection margin (endocervical, exocervical and lateral margins) or negative if the margins were free of neoplasia.[18]

Definitive treatment with hysterectomy was recommended for all post-menopausal patients, and patients were included in the study if the interval between conization and total hysterectomy was <6 months. Residual disease was defined as the presence of CIN 2+ or invasive cancer in hysterectomy specimens.

Ethical Considerations

The study was approved by our institutional review board (No: 2019–033), which waived the requirement for informed consent due to the retrospective nature of the study. We extracted data from the database and deidentified through anonymity to keep data confidentiality. This study was performed in compliance with the "Declaration of Helsinki."

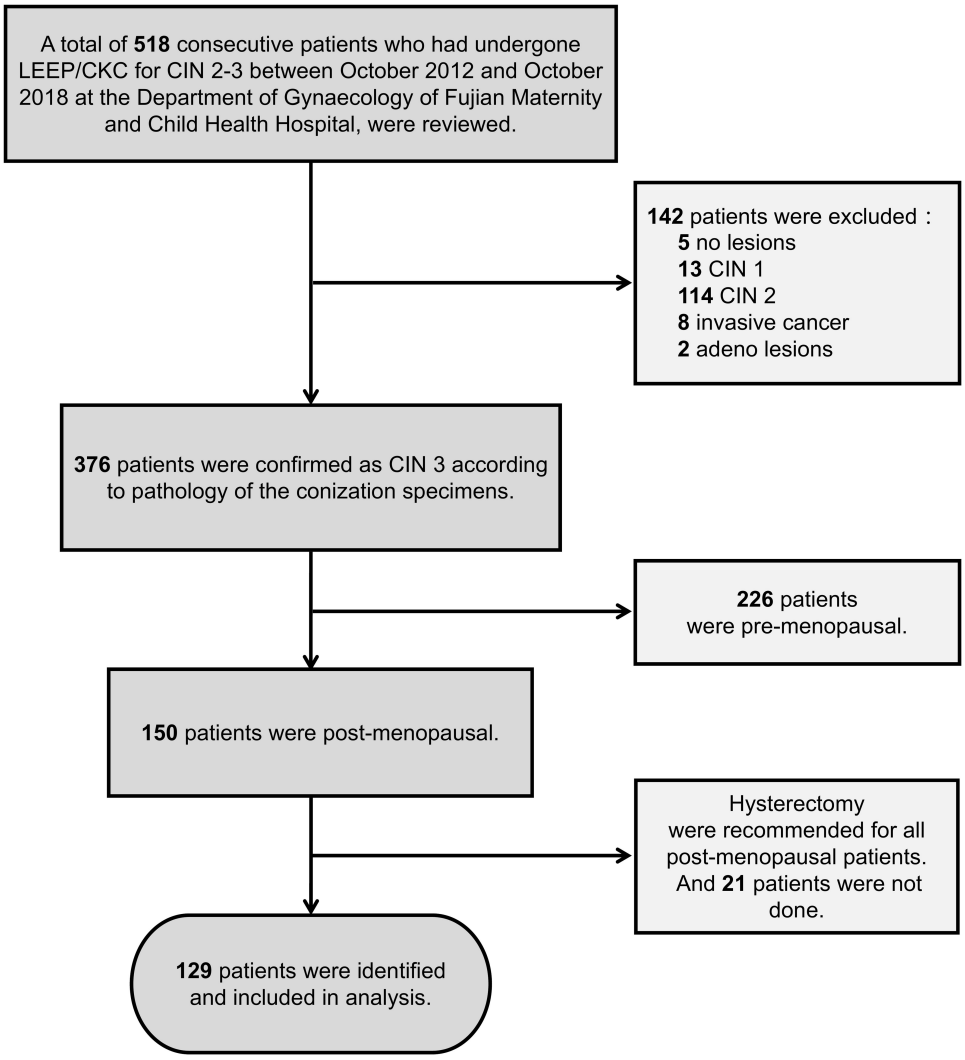


Figure 1 Flow chart of post-menopausal patients underwent hysterectomy for cervical intraepithelial neoplasia grade 3 in the study.
Abbreviations: LEEP, loop electrosurgical excision procedure; CKC, cold knife conization; CIN, cervical intraepithelial neoplasia.

Statistical Analysis

Descriptive statistics were first performed. After that, univariate and multivariate analysis were performed. Univariate analysis used Chi-square test and Mann Whitney *U*-tests, and multivariate analysis used binary logistic regression. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 24.0 for Windows (SPSS, Inc., Chicago, IL).

Results

Clinical Features and Pathological results

A review of the hospital records identified 150 post-menopausal patients for inclusion in this study. Among them, 73 patients (59.59%) were found to have no residual lesions. By contrast, 56 patients (43.41%) were found to have residual lesions: 4 patients (3.10%) with CIN2, 48 (37.21%) with CIN 3 and 4 (3.10%) with invasive cervical squamous cell carcinoma. The clinical features and pathological details following initial conization of these patients are shown in Table 1. The detailed characteristics of the 4 residual invasive cervical carcinoma patients are shown in Table 3.

Risk Factors for Residual Lesions After Conization

Univariate analysis showed that a higher grade according to colposcopy biopsy (>CIN2 vs ≤ CIN2), abnormal pre-cone ECC results, the cone method (LEEP vs CKC), a cone volume >1.57 cm^3, and positive margins in the conization specimens were significantly associated with residual lesions (all $p < 0.05$, see Table 2). Age, parity,

Table 1 General Characteristics of 129 Patients

Parameters	Values
Age, y, mean (range)	54 (44–69)
Parity, median (range)	2 (1–5)
Smoking status, n (%)	
Smoker	0 (0)
Non-smoker	129 (100)
TCT, n (%)	
NILM	1 (0.78)
ASCUS	27 (20.93)
LSIL	8 (6.20)
ASU-H	13 (10.08)
HSIL	55 (42.64)
AGC	2 (1.55)
Unknown	23 (17.83)
HPV status, n (%)	
HR-HPV positive	101 (78.29)
Multiple HR-HPV positive	30 (23.26)
Single HR-HPV positive	34 (26.36)
HPV 16 positive	50 (38.76)
LR-HPV positive	1 (0.78)
Negative	4 (3.10)
Unknown	23 (17.83)
Colposcopic biopsy, n (%)	
CIN1	6 (4.65)
CIN2	33 (25.58)
CIN3	86 (66.67)
Unknown	4 (3.10)
Pre-cone ECC, n (%)	
Normal	29 (22.48)
Abnormal	53 (41.09)
Unknown	47 (36.43)
Operating surgeon, n (%)	
Junior	80 (62.02)
Senior	49 (37.98)
Conization method, n (%)	
LEEP	22 (17.05)
CKC	107 (82.95)
Cone volume, cm^3, median (25th-75th percentiles)	1.57 (0.91,2.62)
Glandular involvement, n (%)	
Negative	9 (6.98)
Positive	120 (93.02)
Margin status, n(%)	
Negative	83 (64.34)
Positive	46 (35.66)
Residual lesion, n(%)	
None	66 (51.16)
CIN1	7 (5.43)
CIN2	4 (3.10)
CIN3	48 (37.21)
Invasive Cancer	4 (3.10)

Abbreviations: TCT, Thinprep cytology test; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AGC, atypical glandular cells; HR-HPV, high-risk human papilloma virus; LR-HPV, low-risk human papilloma virus; CIN, cervical intraepithelial neoplasia; ECC, endocervical curettage; LEEP, loop electrosurgical excision procedure; CKC, cold knife conization.

pre-cone cytology, HPV infection, colposcopy biopsy, operating surgeon, and glandular involvement were not significantly associated with residual lesions. Feasible variables that were found to be significantly associated with residual lesions on univariate analysis were entered into the logistic multiple factor regression equation. Logistic regression analysis revealed that abnormal pre-cone ECC results were an independent risk factor for residual disease (odds ratio 3.99; 95% confidence interval 1.41–11.33; p = 0.009), as shown in Table 4.

Discussion

Main Findings

Treatment with conization is both a diagnostic procedure and a therapeutic procedure that can effectively eradicate CIN2-3 in women at every stage of life. Treatment failure regarding residual and recurrent disease is an important concern after conization. Previous studies have reported that menopausal status and age are both associated with residual lesions after conization.[15,17] In the present study, in 56 (43.41%) post-menopausal women, residual disease was discovered in hysterectomy specimens, representing a rate higher than previously reported data in younger patients. This may be explained by the specific study population of post-menopausal women and the identification of residual lesions in the hysterectomy specimens. Lower regression rate and higher surgical difficulty in postmenopausal patients could be the underlying reason. Therefore, with this high residual rate, consideration of

Table 2 Univariate Analysis on Factors Correlated with Residual Lesions in Hysterectomy Specimens

Parameters		Residual Rate		P
		≤CIN1	≥CIN2	
Age, y	Median	53	55.5	0.181
	IQR	9	9.75	
	≤ 60	60(57.14)	45(42.86)	0.791
	> 60	13(54.17)	11(45.83)	
Parity, n	Median	2	2.5	0.203
	IQR	1	1.75	
	≤ 2	44(61.11)	28(38.89)	0.244
	> 2	29(50.88)	28(49.12)	
Pre-cone cytology	≤ LSIL	20(55.56)	16(44.44)	0.901
	≥ ASC-H	38(54.29)	32(45.71)	
HPV status	Multiple infection	16(53.33)	14(46.67)	0.762
	Single or non infection	43(56.58)	33(43.42)	
	16 genotype	28(56.00)	22(44.00)	0.947
	Non-16 genotype infection	31(55.36)	25(44.64)	
Colposcopy biopsy	≤ CIN2	28(71.79)	11(28.21)	**0.012**
	> CIN2	41(47.67)	45(52.33)	
Pre-cone ECC result	Normal	22(75.86)	7(24.14)	**0.001**
	Abnormal	22(41.51)	31(58.49)	
Operating surgeon	Junior	47(58.75)	33(41.25)	0.527
	Senior	26(53.06)	23(46.94)	
Conization method	LEEP	54(50.47)	53(49.53)	**0.002**
	CKC	19(86.36)	3(13.64)	
Cone volume, cm^3	Median	1.88	1.11	**0.002**
	IQR	2.09	1.31	
	≤ 1.57	34(47.22)	38(52.78)	**0.016**
	> 1.57	39(68.42)	18(31.58)	
Glandular involvement	Positive	68(56.67)	52(43.33)	0.948
	Negative	5(55.56)	4(44.44)	
Margin status	Positive	20(43.48)	26(56.52)	**0.025**
	Negative	53(63.86)	30(36.14)	

Note: Bold values indicate P < 0.05.

definitive management with hysterectomy is reasonable in post-menopausal women in whom fertility is not a desire.

Furthermore, risk factors for residual lesions should be considered through a risk-based strategy for management from previous clinical information in post-menopausal women. In our study, using univariate and multivariate analyses, we found that an abnormal pre-cone ECC result was an independent risk factor for residual lesions. Several previous studies have evaluated clinical and pathological predictors of the persistence of or residual CIN and cervical cancer.[3,5–10,13–17] However, only a few studies have examined whole uterine specimens after hysterectomy[13] and have focused on post-menopausal patients alone. These studies differ from each other methodologically, including the study populations and analysis of variables. However, similar to our results, studies found that ECC positivity[13,19,20] was a significant risk factor for residual disease. The finding that abnormal ECC results were independently associated with residual lesions in uterine specimens indicates the feasibility of identifying risk factors before conization and may be helpful in pre-procedural planning to optimize clinical management.

Table 3 Characteristics of Patients with Residual Invasive Cervical Cancer

	Age, y	G/P, n	TCT	HPV	Biopsy	Pre-Cone ECC	Cone Method	Cone Pathology	Margin	FIGO Stage (2009)	Supplemental Therapy	Follow-Up Time, Month	Recurrence
Case 1	59	6/5	HSIL	16	CIN3	Positive	LEEP	CIN3	Positive	$I A_2$	Chemotherapy	71	No
Case 2	51	5/2	ASCUS	Unknown	CIN3	Negative	LEEP	CIN3	Negative	$I A_1$	None	81	No
Case 3	60	4/4	ASC-H	16, 33	CIN3	Positive	LEEP	CIN3	Positive	$I b_1$	Chemotherapy + radiotherapy	34	No
Case 4	48	5/5	HSIL	Unknown	CIN3	Negative	LEEP	CIN3	Positive	$I A_1$	None	34	No

Abbreviations: G/P, gravidity/parity; CIS, carcinoma in situ; FIGO, Federation International of Gynecology and Obstetrics.

Interestingly, although pathologic margin status is generally considered a risk factor for the development of recurrent or persistent CIN,[21,22] our results suggested that positive margins were significantly associated with residual lesions in univariate analysis but showed no significant relationship after multivariate analysis. That is, a free margin does not always indicate complete excision. Under this circumstance, in cases that invasive cancer exists and is unevaluated when the margin status is negative, simple follow-up may be inappropriate. On the other hand, undiagnosed cervical cancer may be present regardless of the margin status. For example, 4 patients were found to have invasive squamous cervical cancer after hysterectomy followed by missed diagnoses on initial conization. Even though all of them were followed, and no recurrence or metastasis occurred, a simple total hysterectomy was not adequate. The optimal treatment for post-menopausal patients with CIN 3 is still worth discussing.

Strengths and Limitations

The main strength of our study is the specific group of post-menopausal patients we included. In addition, we investigated residual lesions only in post-menopausal patients with CIN 3 disease confirmed by cone pathology. Considering that CIN 3 is the highest pathologic diagnosis before invasive cervical cancer and the difficulty of follow-up in this population, definitive treatment with hysterectomy were recommended for all postmenopausal patients in our institution. That is, decision for hysterectomy was made based on patients' will. In other words, we have considered factors that may caused systematically biases in the conception stage and this is also a method of controlling bias. Moreover, all patients underwent hysterectomy within six months after conization so that residual disease was defined more accurately and there was little likelihood of new disease or regression/progression. However, this study had an unavoidable limitation of its retrospective design. For example, data on preoperative cytology and HPV tests were missing in some cases. Furthermore, we were not able to assess all variables potentially associated with residual lesions in the single study. Additionally, the small sample size involves only one hospital may have reduced the external validity of our results, and further prospective studies with larger sample size in a broader context are needed.

Table 4 Multivariate Analysis on Factors Correlated with Residual Lesions in Hysterectomy Specimens

Parameters		OR	95% CI	P
Colposcopy biopsy	≤ CIN2 > CIN2	Ref 2.34	0.84–6.53	0.104
Pre-cone ECC result	Normal Abnormal	Ref 3.99	1.41–11.33	**0.009**
Cone volume, cm^3	≤ 1.57 > 1.57	Ref 0.57	0.21–1.54	0.266
Margin status	Negative Positive	Ref 1.64	0.59–4.60	0.344

Note: Bold value indicates P < 0.05.

Conclusion

In summary, the results of this study suggest that the rate of residual lesions from uterine specimens is high regardless of the cone margin status in post-menopausal women with CIN 3. An abnormal pre-cone ECC result was an independent risk factor for residual lesions. The application of risk factors associated with residual lesions may provide evidence of intensive follow-up or preventive hysterectomy and may reduce the incidence of delayed treatment and inadequate treatment for post-menopausal patients with CIN 3 in clinical practice.

Funding

There is no funding to report.

Disclosure

The authors declare no conflicts of interest.

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