Risk Factors Predicting Positive Surgical Margins Following Conization and Residual Disease in Subsequent Hysterectomy Among Postmenopausal Women With Cervical Intraepithelial Neoplasia

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AIM: To assess the risk factors for positive margin and residual high-grade lesions after cold knife conization (CKC) in postmenopausal patients.

METHODS: This retrospective study included a total of 173 postmenopausal patients aged ≥50 years who underwent hysterectomy after CKC at Peking University Third Hospital between September 2012 and February 2023. Statistical analyses were carried out using SPSS 22.0 for Windows. Variables with *p*-values ≤ 0.05 on univariate analysis were included in multiple logistic regression analysis, which utilized the forward likelihood ratio method.

RESULTS: Among the 173 patients, 27.17% (47/173) patients exhibited positive endocervical margins after conization, including seven patients (14.89%) with cervical intraepithelial neoplasia (CIN)2, and 40 patients (85.11%) with CIN3. Independent predictors of positive endocervical margin (> CIN1) were identified, including abnormal ThinPrep cytologic test (TCT) type (> low-grade squamous intraepithelial lesion, LSIL) (odds ratio [OR] = 2.193, 95% CI: 1.058–4.546, $p = 0.035$). All patients received hysterectomy. Pathological findings of uterine specimens revealed residual CIN2 in 18 patients (10.40%), CIN3 in 18 patients (10.40%), and cervical cancer in 3 patients (1.73%). Endocervical curettage (ECC) results (> CIN1) (odds ratio (OR) = 2.663, 95% CI: 1.049–6.764; $p = 0.039$) along with endocervical margin status (OR = 6.510, 95% CI: 2.935–14.444; $p < 0.001$) were identified as significant independent predictors of residual lesions. A regular post-hysterectomy follow-up in 97 patients revealed vaginal intraepithelial neoplasia (VaIN) grade 2/3 in two individuals six months later.

CONCLUSIONS: CKC can serve as a primary diagnostic modality for high-grade intraepithelial lesions in postmenopausal patients. Although this study did not identify cone height as a risk factor for positive endocervical margins, it is still recommended to maintain sufficient cone height, given that atrophy and upward migration of the cervical transformation zone are common in postmenopausal patients. For menopausal patients with positive endocervical margin, glandular involvement, and abnormal ECC results (> CIN1), immediate treatment such as hysterectomy is recommended.

Keywords: postmenopause; cervical high-grade intraepithelial neoplasia; cold knife conization; positive surgical margin; hysterectomy; residual disease

Introduction

Cervical cancer ranks as the second most prevalent malignancy among women worldwide [1,2]. Cervical intraepithelial neoplasia (CIN), categorized histologically into CIN1, CIN2, and CIN3, serves as a precursor lesion for cervical cancer. Approximately 60% of CIN1 (also known as low-grade squamous intraepithelial lesion, LSIL) can be naturally eliminated by the immune system. Without intervention, around one-third of CIN2/3 cases (also referred to as high-grade squamous intraepithelial lesion, HSIL) will progress to cervical cancer within a span of 10 to 20 years [3]. Cervical conization serves as the primary modality for both diagnosis and treatment of CIN2/3. According to the guidelines established by the American Society of Colposcopy and Cervical Pathology (ASCCP), colposcopically-guided cervical conization can yield satisfactory clinical outcomes in patients with CIN2/3. Nevertheless, numerous studies have demonstrated that postmenopausal and older patients (≥50 years old) with CIN exhibit a higher likelihood of residual lesions, relapse, and progression to invasive cervical cancer [4–7].

Studies have shown that menopausal status is an inherent risk factor for residual lesions [8–10]. The menopausal

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transition is characterized by decreased estrogen levels, cervical atrophy, retraction of the squamocolumnar junction, and reduced cellular exfoliation, which collectively contribute to an unsatisfactory colposcopy [11,12]. Furthermore, postmenopausal women exhibit a higher prevalence (44%) of canal-localized CIN [13]. These physiological changes during the postmenopausal period pose challenges in diagnosing and treating cervical lesions. While study has investigated risk predictors for residual CIN and cervical cancer in reproductive-aged women [14], limited research has focused on examining whole uterine specimens after hysterectomy, specifically in postmenopausal patients.

The objective of this study was to investigate the risk factors associated with positive margins and residual high-grade lesions in menopausal patients.

Materials and Methods

This retrospective study included menopausal patients aged ≥50 years who underwent hysterectomy after cervical conization at the Treatment Centers of Peking University Third Hospital between September 2012 and February 2023. Patients with a diagnosis of CIN1 ($n = 5$) or cervical cancer ($n = 8$) based on punch biopsy, those who underwent repeat cervical conization ($n = 6$), and those without available pathological results ($n = 11$) were excluded. A total of 173 patients were enrolled in this study, all of whom provided informed consent. Table 1 presents the demographic and clinical data of all included patients.

The patients in this study underwent a comprehensive "three-step" screening process, which included cytology, colposcopy, and histology. ThinPrep cytologic test (TCT) results were categorized as negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H), LSIL, HSIL, and atypical glandular cells (AGC). High-risk human papilloma virus (HR-HPV) type 16, 18 and the other 12 types (including 30, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) were detected in the sample. Colposcopy-guided cervical biopsy and endocervical curettage (ECC) procedures were performed by experienced gynecologists. If a closed cervix was found, ECC and cervical biopsy under anesthesia were performed after cervical dilation.

Patients diagnosed with CIN2/3 through cervical biopsy underwent cold knife conization (CKC) as the initial treatment. The resection should be performed in a sequential manner, starting from the superficial layers and progressing towards deeper tissues within an area ≥0.5 cm beyond the iodine non-coloring region. Cases with no lesions, inflammatory changes, or CIN1 observed at the margins of conization after CKC were considered negative margin. Margins were classified as positive if HSIL (> CIN1) or cancer was present at or near (≤1 mm) the resection surface [15].

Hysterectomy was performed in patients with positive margins or those who were difficult to follow up after CKC. Uterine specimens showing HSIL were regarded as residual lesions. All pathological results were reviewed by senior pathologists. TCT and HR-HPV DNA tests were conducted during the follow-up period. Colposcopy-directed punch biopsy was performed for patients with abnormal results or highly suspected lesions. Recurrence was defined as the histopathological detection of HSIL/cancer during follow-up. Patients were followed up two months after hysterectomy, through outpatient visits and telephone follow-up.

Statistical analyses were carried out using SPSS 22.0 for Windows (SPSS, Inc., Chicago, IL, USA). Continuous data were first tested for normality by using the Shapiro Wilk test, which revealed that the data followed a non-normal distribution. Non-normally distributed continuous variables are presented as median and interquartile range [M (Q25, Q75)]. The data were analyzed using the Mann–Whitney U test. Expressed as count and percentage, categorical variables between groups were compared using the Chi-squared test. Variables with p-values ≤ 0.05 on univariate analysis were included in multiple logistic regression analysis, which employed the forward likelihood ratio method. Results with p-values ≤ 0.05 were considered statistically significant.

Results

A total of 173 postmenopausal patients who underwent CKC and subsequently received hysterectomy were included in this study. Their data were gathered through a review of the hospital records. The median age was 58 years (Q25–Q75, 55–63 years), with a median duration of menopausal time of 8 years (Q25–Q75, 5–13 years). Among these patients, approximately 31.79% of them (55/173) presented with clinical symptoms, while 53.76% (93/173) experienced one or more comorbidities, such as hypertension, hyperlipidemia, or diabetes. Additionally, among those diagnosed with CIN2/3 through colposcopy and biopsy, vaginal intraepithelial neoplasia (VaIN) was observed in 9.24% cases (16/173). The mean outer diameter of the conization specimen was measured at 1.5 cm (Q25–Q75, 1.1–2.0 cm), whereas the mean internal diameter and height were found to be approximately 0.8 cm (Q25–Q75, 0.6–1.0 cm) and 1.1 cm (Q25–Q75, 0.8–1.5 cm).

Risk Factors for Positive Margins in the Conization Specimen

The positive surgical margins of the conization specimens were observed in 32.37% of the patients (56/173), among whom 83.92% (47/56) had positive endocervical margins, including 14.89% (7/47) with CIN2 and 85.11% (40/47) with CIN3. Univariate analysis (Table 2) showed that patients with abnormal TCT type (> LSIL, $p = 0.027$) and glandular involvement ($p = 0.002$), and those with a lower

Table 1. The demographic and clinical data of all included patients (*n* = 173).

	Characteristics		Description
Demographic information	Age at natural menopause (years)		58 (55, 63)
	Menopausal period (years)		8 (5, 13)
	Gravidity (%)	≤2	65 (37.6)
		>2	108 (62.4)
	Parity (%)	≤2	151 (87.3)
		>2	22 (12.7)
	Delivery mode (%)	Vaginal delivery	168 (97.1)
		Cesarean section	5 (2.9)
	Clinical symptoms (%)	None	118 (68.2)
		Hypogastralgia	3 (1.7)
		Leukorrhea/vaginal discharge	8 (4.6)
		Vaginal bleeding	31(17.9)
		Two or more symptoms	13 (7.5)
	Comorbidities (%)	None	80 (46.2)
		Hypertension	26 (15.0)
		Diabetes mellitus	21 (12.1)
		Hyperlipidemia	7 (4.1)
		Others	6 (3.5)
		Two or more comorbidities	33 (19.1)
Three-stage screening of cervical precancerous lesions	TCT (%)	Normal	27 (15.6)
		ASCUS	44 (25.4)
		LSIL	24 (13.9)
		ASC-H/HSIL	70 (40.5)
		AGC	1 (0.1)
		Unknown	7 (4.0)
	HPV types (%)	Negative	12 (5.8)
		16, 16 and other 12	67 (38.7)
		18, 18 and other 12	4 (2.3)
		Other 12	82 (47.4)
		16 and 18	8 (4.1)
	Punch biopsy (%) *	CIN2	58 (33.5)
		CIN3	115 (66.5)
	ECC (%)	Normal	60 (34.7)
		CIN1	12 (6.9)
		CIN2	33 (19.1)
		CIN3	36 (20.8)
		Unknown	32 (18.5)
	Vaginal intraepithelial lesions (%)	Normal	151 (87.3)
		VaIN1	2 (1.2)
		VaIN2	9 (5.2)
		VaIN3	5 (2.9)
		Unknown	6 (3.5)
Conization of cervix	Ectocervical pathology (%)	CIN1	14 (8.1)
		CIN2	34 (19.7)
		CIN3	125 (72.3)
	Endocervical margin (%)	Normal	126 (72.8)
		CIN2	7 (4.1)
		CIN3	40 (23.1)
	Ectocervical margin (%)	Normal	161 (93.1)
		CIN1	3 (1.7)
		CIN2	6 (3.5)
		CIN3	3 (1.7)
	Glandular involvement (%)	No	33 (19.1)
		Yes	140 (80.9)
	Measurement of cervical conization specimen	Outer diameter (cm)	1.5 (1.1, 2.0)
		Internal diameter (cm)	0.8 (0.6, 1.0)
		Cone height (cm)	1.1 (0.8, 1.5)
		Volume (cm^3)	2.32 (1.67, 2.96)

Table 1. Continued.

Characteristics			Description
Clinicopathologic characteristics after hysterectomy		Operation interval (months)**	1.5 (0.5, 3.0)
	Residual disease in post-cone hysterectomy specimen (%)	Normal	86 (49.7)
		CIN1	48 (27.7)
		CIN2	18 (10.4)
		CIN3	18 (10.4)
		Cancer	3 (1.7)
	Follow-up period (years)		1.5 (0.5, 5.0)

* Only the patients whose colposcopic cervical biopsy results were CIN2/3 underwent cold knife conization (CKC) and hysterectomy.

** Time interval between CKC and hysterectomy.

TCT, ThinPrep cytologic test; HPV, human papilloma virus; ECC, endocervical curettage; ASCUS, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AGC, atypical glandular cells; CIN, cervical intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia.

cone height ($p = 0.007$), were significantly associated with an increased likelihood of having residual lesions (> CIN1) at the endocervical margin. Multivariate logistic regression analysis (Table 3) revealed that abnormal TCT type (> LSIL) (odds ratio [OR] = 2.193, 95% CI: 1.058–4.546, $p = 0.035$) was independent risk factor for positive margins (> CIN1) in conization specimens (> CIN1).

Risk Factors for Residual Disease in Post-cone Hysterectomy Specimen

Among the 173 patients who underwent extrafascial hysterectomy after conization, the median surgical interval was 1.5 months (Q25–Q75, 0.5–3.0 months). A total of 134 patients showed no residual lesions. Residual CIN2 was observed in 18 patients (10.40%), while CIN3 was found in another 18 patients (10.40%), and microinvasive cervical squamous cell carcinoma was observed in three patients (1.73%). Residual lesions could still be seen in total hysterectomy specimens in 16 patients with negative conization margins. Table 4 shows univariate analysis of factors correlated with residual lesions. ECC results ($p = 0.027$) and endocervical margin status in conization specimens ($p < 0.001$) were identified as potential predictors of positive lesions (all $p < 0.05$). While in multivariate analysis, ECC results (> CIN1) (odds ratio (OR) = 2.663, 95% CI: 1.049–6.764; $p = 0.039$) and endocervical margin status (OR = 6.510, 95% CI: 2.935–14.444; $p < 0.001$) were independent preoperative predictors of residual lesions (Table 5). Among the three patients diagnosed with cervical cancer, two patients were of pathological stage IA1, while the other was classified as pathological stage IA2. None of the patients received adjuvant therapy. The characteristics of the cervical cancer patients are summarized in Table 6.

Follow-up

A total of 97 patients were regularly followed up for a median duration of 18 months (range: 0.5–5 years). During the follow-up period, VaIN was identified in seven patients (7.22%). Among them, five patients were diagnosed with VaIN1, one patient with VaIN2, and one patient with VaIN3. No lesions beyond VaIN3 were detected. Patients experiencing relapse showed persistent HR-HPV infection. Three cervical cancer patients did not experience recurrence during the study period. The characteristics of patients with VaIN during the follow-up period are summarized in Table 7.

Discussion

According to the 2023 China HPV and Related Diseases Report, issued by the Information Center on HPV and Cancer/International Agency for Research on Cancer (ICO/IARC), China recorded approximately 109,741 new cases of cervical cancer annually, with 24.8% of the total cases being patients aged 60 or older [16]. These individuals have not received the HPV vaccine, thereby increasing their susceptibility to cervical cancer. Mortality rates rise significantly with age, with the highest death rate from cervical cancer observed in the age group of 60–64 (25/100,000). Those aged 60 and above account for 45.07% of all deaths across all age groups [15]. Immediate treatment is typically necessary for CIN2 and CIN3 as these stages have low rates of spontaneous regression (32%–43%). If left untreated, the risk of progression to invasive cancer increases substantially by 5%–12% [17]. A cohort study revealed that women aged ≥50 years at CIN3 diagnosis had a sevenfold increased risk of developing cervical cancer, while those with recurrent CIN3 faced a ninefold increased risk [18]. These patients typically present with an atrophic cervix, which makes it challenging to observe the transformation zone through colposcopy and augments the difficulties in performing conization treatment. Previous studies have indicated that over 40% of conizations were conducted for diagnostic purposes in patients aged 60 years or older, while high-grade CIN and invasive cancer are fre-

Table 2. Univariate analysis of positive endocervical margin in conization specimens.

Characteristics	Surgical margins		χ^2/z	*p*-value
	Negative (≤ CIN1)	Positive (> CIN1)		
Age (years)	58 (55, 62)	59 (57, 64)	–1.755	0.079
Age at natural menopause (years)	50 (48, 52)	50 (48, 53)	–1.321	0.187
Menopausal duration (years)	8 (4, 13)	10 (6, 13)	–0.846	0.398
Gravidity (%)				
≤2	48 (38.1)	17 (36.2)	0.054	0.816
>2	78 (61.9)	30 (63.8)		
Parity (%)				
≤2	112 (88.9)	39 (83.0)	1.077	0.299
>2	14 (11.1)	8 (17.0)		
Delivery mode (%)				
Vaginal delivery	122 (96.8)	46 (97.9)	<0.001	1.000
Cesarean section	4 (3.2)	1 (2.1)		
TCT (%)				
≤LSIL	76 (60.3)	19 (40.4)	7.247	0.027
>LSIL	44 (34.9)	27 (57.4)		
Unknown	6 (4.8)	1 (2.1)		
HPV types (%)				
Negative	8 (6.3)	4 (8.5)	8.98	0.062
16, 16 and other 12	42 (33.3)	25 (53.2)		
18, 18 and other 12	2 (1.6)	2 (4.3)		
Other 12	67 (53.2)	15 (31.9)		
16 and 18	7 (5.6)	1 (2.1)		
Glandular involvement (%)				
No	31 (24.6)	2 (4.3)	9.181	0.002
Yes	95 (75.4)	45 (95.7)		
Vaginal intraepithelial lesions (%)				
≤ VaIN1	112 (88.9)	41 (87.2)	0.135	0.935
> VaIN1	10 (7.9)	4 (8.5)		
Unknown	4 (3.2)	2 (4.3)		
ECC (%)				
≤ CIN1	56 (44.4)	16 (34)	1.680	0.432
> CIN1	47 (37.3)	22 (46.8)		
Unknown	23 (18.3)	9 (19.1)		
Cervical conization specimen				
Outer diameter (cm)	1.5 (1.2, 2)	1.5 (1, 2)	–0.088	0.930
Cone height (cm)	1.3 (0.9, 1.5)	1 (0.8, 1.2)	–2.683	0.007
Volume (cm^3)	2.29 (1.62, 2.99)	2.07 (1.79, 2.67)	–0.669	0.504

Table 3. Multivariate analysis of risk factors for positive endocervical margin in conization specimens.

Characteristics	95% CI		Exp(B)	S.E.	Wald	*p*-value	OR
	Lower	Upper					
TCT	1.058	4.546	0.785	0.372	4.453	0.035	2.193
Glandular involvement	0.642	17.202	1.201	0.839	2.051	0.152	3.324
Cone height	0.288	1.001	–0.622	0.318	3.827	0.050	0.537

OR, odds ratio.

quently observed in women aged ≥50 years [19,20]. Therefore, it is imperative to investigate the efficacy of treatment options and identify risk factors associated with residual lesions of high-grade CINs in postmenopausal women.

Influencing Factors of Positive Margin in Conization Specimens

A meta-analysis by Ghaem-Maghami *et al.* [21] revealed that the positive margin rate of conization was higher in postmenopausal patients. Based on a study to analyze the

Table 4. Univariate analysis of residual lesions in post-cone hysterectomy specimens.

Characteristics	Residual		χ^2/z	*p*-value
	Negative (≤ CIN1)	Positive (> CIN1)		
Age (years)	58 (56, 63)	58 (54, 63)	–0.579	0.563
Age at natural menopause (years)	50 (48, 52)	50 (49, 52)	–1.211	0.226
Menopausal duration (years)	8 (5, 13)	7 (4, 12)	–1.039	0.299
Gravidity (%)				
≤2	48 (35.8)	17 (43.6)	0.777	0.378
>2	86 (64.2)	22 (56.4)		
Parity (%)				
≤2	115 (85.8)	36 (92.3)	0.635	0.425
>2	19 (14.2)	3 (7.7)		
Delivery mode (%)				
Vaginal delivery	131 (97.8)	37 (94.9)	0.164	0.686
Cesarean section	3 (2.2)	2 (5.1)		
Symptom (%)				
No	90 (67.2)	28 (71.8)	0.299	0.585
Yes	44 (32.8)	11 (28.2)		
TCT (%)				
≤ LSIL	78 (58.2)	17 (43.6)	3.461	0.177
> LSIL	50 (37.3)	21 (53.8)		
Unknown	6 (4.5)	1 (2.6)		
HPV types (%)				
Negative	10 (7.5)	2 (5.1)		
16, 16 and other 12	48 (35.8)	19 (48.7)	2.414	0.660
18, 18 and other 12	3 (2.2)	1 (2.6)		
Other 12	67 (50.0)	15 (38.5)		
16 and 18	6 (4.5)	2 (5.1)		
Glandular involvement (%)				
No	29 (21.6)	4 (10.3)	2.537	0.111
Yes	105 (78.4)	35 (89.7)		
Endocervical margin (%)				
Negative	110 (82.1)	16 (41.0)	25.744	<0.001
Positive	24 (17.9)	23 (59.0)		
Vaginal intraepithelial lesions				
≤ VaIN1	121 (90.3)	32 (82.1)	1.847	0.397
> VaIN1	9 (6.7)	5 (12.8)		
Unknown	4 (3.0)	2 (5.1)		
ECC				
≤ CIN1	63 (47.0)	9 (23.1)	7.188	0.027
> CIN1	49 (36.6)	20 (51.3)		
Unknown	22 (16.4)	10 (25.6)		
Severity of cone				
CIN1	12 (9.0)	2 (5.1)	2.412	0.299
CIN2	29 (21.6)	5 (12.8)		
CIN3	93 (69.4)	32 (82.1)		

Table 5. Multivariate analysis of risk factors for residual lesions in post-cone hysterectomy specimens.

Characteristics	95% CI		Exp(B)	S.E.	Wald	*p*-value	OR
	Lower	Upper					
Endocervical margin	2.935	14.444	1.873	0.407	21.233	<0.001	6.510
ECC	1.049	6.764	0.980	0.476	4.243	0.039	2.663

OR, odds ratio.

Table 6. Demographic and clinicopathological parameters of patients with cervical cancer.

Case	Age (years)	Menopause (years)	Gravidity/ parity	TCT	HPV	ECC	Punch biopsy	Glandular involvement	Pathology of CKC	Margin status	FIGO Stage	Follow-up period (months)	Recurrence
1	70	20	4/2	HSIL	16	CIN3	CIN3	Positive	CIN3	Negative	IA1	30	No
2	58	8	5/2	/	16	CIN3	CIN3	Positive	CIN3	CIN3	IA2	18	No
3	77	24	5/2	ASC-H	-	-	CIN3	Positive	CIN3	CIN3	IA1	24	No

FIGO, International Federation of Gynecology and Obstetrics.

Table 7. Demographic and clinicopathological parameters of patients with recurrent lesions.

Case	Age (years)	Menopause (years)	Gravidity/ Parity	TCT	HPV	ECC	Punch biopsy	VaIN	Glandular involvement	Pathology of CKC	Margine status	Residual disease in hysterectomy specimen	Follow-up period (months)	Outcome
1	69	14	3/2	ASCUS	Other 12	-	CIN2	-	No	CIN3	CIN2	CINI	36	VaIN1
2	53	11	4/2	ASCUS	16 & other 12	-	CIN3	2	Yes	CIN3	-	-	24	VaIN1
3	67	20	1/1	ASC-H	Other 12	-	CIN2	2	Yes	CIN2	-	-	6	VaIN2
4	50	1	5/1	-	16	CIN2	CIN3	-	Yes	CIN2	-	CIN1	30	VaIN1
5	53	1	1/1	ASC-H	16	CIN3	CIN3	-	No	CIN3	-	CIN3	6	VaIN3
6	53	3	6/1	LSIL	Other 12	CIN2	CIN3	-	Yes	CIN2	-	CIN2	6	VaIN1
7	52	4	4/1	LSIL	16	-	CIN2	-	Yes	CIN2	-	CIN1	6	VaIN1

ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion.

pathological and clinical characteristics of cervical conization by age (≤50 vs >50 years), patients aged >50 years faced significantly higher rates of positive surgical margins, invasive cancer, postoperative detection of more advanced lesions, additional treatment, and recurrence compared to those aged ≤50 years (all $p < 0.01$) [19]. The higher incidence of residual disease in postmenopausal patients may be attributed to cervical atrophy, which leads to deep inversion of the transformation zone into the endocervical canal. The depth of conization is a crucial factor that can impact margin status. Bilibio *et al*.'s study [22] demonstrated that the depth of the conization specimen could influence lesion recurrence, as insufficient cone height results in residual lesions. Previous studies have reported that a cone depth less than 10 mm significantly increases the rate of residual disease [8], whereas a cone depth greater than 18–20 mm minimizes the risk [22–24]. In this study, cone height was not identified as an independent risk factor for positive margins. This may be related to the single-center design and potential selection bias. However, we suggest that performing a thin and high cone by an experienced gynecologist might reduce the risk of positive endocervical margin. TCT results were identified as an independent risk factor for positive endocervical margin. A comparison of cervical cytology results between older women and women aged 45–64 years revealed a higher rate of cytological abnormalities in the older group (5.1% vs 1.5%, $p = 0.008$). The detection rate of ASCUS was found to be 3.7% in the elderly group compared to 0.5% in the group comprising women in the age range of 45–64 years ($p = 0.005$) [25]. A retrospective study found that the preoperative TCT results in the positive resection margin group were predominantly HSIL and ASC-H, while those in the negative group were mainly NILM and ASCUS [26,27]. Chen *et al*. [28] reported that while the TCT results can serve as a predictive indicator for recurrence in patients with positive margins, it cannot infer residual lesions after conization. Güdücü *et al*. [29] reported that glandular involvement was significantly associated with a higher risk of recurrence. It is worth noting that normal epithelial cells may obscure atypical cells within the endocervical glands, potentially leading to missed diagnoses and an increased likelihood of residual lesions in conization procedures. However, our study did not find any evidence suggesting that gland involvement increases the risk of residual disease.

Predictors of Residual Lesions—A Negative Cone Margin Is Not Tantamount to Complete Lesion Resection

Several studies have consistently demonstrated that a positive surgical margin serves as a significant prognostic indicator for the recurrence of lesions following conization [30–32]. Ramchandani *et al*. [33] reported that both the status of the endocervical margin and the severity of neoplasia are significant predictors of persistent/recurrent disease occurrence subsequent to conization. Our post-cone hysterectomy findings thus corroborate prior observations, indicating that positive endocervical margin is an independent risk factor for residual disease. Bilibio *et al*. [22] found an association between menopausal status and residual disease, particularly highlighting the menopausal women with endocervical margins would face over an 80% risk of persistent lesions. Of concern is the fact that negative conization margins do not necessarily indicate the absence of residual lesions. In our study, residual disease (≥ CIN2) was detected in 39 post-cone hysterectomy patients (22.54%), with 36 patients (20.80%) exhibiting CIN2/3 and three patients (1.73%) presenting microinvasive cervical carcinoma, all of whom had negative margins in conization specimens. Another study conducted by Sun *et al*. [34] suggested that while a positive margin was identified as a risk factor for residual disease in univariate analysis, they did not demonstrate a significant relationship in multivariate analysis, indicating that a positive margin does not always guarantee complete excision. In our study, residual lesions could still be seen on total hysterectomy specimens in 16 patients with negative conization margins. Chen *et al*. [28] confirmed that a high rate of residual lesions after cervical conization may be associated with the multicenter pathogenesis of cervical lesions. Apart from the easily affected cervical squamous column junction, other parts can be simultaneously or successively infected. For postmenopausal patients with positive surgical margins, prompt treatment is recommended. Patients with negative margins should also be closely followed up or consider prophylactic hysterectomy.

We discovered that, apart from positive surgical margins, an abnormal ECC result (> CIN1) was also identified as an independent risk factor for residual lesions. Numerous surveys have consistently demonstrated that ECC positivity significantly increases the risk of residual disease [23,34–37]. In a study conducted by Sun *et al*. [34], which focused on postmenopausal patients with CIN3 undergoing hysterectomy, the proportion of residual disease was found to be 43.41%, and only an abnormal pre-cone ECC result remained statistically significant (OR = 3.99; 95% CI: 1.41–11.33). Therefore, performing ECC is crucial for patients with unsatisfactory colposcopy results. In an investigation of pathological factors associated with missed diagnosis of invasive cervical cancer, Costa *et al*. [38] concluded that ECC can aid in excluding higher-grade lesions and even cervical cancer among postmenopausal patients.

A study conducted by Li *et al*. [15] demonstrated that advancing age and disease severity in the conization specimens were the sole factors that could accurately predict residual dysplasia. Hence, it has been proposed that definitive treatment with hysterectomy should be considered in postmenopausal patients with additional risk factors for recurrence after conization. Although the optimal management of postmenopausal patients with positive margins remains a subject of debate, we strongly advocate immediate

additional treatment, including extrafascial hysterectomy. In cases wherever high-grade CIN diagnosis is unequivocal, immediate hysterectomy may be considered the primary treatment option for postmenopausal patients.

Additionally, patients with a history of CIN were found to have a higher likelihood of developing VaIN following hysterectomy. The incidence rates of VaIN differed significantly between patients with and without CIN history (7.3% vs 0.3%; $p < 0.05$) [25]. In this study, out of the total 173 patients, 16 (9.24%) had pre-existing VaIN before undergoing hysterectomy and these lesions were surgically resected. During follow-up, VaIN was identified in 7 patients (7.22%). However, no lesions above VaIN3 were detected. Therefore, it is recommended that patients with a history of CIN, who had received hysterectomy, should undergo annual screening for both cytology and HR-HPV [30].

Several limitations of this study should be acknowledged. Firstly, it is a single-center study, which may introduce selection bias in the process of patient recruitment. Secondly, the limited follow-up period for patients may affect the accuracy of predicting disease recurrence and evaluating treatment efficacy. Additionally, the small sample size and missing medical records noted in a few cases may compromise the research findings.

Conclusions

Postmenopausal patients face an increased risk for cervical cancer. Cervical atrophy constitute a challenge to the diagnosis and treatment of cervical lesions. Although many previous studies have confirmed that the risk factors for positive margins and residual lesions in postmenopausal women do not significantly differ from those in women of reproductive age, more aggressive screening and treatment strategies should be implemented for postmenopausal women.

A meticulous and precise cone biopsy should be performed by an experienced gynecologist to ensure sufficient cone height. ECC is essential for postmenopausal patients with unsatisfactory colposcopy results. For menopausal patients with positive endocervical margin, glandular involvement, and abnormal ECC results (> CIN1), immediate additional treatment such as hysterectomy is recommended. Patients with a history of CIN should receive annual TCT and HPV screening throughout their lifetime after undergoing hysterectomy.

Availability of Data and Materials

All data generated or analyzed during this study are included in this article.

Author Contributions

HML: methodology, validation, data curation, writing–review and editing. HJD, YYZ: conception and design of the study, software, writing–original draft preparation, writing–review and editing. ML: methodology. HYG: validation, resources. YW: methodology. HJH, KZ: methodology, resources. SW, HYX: data curation. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Peking University Third Hospital Medical Science Research (committee's reference number: M2019207). Informed consent of all study participants was obtained. All procedures involving human participants adhered to ethical standards and were conducted in accordance within institutional ethical guidelines and the principles outlined in the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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