HPV conversion rates after LEEP, cold-knife conization, and laser and drug therapy: A 4-year follow-up study

Huan Yi
Fulian Chen
Shihuang Liu
Jingjing Chen
Diling Pan
Yanying Lin
Shupei Zhang
Yusha Chen
Jiancui Chen
Yulong Zhang
Shaoyu Zhang
Xiangqin Zheng (zhengxq118@126.com)
https://orcid.org/0000-0003-3980-5335

Research Article

Keywords: Cervical intermediately lesions (CIN), Cervical circumferential coning, Colposcopy, Human papilloma virus (HPV), Loop electrosurgery excision procedure (LEEP)

Posted Date: March 10th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1354868/v1

HPV conversion rates after LEEP, cold-knife conization, and laser and drug therapy: A 4-year follow-up study

Huan Yi[1#], Fulian Chen[1 #], Shihuang Liu[1], Jingjing Chen[2], Diling Pan[1], Yanying Lin[1], Shupei Zhang[1], Yusha Chen[1], Jiancui Chen[1], Yulong Zhang[1], Shaoyu Zhang[2]*, Xiangqin Zheng[1]*

Abstract

Objective: To assess the clinical outcomes of women with human papilloma virus (HPV) infection and cervical lesions after treatment with the loop electrosurgical excision procedure (LEEP), cold-knife conization, laser and drug therapies.

Methods: This retrospective study reviewed medical data from 215 women with HPV infection and cervical lesions, treated with LEEP [n=122 (56.74%)], cold-knife conization [n=24 (11.16%)], laser therapy [n=10 (4.66%)], or pharmacotherapy [n=59 (27.44%)], respectively, between October 2016 and August 2017 at Fujian Provincial Maternal and Children's Health Hospital. The risk factors and clinical outcomes of HPV infection and cervical lesions were follow-up for at least 4 years. Furthermore, the Kaplan-Meier method was utilized to analyze the time to HPV regression after treatment.

Results: Overall, 145 patients (67.44%) showed improvement after treatment. The efficacy of conization and LEEP in achieving short-term HPV conversion was significantly better than that of laser and drug treatment (26.43% vs. 5.01%, P=0.04). The study revealed that menopause[odds ratio (OR), 2.61, 95% confidence interval (CI), 0.41-4.81, P=0.01];, high-risk HPV infection (OR, 3.6, 95% CI, 0.69-2.71, P=0.02) and a short follow-up (<6 months) (OR, 4.2, 95% CI, 0.31-8.09, P=0.02) were risk factors for poor treatment outcomes ;and OR, 3.25, 95% CI, 1.24-5.17,

P=0.01, respectively).

Conclusions: Menopause affected outcomes in women with HPV infection. Conization was beneficial for short-term HPV conversion and may be indicated in individuals who were older than 50 years and had high-level cervical lesions and persistent HPV infection. The treatment of HPV infection with laser and pharmacological therapies needs more time.

Keywords: Cervical intermediately lesions (CIN), Cervical circumferential coning, Colposcopy, Human papilloma virus (HPV), Loop electrosurgery excision procedure (LEEP)

1.Background

Cervical human papilloma virus (HPV) infection is a known cause of cervical cancer.[1] The HPV test is an essential component of cervical cancer screening, especially over 30 years old. Currently, almost all studies show that HPV 16 is the most common type of HPV infection related to cervical cancer, followed by HPV 18.[2] In a meta-analysis, the rates of cervical HPV infection in women with a normal cervix, atypical cervical squamous cells, low-grade cervical squamous intermediately lesions (LSIL), high-grade cervical squamous intermediately lesions (HSIL), and invasive cervical cancer were found to be 9%, 55%, 81%, 58%, and 69%, respectively.[3] Although cervical cancer remains one of the most common malignancy in young sexually active women,[4] its incidence has decreased significantly in recent years owing to the increased rates of HPV vaccination and cervical cancer screening programs.[5] In several cases, precancerous lesions are identified during screening, and treatment is initiated. However, an ideal treatment strategy of high-risk HPV infection and precancerous lesions are yet to be unequivocal. Therefore, there is currently a heavy focus on how these lesions should be treated and which treatments should be used to provide quick and complete recovery. Moreover, prophylactic measures that can be utilized to provide the development and progression of cervical

lesions caused by persistent cervical HPV infection are also being studied extensively. Previous studies have shown that colposcopy plays a significant role in controlling the incidence and mortality of cervical cancer. [3, 6] Moreover, cervical conization was also a key tool for the treatment of cervical precancerous lesions.[7] Zheng R et al. proposed that persistent HPV infection was the lone cause of cervical lesions and recurrence after cervical conization.[8]

To further clarify this, the present study aimed to analyze the potential factors affecting cervical HPV conversion after treatment. Moreover, the study also attempted to identify the most effective methods for ameliorating cervical lesions and achieving good outcomes.

2. Methods and design

2.1. Trial design and setting

This study was retrospective in nature and reviewed data from patients treated at Fujian Provincial Maternity and Children’s Hospital between October 1, 2016, and August 31, 2017. Patients underwent preoperative assessments such as thin prep cytologic test (TCT, Hologic, loc), qualitative HPV (Genetic array test kit (YanengBIO), which can identify 23 HPV genotypes, was used for HPV genotype typing in our hospital) testing, cervical biopsy, and colposcopy after providing informed consent. The complete process was precisely supervised by the research team. The inclusion criteria were as follows: (1) Complete cytology and HPV reports; (2) Colposcopy performed in our hospital; (3) Presence of cervical HPV infection or abnormal cytology smear; and (4) Colposcopy suggestive of cervical or endometrial lesions. The exclusion criteria were as follows: (1) Radiotherapy or chemotherapy prior to colposcopy; (2) Contraindications to surgery, such as severe liver and kidney disease; (3) Negative HPV, cytology smear, or cervical tissue biopsy findings; (4) Human immunodeficiency virus infection; (5) History of total

hysterectomy; (6) Lack of treatment; and (7) Incomplete clinical data and pathological findings or unavailable follow-up data. After strict adherence to the inclusion and exclusion criteria, 215 patients were registered. Subjects were divided into four groups: loop electrocautery excision procedure (LEEP, a circular incision was made with a scalpel at 0.3 to 0.5 cm outside the cervical lesion in a vertical direction, inclined 30° to 40° inward, not exceeding the endocervix, and gradually making a conical excision deep into the cervix, with a general conical base width of 2 to 3 cm and a cone height of about 2.5 cm, regardless of the condition of the cut edge), cold-knife conization (Using a scalpel, the cervical lesion area and the entire transformation area are removed, with a general diameter of 3-3.5 cm, the cutting edge is not damaged by the electrothermal reaction and the accuracy of the cutting edge situation is higher than that of LEEP), drug treatment(Continuous treatment with interferon or povidone-based suppositories for 3-6 courses), and laser treatment(The laser method uses the principle of thermal coagulation to destroy the function of cervicitis lesions.)(Figure 1).

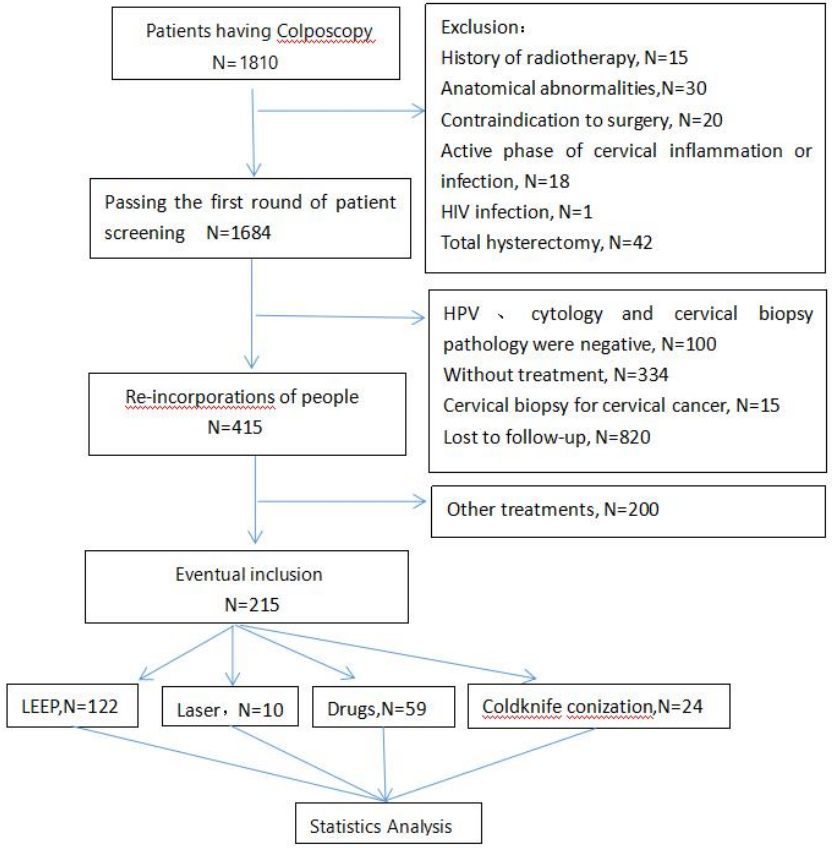

Figure 1. Flow chart of patient selection and data distribution

2.2. Statistical methods and meta-analysis

Patients clinical data were compiled in a Microsoft Excel database. General clinical data, pathological characteristics, and prognosis after the colonoscopy diagnosis of cervical intermediately lesions were analyzed. All analyses were performed using SPSS 21.0 software. Continuous data were expressed as the mean ± standard deviation ($\overline{X}$ ±SD) and compared using the t-test. A χ^2 test or non-parametric test (Fishers exact test) was used to compare categorical variables. P-values ＜0.05 were considered statistically significant [confidence intervals (CIs) of 95%]. The multivariate analysis of prognostic factors was performed using Cox regression models. The Kaplan－Meier method was utilized to analyze the time to HPV regression after treatment. All patients underwent telephonic follow-ups, and HPV infection and lesion regression were assessed using cervical HPV screening, cytology, colposcopy and pathology-based diagnosis. An improved outcome was defined as a change from a HPV positive status to a HPV negative states or a high-risk HPV infection to a low-risk infection. Likewise, recovery was also defined as normal or improved results on repeating cytology. Persistent infection is defined as two consecutive detection of the same high-risk HPV type, or when the original low-risk type of HPV infection changes to a high-risk type of infection.

The keywords used to search for references were as follows: “cervical” or “cervix” or “cervical conization” and “intermediately lesion” or “intermediately lesion” or “treatment of intermediately lesions” and “colposcopy” and “prognosis” or “prognosis”. These terms were used individually as well as cross-searched.

3. Results

3.1. Patients’ clinic characteristics at enrollment

Overall, 215 patients underwent colposcopy. Their average age was 32.0 ± 3.25 years (range, 22 – 77 years). The average gestation was 2.74, and the average number of deliveries was 1.62. Overall, 154 patients (71.63%) showed a cervical HPV infection. Of them, 141 (65.58%) had high-risk (HR) HPV infection and 96 (44.65%) had multiple HPV infections. Moreover, 65 patients (30.23%) were HPV 16/18 positive. Of all the women, 52 cases had experienced menopause, being accountable for 24.2% of all patients. Overall, 23 (20.7%) and 192 (89.3%) patients used barrier and using non-barrier forms of contraception, respectively. Regarding cervical cytology findings, 165 (75.90%) patients had atypical squamous epithelial cells (ASC-US) or higher-grade lesions. Colonoscopy biopsy revealed positive pathological findings in a majority of patients [cervical intermediately neoplasia CIN 1, 73 (33.95%); CIN2, 87 (40.47%); and CIN3, 25 (11.63%)] (Tables 1 and 2).

Table 1. Clinical baseline characteristics (n=215)

Baseline characteristics	Number of patients (%)
Age (mean±SD, range) (years)	32.0±3.25 (22–77)
Gestation±SD(range)	2.74
Parity±SD (range)	1.62
Contraception	
Barrier	23 (10.70%)
Non-barrier	192 (89.30%)

Menopause	
Yes	52 (24.2%)
No	163 (75.8%)
Cervical cytology	
ASC-US/ASC-H	145 (67.4%)
LSIL	55 (25.6%)
HSIL	15 (7.0%)
Treatment modality	
LEEP	122 (56.74%)
CKC	24 (11.16%)
Laser	10 (4.65%)
Drug	59 (27.45%)
Post-treatment review	
Cervical cytology	
Negative	199 (92.6%)
ASC-US/ASC-H	8 (3.7%)
LSIL	4 (1.9%)

HSIL	4 (1.9%)
Colposcopic biopsy	
Inflammation/CIN1	197 (91.63%)
CIN2	9 (4.195%)
CIN3	9 (4.195%)

Abbreviations: CIN: cervical intermediately neoplasia; HSIL: high-grade squamous intermediately lesion; LEEP: loop electrosurgery excision procedure; ASC-US: atypical squamous epithelial cells; ASC-H: atypical squamous epithelial cells not excluding highly squamous intermediately lesions; LSIL: low-grade squamous intermediately lesion; CKC: Cold-knife conization.

Table 2. HPV infection status and distribution

Cervical HPV infection status	Number of patients (%)
HR HPV infection	
Yes	141 (65.58%)
No	74 (34.42%)
HPV status	
Negative	61 (28.37%)
HR HPV	141 (65.58%)

HPV 16/18	65 (30.23%)
Other HR HPV	76 (35.35%)
LR-HPV	13 (6.05%)
Type of HPV infection	
Negative	61 (28.37%)
Mono-HPV infection	58 (26.98%)
Mono-LR-HPV	5 (2.33%)
Mono-HR-HPV	53 (24.65%)
Multiple HPV infection	96 (44.65%)
Multiple LR-HPV	10 (4.65%)
Multiple HR-HPV	86 (40%)
HPV persistence	
Yes	80 (37.21%)
No	135 (62.79%)

Abbreviations: HPV: Human papillomavirus; HR: high-risk; LR: low-risk; HPV persistence: Two consecutive detection of the same high-risk HPV type, or when the original low-risk type of HPV infection changes to a high-risk type of infection.

3.2. Single-factor and multi-factor analysis

Individual risk factors were assessed using university logistic regression. Then, variables with P-values <0.10 were included in the multivariate analysis to evaluate their unique effects on HPV regression. The results are presented in Tables 3 and 4. The university analysis showed that age >51 years (OR 1.09, 95% CI, 1.16−1.02, P=0.01) and menopause (OR, 1.55, 95% CI, 0.00−15.67; P=0.02) were substantially associated with the risk of persistent HPV infection, which affected HPV conversion after treatment, respectively. Contraceptive methods were also linked to the risk of HPV infection (OR, 1.55; 95% CI, 0.00−1.56; P=0.01). Moreover, HPV infection, especially high-risk HPV infection (type 16/18) (OR, 1.17; 95% CI, 0.97−1.37; P=0.01), and multiple high-risk HPV infections (OR, 1.48, 95% CI, 0.04−2.46; P=0.04) were linked to persistent HPV positivity, respectively). The analysis revealed that there was not any difference in the effect of three treatment modalities (cold-knife conization, laser, and drug treatment) on HPV conversion. However, LEEP was associated with better outcomes (OR, 1.23; 95% CI, 0.92−1.54; P=0.03). Further investigation revealed that cervical cytology findings of HSIL were associated with HPV transition (HPV conversion after treatments or switch from high-risk to low-risk HPV infection) (OR, 0.27; 95% CI, 0.05−0.50; P=0.01). Multivariate analysis revealed that menopause (OR, 2.61, 95% CI, 0.41−4.81, P=0.01), high-risk HPV infection (OR, 3.6, 95% CI, 0.69−2.71, P=0.02), high cervical lesion grades (OR, 4.2, 95% CI, 0.31−8.09, P=0.02), and short follow-up duration (<6 months) (OR, 3.25, 95% CI, 1.24−5.17, P=0.01) were linked to poor treatment outcomes. No association was observed between cervical biopsy results and HPV persistence.

3.3. Analysis of HPV conversion after treatment

Finally, age, HPV infection status, cervical pathology, mean time to HPV conversion after treatment, and conversion rate were analyzed in patients treated with the four treatment modalities. (Tables 3 - 6).

Table 3. Risk factors affecting treatment outcomes in women

Factors	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years				
⩾51	1.09 (1.16–1.02)	0.01	0.817 (0.46–1.17)	0.08
41–50	0. 69 (0.19–1.78)	0.25		
31–40	1.36 (0.35–2.08)	0.85		
⩽30	6.78 (1.32–13.20)	0.15		
Contraception				
Barrier	32.67 (13.87–61.59)	0.14		
Non-barrier	1.55 (0.00–1.56)	0.01	1.43 (0.75–1.06)	0.14
Menopause				
No	15.67 (13.87–16.59)	0.14		
Yes	2.61 (13.72–22.6)	0.02	2.61 (0.41–4.81)	0.01
Cervical cytology				
ASC/LSIL	31.05 (0.84–60.15)	0.17		

HSIL	0.27 (0.05–0.50)	0.01	4.20 (0.31–8.09)	0.02
Type of cervical dysplasia				
Negative/CIN1	88.19 (35.80–131.51)	1.36		
CIN2/3	1.18 (0.12–2.24)	＜0.001	0.67 (0.61–0.73)	＜0.001
Treatments				
Laser	11.65 (3.85–19.75)	0.32		
LEEP	1.23 (0.92–1.54)	0.03	1.16 (0.90–1.42)	0.32
CKC	0.07 (0.05–0.09)	0.20		
Drug	4.11 (0.31–7.92)	0.57		

Abbreviations: CIN: Cervical intermediately neoplasia; HSIL: High-grade squamous intermediately lesion; LEEP: Loop electrosurgery excision procedure; LSIL: low-grade squamous intermediately lesion; CKC: Cold-knife conization

Table 4. Univariate and multivariate analysis of prognostic factors for HPV infection

Factors	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
High-risk HPV infection				
Yes	1.46 (0.80–3.18)	0.03	3.60 (0.69–2.71)	0.03

No	3.51 (1.27–5.89)	0.52		
High-risk HPV				
HPV 16/18	1.17 (0.97–1.37)	0.01	2.58 (1.30–3.86)	0.02
Other HR	0.97 (0.30–1.64)	0.01		
Multiple HR infections				
No	3.05 (1.28–4.93)	0.28		
Yes	1.48 (0.04–2.46)	0.04	1.05 (0.62–1.39)	0.81
HPV persistence				
No	0.50 (0.00–1.11)	0.18		
Yes	0.05 (0.03–0.07)	0.03	5.59 (1.67–10.17)	＜0.001
HPV persistence time				
0–6 months	18.49 (0.00–37.58)	0.99		
>6 months	2.62 (3.23–5.87)	＜0.001	2.50 (0.24–4.77)	0.01
Post-treatment review of cervical cytology				
ASC-US/ASC-H	0.60 (1.20–2.77)	＜0.001	0.37 (0.28–0.56)	0.43
LSIL	0.61 (0.11–1.21)	0.48		

HSIL	2.65 (1.20–2.9)	＜0.001	0.05 (0.03–0.08)	0.03

Abbreviations: HSIL: high-grade squamous intermediately lesion; ASC-US: atypical squamous epithelial cells; ASC-H: atypical squamous epithelial cells not excluding highly squamous intermediately lesions; LSIL: low-grade squamous intermediately lesion.

Overall, 154 patients who were HPV-positive and showed lesions on cervical biopsy underwent cervical circumferential conization (including 122 cases of LEEP and 24 cases of cold-knife conization). Of which those who underwent the above treatment were in cervical intermediately neoplasia and did not reach cervical cancer, with a follow-up period of 3 years. Most of the 122 patients who underwent LEEP fell within the age group of 30~50 years, accounting for 65.57% of all patients. Most of these patients (68.85%) had CIN2/CIN3 lesions. The remaining 31.15% with low-grade cervical lesions underwent this procedure owing to concomitant long-term or high-risk mono-/multi-type HPV infection. The shortest time to HPV conversion after treatment was 3 months and the longest was 32 months, with a mean duration of 14.37± 3.24 months. The overall HPV regression rate was 78.69% at the 3-year follow-up mark.

The number of patients treated with the laser was significantly lower than that of patients treated with conization, and most of these patients were also 30−50 years old. The median time to HPV regression after treatment was 28.73±3.72 months, with the lowest duration being 25 months and highest duration being 36 months. The overall 3-year regression rate was 40%.

Cold-knife conization was typically performed in patients who were less than 50 years of age (50%) and had high-grade cervical lesions (91.6%). Mean postoperative HPV regression time was 9.57±4.63 months. The highest conversion rate among the four treatment modalities at the 3-year follow-up was 91.67%. Patients undergoing drug treatment all had normal or low-grade cervical lesions with concomitant HPV infection and

took the longest time for HPV conversion after treatment. Their mean time to conversion and conversion rate was 34±12.35 months and 35.9%, respectively. Finally, 158 (73.49%) patients showed improved findings on repeat TCT opposed to before surgery (P<0.05).

Table 5. Effectiveness of different modalities for the treatment of cervical lesions

Treatment	Number (%)	Age (years, %)			Initial HR-HPV status		Cervical pathology		HPV(+)→(-) (mean±SD, months)	Total improvement rate (%)
		<30	30~50	>50	Negative	Positive	Negative/ CIN1	CIN2/3		
LEEP	22 (56.74%)	24 (19.67%)	80 (65.57%)	18 (14.75%)	40 (32.79%)	82 (67.21%)	38 (31.15%)	84 (68.85%)	14.37±3.24	96/122 (78.69%)
Laser	10 (4.65%)	2 (20.00%)	6 (60.00%)	2 (20.00%)	5 (50.00%)	5 (50.00%)	4 (40.00%)	6 (60.00%)	28.73±3.72	4/10 (40%)
CKC	24 (11.16%)	2 (8.33%)	10 (41.67%)	12 (50%)	8 (33.33%)	16 (66.67%)	2 (8.33%)	22 (91.67%)	9.57±4.63	22/24 (91.67%)
Drug	59 (27.45%)	22 (37.28%)	31 (52.55%)	6 (10.17%)	8 (13.56%)	51 (86.44%)	59 (100.00%)	0	34±12.35	33/59 (55.94%)

Abbreviations: HPV: Human papillomavirus; HR: high-risk; CIN: Cervical intermediately neoplasia; CKC: Cold-knife conization

Table 6. Comparison of treatment results at different follow-up time after treatment

Treatment	Number (%)	Post treatment time (months, %)									
		0–3		3–6		6–12		12–24		>24	
		HPV conversion	Turnaround rate	HPV conversion	Turnaround rate	HPV conversion	Turnaround rate	HPV conversion	Turnaround rate	HPV conversion	Turnaround rate
LEEP	122 (56.74%)	5 (4.10%)	10 (8.20%)	17 (13.93%)	30 (24.59%)	45 (36.89%)	68 (55.73%)	76 (62.30%)	84 (68.85%)	96 (78.69%)	100 (81.97%)
Laser	10 (4.65%)	0	0	0	1 (10%)	1 (10%)	2 (20%)	2 (20%)	4 (40%)	4 (40%)	5 (50%)
Cold-knife conization	24 (11.16%)	2 (8.33%)	5 (20.83%)	3 (12.50%)	12 (79.17%	8 (33.33%)	14 (58.33%)	15 (62.5%)	18 (75%)	19 (79.16%)	20 (83.33%)
Drug treatment	59 (27.45%)	0	1 (1.69%)	3 (5.01%)	7 (11.86%)	5 (8.47%)	13 (22.03%)	7 (11.86%)	19 (32.20%)	17 (28.81%)	33 (55.94%)

Abbreviations: HPV: human papilloma virus; LEEP: Loop electrosurgery excision procedure; CKC: Cold-knife conization

The cervical HPV conversion rate and rate of cervical lesion resolution were highest after cold-knife conization during 0 – 3 months of follow-up (8.33% and 20.8%, respectively). At 3 – 6 months, the outcomes of cold-knife conization remained the best, with a 79.1% improvement rate and 12.5% HPV conversion rate. In 6 – 12 months, the outcomes of LEEP and cold-knife conization became comparable (recovery and HPV conversion rates of 55.7% and 58.3%, and 36.89% and 33.33%, respectively). At 12 – 24 months, the cervical lesion recovery rate began to rise in patients treated with laser and drug therapy; however, the rate remained significantly lower than that observed with the two conization procedures. After 24 months, all four treatment modalities showed a treatment efficiency of at least 50%. Drug treatment was least beneficial for HPV conversion (28.81%), monitored by laser treatment (40%). However, rescue rates for cervical lesions were comparable between both conization modalities (LEEP, 78.69%; cold-knife conization, 79.16%). The peculiar distribution of the therapeutic effects of these modalities is provided in Figures 2 and 3. Statistical analysis showed that there was no significant differences among LEEP, cold-knife conization, and drug treatment ($P>0.05$) (Figure 4).

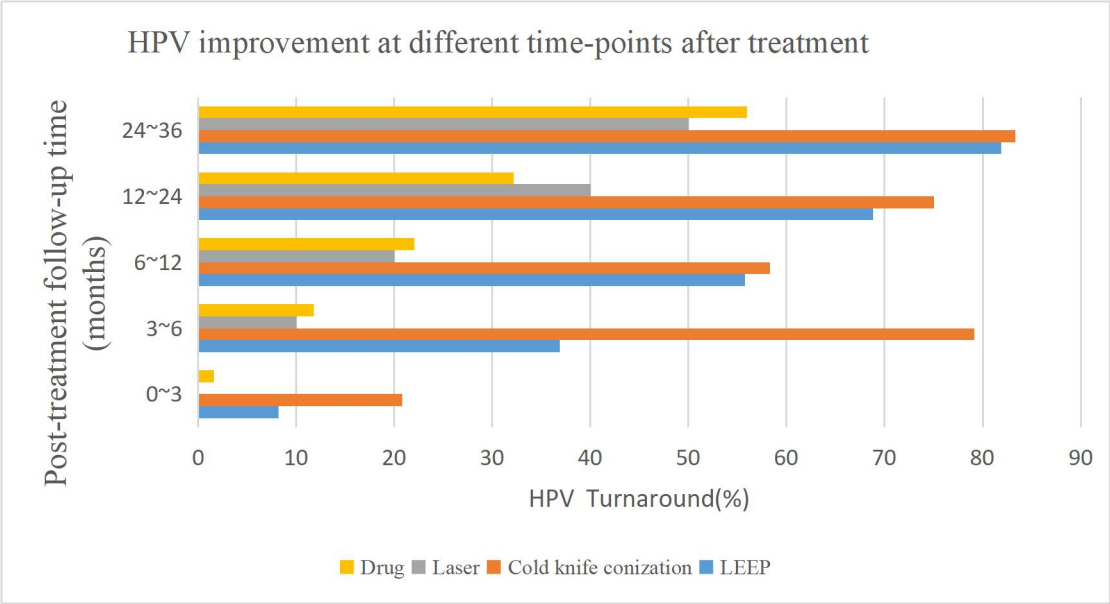

Figure 2. Improvement in HPV infection at different time-points after treatment

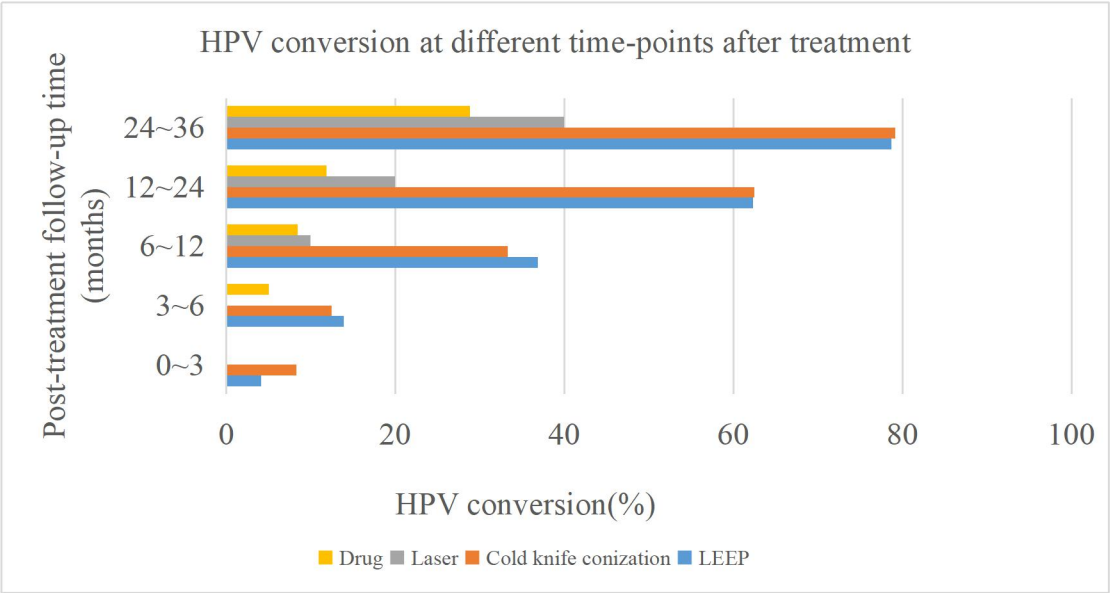

Figure 3. HPV conversion at different time-points after treatment

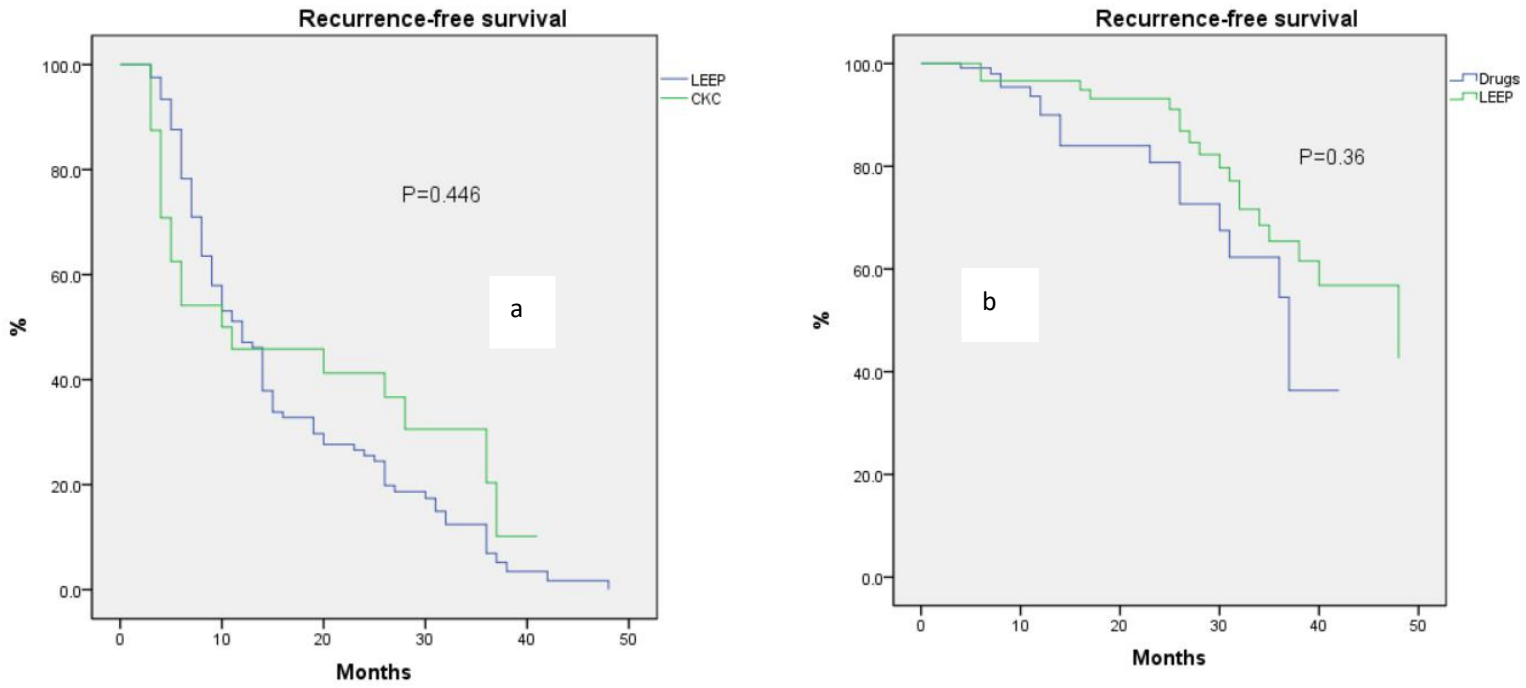

Figure 4(a, b). Kaplan-Meier curves of time and rate to HPV conversion (a. LEEP vs. CKC; b. Drug vs. LEEP)

Abbreviations: HPV: human papilloma virus; LEEP: Loop electrosurgery excision procedure; CKC: Cold-knife conization

4. Discussion

Cervical cancer, which is mainly caused by HPV, is a slowly progressing, multi-step disease. [7] Currently, about 18% of patients with cervical intermediately lesions (17% with high-grade lesions) develop cervical cancer. Therefore, timely treatment is essential. [9, 10]The primary risk

factors for persistent cervical lesions after LEEP are cytological abnormalities and positive high-risk HPV findings. [2] We found in our study found that cervical conization treatment was superior to laser and drug treatment for patients with co-infected HPV cervical lesions, especially in terms of HPV conversion.

Patients with HR-HPV-positive cervical CIN3 lesions had a higher 5-year risk of recurrence, which was eight times higher than that of HPV-uninfected patients.[11] Of the patients examined in the present study, 146 were treated with conization; of them, 118 became HPV-negative within 2 years and 28 showed persistent HPV infection for more than 2 years. All of these patients were less than 35 years; 22 of them did not use barrier contraception and 6 had multiple high-risk HPV infections. Statistical analysis revealed that menopause was an independent risk factor for inadequate treatment outcomes ($P<0.05$). Multiple high-risk HPV infections and age over 50 years are believed to affect treatment efficacy as they cause a higher viral load and lead to lower resistance in patients. [12, 13] Another study that examined 206 menopausal women treated for high-grade cervical lesions found a persistence rate of 20.4% for high-risk HPV infection. Moreover, a higher recurrence rate (12.6%) was observed in this group than in younger women.[14] These findings are in agreement with the present study. Further, several systematic reviews have shown that cytological smears are predictive of high-grade cervical lesions (HSIL/HSIL+). [9, 15, 16] Hence, post-treatment cytology smears and HPV testing are critical, regardless of the treatment modality, especially in older women whose age over 50 years old. Xiao Li et al. suggested that postmenopausal patients with high-grade squamous intermediately lesions should be treated preferentially with cold knife conization. [17] They were consistent with the findings of the study.

The results showed that cervical circumferential conization was effective for HPV transformation and improvement of cervical cytologic outcomes, namely, patients with cervical intermediately neoplasia can be treated with cervical circumferential conization. Therefore, cervical

conization is advised for patients with CIN 1-3 lesions, especially those with co-infection with HPV. Based on the possibility of continued progression of lesions after conization in patients with high-grade cervical lesions, regular follow-up with HPV and TCT was recommended for patients with CIN grade 2-3, especially when combined with high-risk HPV infection, to detect progressive lesions in a timely manner. In this retrospective study, the percentage of HPV conversion after cervical conization was relatively higher in patients with CIN 2-3 than in patients with CIN 1 (51.06% vs. 48.94%, $P<0.05$), probably because the extent and depth of interpretative conization was greater in patients with high-grade lesions than in patients with low-grade cervical lesions. Six of 215 patients underwent multiple conization or other treatments. Two of them were addressed in LEEP for preoperative cytology suggestive of ASC-US, combined with HPV type 16 and 18 infection, and cervical biopsy pathology CIN 2. 12 months after surgery, the repeat cytology suggested LSIL, HPV type 16 and 18 were still positive with cervical biopsy CIN 1. LEEP was performed again, 12 months after the 2 procedures, repeat HPV type 18 was positive and the biopsy pathology VAIN. Of them, 1 case underwent LEEP for cytological results suggestive of ASC-US, HPV 51, 52, 56 infections, 12 months after surgery, HPV 51, 52 continued to be positive, TCT suggestive of ASC-US. Therefore, LEEP was performed again with postoperative pathology CIN 1. Regular follow-up was ordered. 36 months of follow-up, the remaining HPV51 was positive and the cytology result was not intermediately lesion cells or malignant cells were seen (NILM).One case with cytology suggestive of ASC-H, HPV16 infection, underwent LEEP, postoperative pathology CIN grade 1.After 18 months of follow-up, HPV 6 still positive, cytology results suggest LSIL, so undergoing second LEEP with CIN 1 lesion. Follow-up of 27 months, HPV and cytology screening were normal. One case was hospitalized for a total hysterectomy because 29 months after LEEP. HPV still positive with cytology showed HSIL and cervical biopsy revealed AIS. Six months of postoperative follow-up, HPV 43 infection, cytology found no abnormality. One case of HPV type 56 infections with cytological findings of LSIL underwent LEEP that resulted

in postoperative pathological CIN 2 with positive cut margins, which led to hospitalization for hysterectomy. The results of which normal on review 12 months after surgery. Thus, the necessity of recurrent postoperative follow-up is thus evident, alerting to persistent or further cervical lesions due to persistent HPV infection for timely treatment. A study of 295 cases analyzed after LEEP showed that older women presenting or still having HPV16/18 infection after treatment have a higher likelihood of short-term cervical lesion recurrence and must be closely followed up.[18] Risk factors for persistent cervical lesions after LEEP are mainly cytological abnormalities and positive HR-HPV test.[10, 19]

Cervical laser vaporization can be used to treat patients with cervical intermediately lesions who wish to preserve their fertility, with a 2-year recurrence rate of 18.9% and a retreatment rate of 12.6%, and a 5-year recurrence rate of 46.5% and a retreatment rate of 30.5%. Close follow-up is recommended for patients with glandular involvement, older age, large BMI to prevent recurrence and disease progression.[20, 21] In our study, among the 10 laser-treated patients, one case with multiple high-risk HPV infections (types 16, 51, and 31) was hospitalized for radical cervical cancer surgery after 2 years of laser treatment, with TCT suggesting HSIL and cervical pathology biopsy suggesting cervical cancer. There were 52 people (88.13%) who had HPV turned negative more than two years after drug therapy, of whom 6 (100%) were menopausal, 30 (50.85%) were younger than 35 years old, a majority (70%) were infected with high-risk HPV types other than 16 and 18.

In the present study, the cumulative rate of HPV Regression 4 years after conization was 78.69%, consistent with previous findings. However, there were certain limitations to our study. First, the sample size was low, which could lead to some bias. Second, the study was retrospective in nature; therefore, some epidemiological data were missing or unclear (e.g., number of sexual partners and body mass index). Moreover, factors like smoking status, which affects the regression of CIN2 lesions in high-risk HPV-positive patients, were not regarded as.[16] Furthermore, the

follow-up period was not long enough to achieve the follow-up endpoint. Therefore, additional clinical manifestations that may have occurred after the follow-up could not be observed.

5. Conclusion

In conclusion, the findings showed that menopause was a danger factor for poor HPV regression after therapy. LEEP and cold-knife conization accelerate HPV regression and the resolution of cervical lesions. Three small prospective studies have demonstrated that cold-knife conization and LEEP provide similar diagnostic and therapeutic results, consistent with our findings.[4, 7, 22] In contrast, drugs and laser treatment were less beneficial for HPV conversion, especially within the first year after treatment. However, evidence on their effectiveness is still lacking and further research is justified.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files. Additional information is available from the corresponding author on reasonable request.

Code availability

Not applicable.

References

[1].Fan A, Wang C, Han C, Wang Y, Xue F, Zhang L（2018）Factors affecting residual/recurrent cervical intraepithelial neoplasia after cervical conization with negative margins. J Med Virol 90(9):1541-1548.

[2].Tanaka Y, Ueda Y, Kakuda M et al（2017）Predictors for recurrent/persistent high-grade intraepithelial lesions and cervical stenosis after therapeutic conization: a retrospective analysis of 522 cases. Int J Clin Oncol 22(5):921-926.

[3].Rodríguez-Álvarez MI, Gómez-Urquiza JL, Husein-El Ahmed H et al（2018）Prevalence and Risk Factors of Human Papillomavirus in Male Patients: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health 15(10).

[4].Sand FL, Kjaer SK, Frederiksen K, Dehlendorff C（2020）Risk of cervical intraepithelial neoplasia grade 2 or worse after conization in relation to HPV vaccination status. Int J Cancer 147(3):641-647.

[5].Siegel RL, Miller KD, Jemal A（2020）Cancer statistics, 2020. CA Cancer J Clin 70(1):7-30.

[6].Duggan BD, Felix JC, Muderspach LI, Gebhardt JA et al（1999）Cold-knife conization versus conization by the loop electrosurgical excision procedure: a randomized, prospective study. Am J Obstet Gynecol 180(2 Pt 1):276-282.

[7].Chen L, Liu L, Tao X, Guo L, Zhang H, Sui L（2019）Risk Factor Analysis of Persistent High-Grade Squamous Intraepithelial Lesion After Loop Electrosurgical Excision Procedure Conization. J Low Genit Tract Dis 23(1):24-27.

[8].Zheng R, Heller DS（2020）High-Risk Human Papillomavirus Identification in Precancerous Cervical Intraepithelial Lesions. J Low Genit Tract Dis 24(2):197-201.

[9].Gu L, Cheng M, Hong Z, Di W, Qiu L（2021）The effect of local photodynamic therapy with 5-aminolevulinic acid for the treatment of cervical low-grade squamous intraepithelial lesions with high-risk HPV infection: A retrospective study. Photodiagnosis Photodyn Ther 33:102172.

[10].Sun X, Lei H, Xie X, Ruan G, An J, Sun P（2020）Risk Factors for Residual Disease in Hysterectomy Specimens After Conization in Post-Menopausal Patients with Cervical Intraepithelial Neoplasia Grade 3. Int J Gen Med 13:1067-1074.

[11].Bogani G, Sopracordevole F, Di Donato V et al（2021）High-risk HPV-positive and -negative high-grade cervical dysplasia: Analysis of 5-year outcomes. Gynecol Oncol 161(1):173-178.

[12].Lehtovirta P, Paavonen J, Heikinheimo O（2008）Risk factors, diagnosis and prognosis of cervical intraepithelial neoplasia among HIV-infected women. Int J STD AIDS 19(1):37-41.

[13].Uijterwaal MH, Polman NJ, Van Kemenade FJ et al（2015）Five-Year Cervical (Pre)Cancer Risk of Women Screened by HPV and Cytology Testing. Cancer Prev Res (Phila) 8(6):502-508.

[14].Kang WD, Kim SM（2016）Human papillomavirus genotyping as a reliable prognostic marker of recurrence after loop electrosurgical excision procedure for high-grade cervical intraepithelial neoplasia (CIN2-3) especially in postmenopausal women. Menopause 23(1):81-86.

[15].Castle PE, Murokora D, Perez C, Alvarez M et al（2017）Treatment of cervical intraepithelial lesions. Int J Gynaecol Obstet 138 Suppl 1:20-25.

[16].Koeneman MM, Hendriks N, Kooreman LF et al （2019） Prognostic factors for spontaneous regression of high-risk human papillomavirus-positive cervical intra-epithelial neoplasia grade 2. Int J Gynecol Cancer 29(6):1003-1009.

[17].Kodama K, Yahata H, Okugawa K et al（2021）Prognostic outcomes and risk factors for recurrence after laser vaporization for cervical intraepithelial neoplasia: a single-center retrospective study. Int J Clin Oncol 26(4):770-776.

[18].Chen X, Fan B, Jiang L et al（2021）Predictors of treatment failure after top-hat procedure in squamous intraepithelial lesion. J Obstet Gynaecol Res 47(2):661-668.

[19].Dou Y, Zhang X, Li Y,et al（2017）Triage for management of cervical high-grade squamous intraepithelial lesion patients with positive margin by conization: a retrospective analysis. Front Med 11(2):223-228.

[20].Huang HJ, Tung HJ, Yang LY et al（2021）Role of human papillomavirus status after conization for high-grade cervical intraepithelial neoplasia. Int J Cancer 148(3):665-672.

[21].Li X, Liu M, Ji Y, Qu P（2021）The effectiveness of cold-knife conization (CKC) for post-menopausal women with cervical high-grade squamous intraepithelial lesion: a retrospective study. BMC Surg 21(1):241.

[22].Chen H, Liu X, Xu L（2016）Incisal margin condition after LEEP for cervical intraepithelial neoplasia patients and prognosis. Exp Ther Med 12(2):1019-1021.

Acknowledgments

We would like to acknowledge all of the members of the Oncology and Colposcopy Department of Fujian Provincial Maternity and Children's

Hospital.

Funding

This project was financially supported by National Natural Science Foundation Youth Project of China (81802604), Natural Science Foundation Projects of Fujian Province, China (2019J01512, 2020J01336), and Joint Funds for the innovation of science and Technology， Fujian province (2020Y9151).

Author information

Affiliations

1Department of Obstetrics and Gynecology, Fujian Provincial Maternity and Children's Hospital, Affiliated Hospital of Fujian Medical University, Fujian 350001, China

[2]Fuding General Hospital, Fuding 355200, China

[#] Equal contributions

*Correspondence authors

Contributions

Shaoyu Zhang and Xiangqin Zheng conceived the draft by identifying the clinical need. Yusha Chen and, Jiancui Chen data collection and critical review. Shihuang Liu, Jingjing Chen, Diling Pan and Yulong Zhang analysis and interpretation. Huan Yi and Yanying Lin and Shupei Zhang critical review. Fulian Chen substantial contributions to the concept, data collection and writing the article.

Corresponding author

Correspondence to Xiangqin Zheng and Shaoyu Zhan.

Ethics declarations

Conflict of interest

The authors declare no conflict of interest or competing interest.

Ethics approval

The data provided were audited by a clinical committee of the registered hospital. Written informed consent was provided by all patients before the procedures were performed.

Consent to participate

Not applicable.

Consent for publication

Not applicable.