Submitted: 05 June, 2024 Accepted: 26 August, 2024 Published: 15 October, 2024 DOI:10.22514/ejgo.2024.105

ORIGINAL RESEARCH

European Journal of Gynaecological Oncology

Efficacy and safety of radiofrequency ablation in the treatment of low-grade squamous intraepithelial lesions complicated with high-risk human papillomavirus infection

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Abstract

This study evaluates the efficacy and safety of radiofrequency ablation (RFA) in treating low-grade squamous intraepithelial lesions (LSIL) with high-risk human papillomavirus (hrHPV) infection. The clinical data of 100 patients with LSIL and hrHPV infection were retrospectively analyzed. Patients were divided into the RFA group and the 5-aminolevulinic acid photodynamic therapy (ALA-PDT) group according to the treatment protocol, with 50 patients per group. Efficacy, negative hrHPV seroconversion, mental status, treatment satisfaction, and the occurrence of adverse reactions were compared between the two groups. The RFA group had a significantly higher total effective rate (94.00%) than the ALA-PDT group (74.00%). At 3 and 6-month follow-ups, the negative hrHPV seroconversion rate was significantly higher in the RFA group than in the ALA-PDT group ($p < 0.05$). At 6 months after treatment, the RFA group showed significantly lower Self-Rating Anxiety Scale scores and Self-Rated Depression Scale scores and higher satisfaction compared to the ALA-PDT group (all $p < 0.05$). The incidence of postoperative complications rate was not significantly different between the RFA group and ALA-PDT group ($\chi^2 = 3.184$, $p = 0.074$). RFA is an effective and safe treatment that improves anxiety, depression, and satisfaction in patients with LSIL complicated by hrHPV infection.

Keywords

LSIL; hrHPV infection; Radiofrequency ablation; Efficacy; Safety

1. Introduction

Squamous intraepithelial lesion (SIL) is a cervical precancerous lesion primarily caused by human papillomavirus (HPV) infection and is manifested as increased vaginal discharge with or without a foul odor [1]. The widespread application of sloughing cytology, high-risk HPV (hrHPV) detection, and colposcopy in recent years has led to increased detection of SIL every year, particularly among younger populations [2]. hrHPV infects the squamous epithelium of the lower genital tract and causes localized intraepithelial lesions, which may gradually progress to invasive cancer if the virus is not cleared by the host immune system [3]. A global meta-analysis showed that 70% of invasive cervical cancers were associated with HPV16 (55%) and HPV18 (15%), followed by HPV31, HPV33, HPV45, HPV52 and HPV58. HPV58 and HPV52 infections are more likely to progress to invasive cervical cancer in Asians. They are particularly common in China and Japan, highlighting a distinct regional distribution pattern of hrHPV infection in the lower genital tract [4]. Studies confirmed that hrHPV infection is closely related to squamous intraepithelial lesions in the lower genital tract [5]. Limited awareness of hrHPV and SIL has led to undue psychological stress in patients, affecting their quality of life and causing depression and anxiety in some cases [6]. Patients in certain regions are difficult to track and may have already developed high-grade squamous intraepithelial lesions (HSIL) or malignant tumors by the time they return for a follow-up visit [7]. Therefore, simple and affordable treatments for persistent hrHPV infection and low-grade SIL (LSIL) are needed to prevent the development and progression of HSIL and reduce the incidence of malignant tumors. Several studies have reported that physical therapies (CO_2 laser, ultrasonic vaporization, electrofulguration and cryotherapy) are effective against persistent hrHPV infection and LSIL [8–10]. 5-aminolevulinic acid photodynamic therapy (ALA-PDT) is a drug-device combination based on the interaction of light, photosensitizer and oxygen. It is a safe and non-invasive targeted therapy widely used in skin diseases, oral diseases, and tumors with remarkable therapeutic effects [11–13]. Radiofrequency ablation (RFA) is also a physical therapy commonly used in gynecology to treat uterine fibroids, chronic cervicitis, and

condyloma acuminatum [14, 15]. This study compared the efficacy and safety of RFA with ALA-PDT in the treatment of LSIL with hrHPV infection.

2. Materials and methods

2.1 General information

A single-center retrospective study was conducted to collect clinical data from 100 patients with cervical LSIL, confirmed by thin-layer cytology (TCT), high-risk human papillomavirus (hrHPV) detection, colposcopy and pathological biopsy at the Affiliated Hospital of Chengde Medical University gynecology clinic between January 2022 and October 2023. Inclusion criteria included: (1) LSIL confirmed by histopathology [16]; (2) Histopathological examination confirmed the diagnosis of cervical intraepithelial neoplasia grade 1 (CIN 1) with persistent hrHPV infection; (3) No plan for pregnancy from the end of the last menstrual period to 6 months after trial initiation; (4) Has complete clinical data. Exclusion criteria: (1) History of treatment for the disease within 3 months; (2) Pregnant or lactating; (3) Invasive cancer not ruled out by colposcopy or lesion affecting the vaginal wall; (4) Cervical cancer or other malignant reproductive tumors; (5) Acute reproductive tract infection; (6) Undiagnosed vaginal bleeding; (7) Other systemic diseases, severe immune diseases, gonorrhea or acute pelvic inflammatory disease; (8) Acquired Immune Deficiency Syndrome (AIDS), known severe immunodeficiency or requiring long-term treatment with glucocorticoids and immunosuppressants; (9) Has surgical contraindications or incomplete clinical data. The subjects were divided into the RFA group and ALA-PDT group with 50 patients per group according to their treatment plans. The mean age and disease course of subjects were comparable between the ALA-PDT (46.01 $\pm$ 6.11 years and 1.48 $\pm$ 0.37 years, respectively; HPV infection: 29 cases were positive for hrHPV16/18, 18 cases were positive for other hrHPV types, and 3 cases were negative) and RFA group (47.56 $\pm$ 6.49 years and 1.57 $\pm$ 0.31 years, respectively; HPV infection: 27 cases were positive for hrHPV16/18, 19 cases were positive for other hrHPV types, and 4 cases were negative).

2.2 Treatment methods

The ALA-PDT group was treated by photodynamic therapy using aminolevulinic acid hydrochloride topical powder (Shanghai Fudan—Zhangjiang Biopharmaceutical Co., Ltd., GYZZ20070027, strength: 118 mg/vial) on the YG light emitting diode (LED) therapy instrument (models LED-IBL and LED-IBS, Wuhan Yajie Optoelectronic Technology Co., Ltd., Wuhan, Hubei, China) at an output wavelength of 633 $\pm$ 10 nm, and output power density of 20–100 mW/cm^2 under continuous-wave or pulse mode. LD600-C semiconductor laser instrument: Output wavelength (635 $\pm$ 10) nm, output power 0–500 mW with continuous adjustment, and single light path continuous output. Treatment method: Three packs of aminolevulinic acid hydrochloride topical powder were dissolved in 1.5 mL of temperature-sensitive gel to generate a 20% solution. A tampon was fully soaked in the solution and inserted 1–2 cm into the cervical canal. Then, cotton pad soaked with the solution was placed against the cervix, and sterile gauze was packed into a condom and inserted into the vagina for 3–4 hours. A cylindrical optical fiber was encased in a disposable optical fiber sleeve and inserted 2 cm into the cervix. Radiation was performed at an output power of 260 mW for 25 min. The LED therapeutic device was encased in a disposable sleeve, inserted through the vaginal speculum, and placed at 2 cm away from the cervical surface. Radiation was performed at an output power of 90 mW for 25 min. Treatment was performed once every 10 days in a 30-day cycle for 2 cycles.

The RFA group was treated with RFA using the integrated radiofrequency device (TJSM-RF-III, Tianjin Simon Medical Technology Co., Ltd., Tianjin, China) at an output power of 20–30 W. Patients were positioned supine on the operating table at 3 to 7 days after the end of menstruation. Routine disinfection, draping and preoperative colposcopy assessment were then performed. The cervix and vaginal wall were stained with Lugol's iodine solution to determine the site and extent of the lesion (for patients with vaginal SIL, 2% lidocaine solution was injected subcutaneously at the lesion to act as a water cushion that protects surrounding organs from damage and smooths out the vaginal fold at the lesion site to ensure the lesion is not missed). RFA was performed on the patient's lesion at a depth of 2–3 mm and a width of 5 mm around the lesion. In the case of large lesions, treatment was performed several times at an interval of 1–2 months.

2.3 Outcome measures

2.3.1 TCT

TCT was performed using the cervical cancer screening system/cellular DNA ploidy analysis system (Wuhan Landing Hi-Tech Co., Ltd. Model: LD BX41TF, Wuhan, Hubei, China). Cytological diagnosis was made by a cytopathologist according to the criteria of the Bethesda system (TBS) [16].

2.3.2 hrHPV test

hrHPV testing was performed using the hrHPV DNA genotyping kit (Bohui, Jiangsu Jianyou Medical Technology Co., Ltd., Danyang, Jiangsu, China). The main hrHPV types tested include hrHPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

2.3.3 Colposcopy

Colposcopy was completed within 6 weeks of cytology or hrHPV screening. For patients with hrHPV infection or abnormal cytological findings, colposcopy, visual inspection with acetic acid test, and iodine test were sequentially performed on the vaginal wall and then observed under a colposcope. Under the guidance of colposcopy, tissues from the suspicious lesions were harvested for pathological and histopathological examinations. If a lesion involved the cervical canal or type 3 transformation zone, cervical curettage was also performed.

2.3.4 Efficacy evaluation

HPV-DNA typing, TCT, colposcopy and colposcopy-guided biopsy were carried out at 6 months after the completion of treatment. Assessment was carried out by at least two

gynecologists who were not involved in the treatment and blinded to the patient's treatment. Colposcopy was performed before and after treatment by two experienced gynecologists to evaluate the appearance of the cervix, degree of tissue whitening, and area of iodine discoloration. Cure was defined as having negative results for HPV-DNA typing, TCT and colposcopy-guided cervical biopsy. Remission was defined as the downgrade of a high-grade biopsy to a lower grade, regardless of the HPV-DNA and TCT results. Pathological efficiency rate was calculated as the percentage of patients with cure and remission as the outcome. HPV negative rate was determined based on the percentage of patients who were tested negative for all HPV types. Patients with partial HPV negativity or persistent HPV infection were considered HPV-positive.

2.3.5 Negative hrHPV seroconversion

The negative hrHPV seroconversion rate was compared between the two groups at 6 months and 12 months after the end of treatment.

2.3.6 Comparison of mental status

The mental status of the patients was assessed before treatment and at 6 months after the end of treatment using the Self-Rating Anxiety Scale (SAS) and Self-Rated Depression Scale (SDS) [17]. The Cronbach's α coefficients of the two scales were 0.852 and 0.895, respectively.

2.3.7 Satisfaction and adverse reactions

Treatment satisfaction of the two groups of patients was assessed 6 months after the end of treatment [18]. Adverse reactions were recorded during treatment and follow-up, including increased vaginal discharge, vaginal bleeding, scarring, adhesion and local pain. Pain was assessed on the visual analogue scale (VAS), with 0 indicating no pain and 10 indicating the most unbearable pain.

2.4 Statistical analysis

Data were processed and analyzed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Measurement data with normal distribution were compared using the independent sample *t*-test. Count data are expressed as cases (percentages) and compared using the Chi-squared test. A $p < 0.05$ was considered statistically significant.

3. Results

3.1 Clinical efficacy

Only patients who were lesion-free and HPV-negative were considered cured. Assessment at the 6-month follow-up showed that the cure rate was significantly higher in the RFA group (94.00%) compared to in the ALA-PDT group (74.00%; $p < 0.05$). Despite the absence of lesion progression in either group at the 6-month follow-up assessments, 3 patients in the RFA group and 13 patients in the ALA-PDT group had persistent lesions (Table 1).

3.2 Negative hrHPV seroconversion

At 6 months after treatment, the rate of negative hrHPV seroconversion was significantly higher in the RFA group (27/50, 54.00%) compared to the ALA-PDT group (17/50, 45.00%) ($\chi^2 = 4.058$, $p = 0.044$). At 12 months after treatment, the rate of negative hrHPV seroconversion remained significantly higher in the RFA group (36/50, 72.00%) than in the ALA-PDT group (26/50, 52.00%) ($\chi^2 = 4.244$, $p = 0.039$).

3.3 Mental status

SAS and SDS scores were similar between the two groups before treatment ($t = 1.853$ and 0.633, $p = 0.067$ and 0.528, respectively) and decreased at 6 months after treatment. In addition, SAS and SDS scores were significantly lower in the RFA group than in the ALA-PDT group (both $p < 0.05$) (Table 2).

3.4 Satisfaction

The RFA group had a significantly higher satisfaction rate than the ALA-PDT group (90.00% *vs.* 76.00%, $p < 0.05$) (Table 3).

3.5 Adverse reactions

During the treatment period, 33 patients in the ALA-PDT group and 29 patients in the RFA group reported mild to moderate burning sensations and lower abdominal distension, which were tolerated by all patients. During the follow-up period, colposcopy of the RFA group showed smooth and elastic vaginal mucosa at the surgical site. Four patients experienced increased postoperative vaginal discharge, which was reduced after treatment with Baofukang suppositories. Two patients had mild vaginal bleeding (less than 5 mL) that resolved after compression. No vaginal scar formation was observed in any patient. In the ALA-PDT group, 7 patients had increased vaginal discharge, 5 had mild vaginal bleeding, and 1 showed vaginal scar formation. The postoperative complication rates were similar between the RFA and ALA-PDT groups (12.0% *vs.* 26.0%; $\chi^2 = 3.184$, $p = 0.074$) (Table 4).

4. Discussion

According to the latest cancer statistics, cervical cancer is ranked as the fifth most common cancer among women and the sixth leading cause of cancer death in China, with 150,000 new cases and 55,700 deaths in 2022 [19]. It was found that age is positively correlated with SIL disease grade, and postmenopausal women are more likely to be diagnosed with SIL than premenopausal women [20]. Intermediate-grade SIL (ISIL) represents an intermediate stage in the gradual progression from normal cervical epithelium to invasive cancer. ISIL may spontaneously regress in 60% of cases, persist in 30% of cases, and progress to HSIL within 2 years in 10% of cases [21]. Although observation and follow-up are recommended for ISIL, there remain many challenges in ISIL management during actual clinical practice. These include the large number of patients seeking treatment due to psychological stress and the social impact of the diagnosis, as well as concerns about the risk of disease progression [22]. Various expert consensus

TABLE 1. Comparison of clinical efficacy.

Group	Number of cases	Cure	Remission	Ineffective	Total effective rate
ALA-PDT group	50	26 (52.00)	11 (22.00)	13 (26.00)	74.00%
RFA group	50	39 (78.00)	8 (16.00)	3 (6.00)	94.00%
χ^2					7.440
p					0.006

ALA-PDT: aminolevulinic acid photodynamic therapy; RFA: radiofrequency ablation.

TABLE 2. Comparison of mental status.

Group	Number of cases		SAS score	SDS score
ALA-PDT group	50	Pre-treatment	57.75 ± 5.07	58.81 ± 5.37
		6 months post-treatment	50.86 ± 6.10	50.07 ± 4.94
RFA group	50	Pre-treatment	55.84 ± 5.23	58.08 ± 6.23
		6 months post-treatment	42.77 ± 4.98	40.95 ± 4.11
t			7.266	10.020
p			<0.001	<0.001

ALA-PDT: aminolevulinic acid photodynamic therapy; RFA: radiofrequency ablation; SAS: Self-Rating Anxiety Scale; SDS: Self-Rated Depression Scale.

TABLE 3. Comparison of satisfaction.

Group	Number of cases	Satisfied	Somewhat satisfied	Dissatisfied
ALA-PDT group	50	22 (44.00)	16 (32.00)	12 (24.00)
RFA group	50	34 (68.00)	11 (22.00)	5 (10.00)
χ^2				6.380
p				0.041

ALA-PDT: aminolevulinic acid photodynamic therapy; RFA: radiofrequency ablation.

TABLE 4. Adverse reactions after treatment.

Symptom	ALA-PDT group N (%)	RFA group N (%)
Increased vaginal discharge	7 (14.00)	4 (8.00)
Vaginal bleeding	5 (10.00)	2 (4.00)
Scars	1 (2.00)	0
Adhesion/Ulcer	0	0

ALA-PDT: aminolevulinic acid photodynamic therapy; RFA: radiofrequency ablation.

recommendations include regular follow-up, pharmacological therapy or physical therapy for hrHPV infection with LSIL of the lower genital tract and surgical resection for HSIL [23].

ALA-PDT is a novel treatment for HPV-associated diseases that combines light with photosensitizers to generate phototoxicity. Yuan *et al.* [24] found that the ISIL reversal rate was 81.25% at 9 months after the end of ALA-PDT, suggesting that the treatment demonstrates favorable efficacy in ISIL. Compared with other physical therapies, RFA can accurately determine the location and extent of the lesion and effectively destroy the lesion. It is a simple and minimally painful procedure with low surgical risk, and most wounds heal after 6–8 weeks [25]. It has been shown that RFA can cause coagulative necrosis of subepithelial tissue at a depth of 3 mm. Since LSILs of the lower genital tract are typically located 1 mm deep in the subepithelial tissue, RFA is a promising approach for curing persistent lower genital hrHPV infection and LSIL, as well as for preventing the progression of SIL [26]. In this context, the present study evaluated the efficacy and safety of RFA and ALA-PDT in SIL.

Efficacy assessment at 6 months post-treatment showed that the overall effective rate was significantly higher in the RFA group (39 cured and 3 ineffective; 94.00%) than in the ALA-PDT group (26 cured and 13 ineffective). In addition, hrHPV testing revealed that the RFA group had a significantly higher negative hrHPV seroconversion rate than the ALA-PDT group at 6 months or 12 months after treatment, further confirming the long-term therapeutic effects of RFA. This difference may be attributed to the use of radiofrequency current through human tissue during RFA. When molecular friction occurs

within the cell nucleus, the temperature at the lesion site rises and accelerates water evaporation from both inside and outside of the cell. This process promotes desiccation and cell shrinkage, effectively eliminating HPV-infected tissues [27]. Previous studies have shown that a diagnosis of malignant tumors can lead to varying degrees of anxiety and depression in patients, significantly affecting their quality of life and prognosis [28]. Comparison of SAS and SDS scores revealed that the levels of anxiety and depression were high in both groups before treatment and were significantly decreased after treatment. Furthermore, the reduction in SAS and SDS scores was significantly greater in the RFA group than in the ALA-PDT group, demonstrating that RFA can effectively improve anxiety and depression in patients. None of the patients in this study were vaccinated with HPV vaccine, thus intuitively demonstrating the effects of the two treatments. Though, it is worth noting that vaccination against HPV may be beneficial both in the early stage of HPV infection, when LSIL (CIN 1) develops, and may also prove to be a valuable option for patients who have never given birth and do not consent or are afraid of surgical treatment [29].

The inpatient satisfaction survey is a key tool that benefits healthcare providers and positively influences patient's medical experience and safety. Our results showed that 90.00% of patients in the RFA group were satisfied with their care, compared to the ALA-PDT group, indicating a preference for RFA among the patients in this study. To assess the safety of the two regimens, we compared their adverse effects and found that both groups experienced mild to moderate burning sensations and lower abdominal distension during treatment. These side effects were tolerable to patients and were related to the treatments. In subsequent follow-ups, we found that both groups had a small amount of vaginal bleeding and increased vaginal secretion, which were resolved after treatment with Baofukang Suppositories. There was no significant difference in the incidence of postoperative complications between the two groups, confirming that both regimens were safe.

5. Conclusions

In conclusion, both RFA and ALA-PDT are effective treatments that improve the cure rate of LSIL with hrHPV infection. However, RFA is more effective than ALA-PDT in alleviating anxiety and depression and improving treatment satisfaction, with a comparable safety profile. This treatment offers the benefits of a simple procedure, low operational risk and minimal pain. Most wounds heal within 6–8 weeks without the need for hospitalization, making the treatment highly cost-effective. Therefore, RFA is worthy of being promoted for nationwide use, especially in small and medium-sized cities, due to its straightforward methodology, easy equipment operation, and wide applicability. Limitations of this study include its single-center retrospective design and small sample size. Further large-cohort studies with improved design and longer follow-up periods are warranted to confirm the efficacy of these two treatments.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

PHC—designed the study and carried them out, prepared the manuscript for publication and reviewed the draft of the manuscript. PHC, LJL, YQL, XCW, LXC—supervised the data collection; analyzed the data. PHC, LJL, YQL—interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Affiliated Hospital of Chengde Medical University (Approval no. 2021046). Written informed consents were obtained from legally authorized representatives for anonymized patient information to be published in this article.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This work was supported by 2023 Medical Science Research Directive Project in Hebei Province (Grant No. 20230210).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Penghua Cui, Lijing Li, Yaqian Lin, Xingcha Wang, Lixin Cheng. Efficacy and safety of radiofrequency ablation in the treatment of low-grade squamous intraepithelial lesions complicated with high-risk human papillomavirus infection. European Journal of Gynaecological Oncology. 2024; 45(5): 168-173. doi: 10.22514/ejgo.2024.105.