



# Clinical Observation of 212 Cases of Cervical Low-Grade Squamous Intraepithelial Lesion (LSIL) Treated by Photodynamic Therapy (PDT)

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## Abstract

**Objective:** Cervical cancer is a malignant tumor threatening the life and health of women. How to intervene in the stage of precancerous lesions, prevent the further progression of lesions and block the occurrence of cervical cancer is an important issue we face. Photodynamic Therapy (PDT) is a targeted combination of drug and device therapy, which has the characteristics of specific, efficient and safe. This paper aims to investigate the efficacy of PDT in the treatment of Low-Grade Squamous Intraepithelial Lesion (LSIL). **Methods:** 212 cases of LSIL were confirmed by cervical biopsy histopathology. Immune system disease, photoallergy, pregnancy and other conditions were excluded. The reversal rate of LSIL and the negative rate of HPV were observed after three times or six times of photodynamic therapy.

**Results:** At 3 months follow-up after the end of treatment, 157 cases of HR-HPV in 212 patients turned negative, increased to 162 cases at 6 months, 162 cases remained HPV negative at 12 months, and the total negative conversion rate was 76.42%. At 3 months, 6 months and 12 months follow-up, LSIL conversion rate reached 85.85%. No serious side effects occurred.

**Conclusion:** ALA-PDT is effective and less toxic in the treatment of LSIL caused by cervical HR-HPV infection, which is especially suitable for women with fertility requirements. It has good efficacy and small side effects in elderly patients, and is worthy of further study.

**Keywords:** Photodynamic Therapy (PDT); Cervical Low-Grade Squamous Intraepithelial Lesion (LSIL); HPV Infection

## INTRODUCTION

Cervical cancer is a malignant tumor that threatens women's life and health. In 2020, there will be 604,000 new cases and 342,000 deaths worldwide. However, cervical cancer is the only malignant tumor with clear etiology at present, and cervical precancerous lesions and early cervical cancer can be detected through cytological and High-Risk Human Papilloma Virus (HR-HPV) screening. How to intervene in the stage of precancerous lesions, prevent further progression of lesions, and block the occurrence of cervical cancer is an important problem we face. Photodynamic therapy is a targeted combination of drugs and instruments, with specific, efficient and safe characteristics, has been used in the treatment of a variety of skin tumors, and has been written into the low-risk HPV infection caused by condyloma acuminatum treatment international guidelines, in July 2022, China published the "Chinese Expert Consensus on the Clinical Applications of Aminolevulinic Acid-Based Photodynamic Therapy in Female Lower Genital Tract Diseases (2022)". The application of photodynamic therapy for cervical lesions was standardized. Since 2008, our hospital has carried out photodynamic treatment of HPV infection-related diseases, and 212 cases of Cervical Low-Grade Squamous Intraepithelial Lesion (LSIL) treated by recent

photodynamic therapy have been clinically analyzed.

## MATERIALS AND METHODS

### Study Design

The patients who visited the gynecological outpatient department of Beijing Hospital from January 2018 to December 2020 were selected. A total of 212 patients with cervical Low-Grade Intraepithelial Lesion (LSIL) confirmed by cervical biopsy pathology were included in the study. The age distribution ranged from 25 to 67 years. The number of pregnancies was 0-3, with an average of 1.2. HPV infection lasts from 6 months to 15 years.

### Indications:

Histological LSIL/CIN I patients with high risk factors;  
Voluntarily undergo photodynamic therapy.

### Contraindications:

Cytological and histological examination of Atypical Adenocarcinoma (AGC), in situ Adenocarcinoma (AIS), or suspected malignant lesions;

- 1) The possibility of malignant lesions cannot be ruled out;
- 2) Photoallergy;
- 3) Pregnant women.

The treatment was approved by Beijing Hospital and Ethics Committee as a new technology. Informed consent was signed before starting treatment.

### Diagnosis

Samples were collected with a dedicated cervical exfoliated cell collector. The cervical cytology test was performed using Holloger's liquid-based ultra-Thin Cytology (TCT), and the HR-HPV test was performed using the HC2 method from Kejer or the cobas

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HPV test from Roche Diagnostics for HPV 2+12 typing. Colposcopy was performed for patients with  $\geq$  Atypical Squamous Cell (ASCUS) or HPV16, 18 subtype infection or HPV persistent infection for more than 1 year, histologically confirmed LSIL for more than 1 year, or clinically suspected cervical lesions. Finally, LSIL cases confirmed by cervical biopsy pathology were selected as the study object. Rule out immune system disease, photoallergy, pregnancy and other conditions.

### Photodynamic Therapy

Treatment was carried out during the non-menstrual period. After removing secretions from the vagina and cervix surface, the vagina, cervix and cervical canal were cleaned and sterilized. ALA solution (20%) was freshly prepared by mixing ALA powder (Fudan Zhangjiang Biopharmaceutical Co. Ltd., Shang-hai, China) with temperature-sensitive gel. Each vial contained 118 mg ALA and could be applied to an area of 3.14 cm<sup>2</sup> at the ALA dose of 38 mg/cm<sup>2</sup>. The amount of ALA was administered according to the lesion size plus 0.5 cm margin. After soaking medical cotton in ALA solution, the ALA-absorbed cotton would be placed evenly over the cervix surface. For the concurrent cervical canal lesion, ALA-soaked cotton containing 118 mg ALA was also inserted into the cervical canal. For the concurrent vaginal lesion, the amount of ALA applied was determined by the lesion size plus 0.5 cm margin. The cottons were removed after 3h of incubation. ALA applied areas of the cervix and cervical canal were irradiated with lensed fiber and cylindrical diffusor fiber connected to a 635 nm laser (LD-600, Wuhan Yage Optic & Electronic Technique Co., Ltd., Wuhan, China) for 30min at the energy density of 100 J/cm<sup>2</sup>. If accompanied with Vaginal Intraepithelial Neoplasia (VaIN), ALA of the same dose would also be applied to the vaginal wall at the same time and the vaginal lesions would be irradiated by an intravaginal corn shape LED illuminator (LED-IBL, Wuhan Yage Optic & Electronic Technique Co., Ltd.) for 30 min at 100 J/cm<sup>2</sup> [1]. Similar PDT procedure was repeated every one to two weeks for a total of 3 times as one session. Typically, one session was used for patients with cervical LSIL only and two sessions for patients with cervical canal lesion and cervical LSIL plus concurrent lesions in the cervical canal or vaginal wall [2]. If possible, the cervical lesion and vaginal lesion would be irradiated at the same time to reduce overall length of treatment. If impossible, the irradiation of vaginal lesion would be carried out after the completion of cervical

irradiation. The manifestation, severity, duration, measures taken and outcomes of adverse reactions during and after each treatment were recorded.

### Evaluation and Follow-Up

For the evaluation of HPV clearance and lesion regression, HPV typing and TCT examination of cervical lesion areas were carried out during follow up visits at 3 months, 6 months and 12 months after treatment, respectively. LSIL regression was defined as TCT became normal and HPV turned negative. If TCT  $\geq$  ASCUS or HPV remained positive, colposcopy biopsy and normal histopathology was required for the confirmation of LSIL regression. Colposcopy examination would be performed if TCT was abnormal or HPV was still positive. For patients with concurrent cervical canal and vaginal lesions, all lesion areas would be examined and evaluated together.

### Statistical Analysis

Statistical software SPSS was used for data processing and statistical analysis. Measurement data were described by mean  $\pm$  standard deviation ( $X \pm SD$ ), counting data by frequency and percentage.  $X^2$  test was used for comparison between groups.  $p < 0.05$  was considered statistically significant (Table 1).

## RESULTS

### Patient Demographic Data

Among the 212 patients with LSIL, 31 (14.62%) were 25-29 years old, 73 (34.43%) were 30-39 years old, 63 (29.72%) were 40-49 years old, 24 (11.32%) were 50-59 years old, and 21 (9.91%) were 60-69 years old, most of which were 30-39 years old.

### Clinical Outcomes

Patients with abnormal cervical cancer screening accounted for 47.01%, patients with simple history of HPV infection (infection time ranging from 3 months to 15 years, no history of cervical disease diagnosis) accounted for 24.29%, patients with cervical disease history follow-up accounted for 12.15%, patients with irregular vaginal bleeding accounted for 11.80%, and patients

**Table 1:** Analysis of 6-month results of treatment groups of different ages.

Age	Number	LSIL regression number	LSIL regression rate	HPV negative conversion number	HPV negative conversion rates	P value
25-29	31	25	80.65%	25	80.65%	< 0.001
30-39	73	65	89.04%	71	77.17%	< 0.001
40-49	63	53	84.13%	45	71.43%	< 0.001
50-59	24	21	87.50%	22	91.67%	< 0.001
60-69	21	18	85.71%	18	85.71%	< 0.001
Total	212	182	85.84%	162	76.41%	

The statistical curative effect of each age group was less than 0.001.



with other cervical abnormalities due to MRI and ultrasound examination accounted for 2.81%. Abdominal pain and lumbago accounted for 1.41%, vulvar pruritus accounted for 0.53%. Symptoms or abnormal medical history accounted for 52.99%.

Among the 212 patients, cervical cytology screening (TCT) showed no intraepithelial neoplasia and cancer cells (NILM) in 103 cases (48.58%), abnormal in 109 cases (51.42%), including 40 cases (18.87%) of squamous epithelial cells (ASCUS) without clear significance. There were 54 cases (25.47%) of low-grade squamous epithelial lesions (LSIL) and 15 cases (7.07%) of High-Grade Squamous Epithelial Lesions (HSIL). 100% of the patients were positive for high-risk Human Papillomavirus (HPV), mainly single infection, and 16 subtypes were the most common infection, accounting for 37.12%.

### Evaluation of Age Effect on HPV Negative Conversion Rates

At 3 months follow-up after the end of treatment, 157 of 212 patients had HR-HPV negative, which increased to 162 cases at 6 months, and 162 cases remained HPV-negative at 12 months, with a total negative conversion rate of 76.41%.

### Evaluation of Age Effect on LSIL Regression Rate

At 3 months, 6 months and 12 months, LSIL reversal rate reached 85.84%. The LSIL reversal rates at 6 months and 12 months after treatment were 80.65% (25/31), 89.04% (65/73), 84.13% (53/63), 87.50% (21/24) and 85.71% (18) at ages 25-29, 30-39, 40-49, 50-59 and 60-69, respectively. The negative rates of HPV were 80.65% (25/31), 71.23% (52/73), 71.43% (45/63), 91.67% (22/24) and 85.71% (18/21), respectively. In this study, 104 women of childbearing age had 86.54% LSIL reversal rate and 74.03% HPV negative conversion rate.

Of the 30 patients who failed to achieve LSIL reversal, all were patients with prolonged HPV infection (3 to 5 years), and one had a new vaginal wall lesion (HSIL) at 12 months follow-up.

### Adverse Reactions

189 patients in the treatment group had mild pain and discomfort in the lower abdomen, and all of them were relieved by themselves the next day without medical intervention; increased secretions were found in 170 patients after Treatment, and vaginitis and cervicitis were excluded in clinical examination. Dull toxicity occurs. Colposcopy showed no scar formation, complete shape and good elasticity on the cervical surface.

### DISCUSSION

Cervical cancer seriously affects the health of women, but it usually goes through the process of HR-HPV infection, low-grade cervical intraepithelial neoplasia, and high-grade cervical intraepithelial neoplasia. Control in any link can prevent the occurrence of cervical cancer. Many factors affect the outcome of LSIL, including HPV subtypes, colposcopic image characteristics, and the patient's systemic condition. HPV infection is usually cleared within 1 to 2 years, and the vast majority of LSIL patients can heal themselves, but about 35% of the lesions persist. Moreover, it must be noted that HSIL may still be missed in patients with abnormal cervical cancer screening despite the colposcopic biopsy being LSIL. A meta-analysis showed that the overall risk of CIN2+ in colposcopy for low-grade impressions ranged from 11% to 69% depending on the screening risk [3]. Cytological screening of atypical squamous epithelial cells (ASC-H) and HPV16/18  $\geq$  not excluding high-grade intraepithelial lesions are independent predictors of CIN2+ [4]. Kaiser (KPNC) studies have shown that in

women diagnosed with normal and  $\leq$  CIN1 by colposcopic biopsy, the potential CIN3+ risk is associated with previous cytological screening results [5]. Scholar Qian Min's research also showed [6] that follow-up or further intervention was decided according to the severity of previous cytology.

In principle, patients diagnosed with LSIL by histopathology need not be treated and should be observed clinically. LSIL that may be at risk for HSIL should be carefully managed and stratified based on cytological screening results before colposcopy [7]. Early intervention is necessary for patients at high risk of LSIL (long duration of LSIL, infection with HPV16/18 subtype, high cytological grade, combined immunodeficiency disease, etc, [8]. Currently, there is a lack of specific and effective anti-HPV drugs in clinical practice. In the treatment of LSIL, traditional treatment methods such as physical destruction or surgical resection are mainly used, but there are severe complications such as trauma, pain and possible postoperative cervical dysfunction, which may cause infertility, premature delivery and low birth weight infants [9]. A specific, efficient and safe treatment is needed in clinic.

A recent systematic review and meta-analysis suggests that PDT maybe a practical approach to treat LSIL [8]. Photodynamic therapy is a new technique based on the interaction of light, photosensitizer and oxygen to diagnose and treat diseases by photochemical reaction. Photosensitizers are special chemicals whose basic function is to transfer energy. When illuminated, the photosensitizer absorbs photons and is excited, and the absorbed light energy is quickly transmitted to the ground state oxygen, which is excited to produce reactive oxygen species, thus oxidizing and destroying biological macromolecules, and ultimately causing cell necrosis or apoptosis.

5-Amino-Ketovaleic Acid Photodynamic Therapy (ALA-PDT) has been used for the treatment of Non-Melanin Skin Tumors (NMST) since 2000, in China, CFDA approved ALA-PDT for the treatment of condyloma acuminatum in 2007, and then its clinical application is more and more extensive, can treat skin tumors, infectious skin diseases, inflammatory skin diseases and so on. ALA is the precursor of photosensitizing agent hematoporphyrinIX (PpIX), which is converted into PpIX in proliferative cells, and photochemical reactions occur under specific wavelengths of light to produce singlet oxygen and free radicals and other active substances, which can kill or kill tumor cells. Pahernik, et al. confirmed that after 5h of local administration of 5-ALA, the ratio of photosensitizers in CIN1 of diseased cells to those in surrounding normal tissues was 3:1 [10] and ALA could selectively enrich in tumor tissues, with little damage to normal tissues. Photodynamic therapy has good specificity.

The anti-tumor effect of photodynamic therapy is accurate and efficient. Photodynamic therapy achieves anti-tumor effect by directly killing tumor cells [11], damaging tumor blood vessels, and inducing anti-tumor immunity [12,13]. The immune response induced by PDT is mainly achieved through two ways: (1) activating the innate immunity of the body. After PDT treatment, acute inflammation is triggered, neutrophil infiltration is promoted, and the innate immunity of the body is activated. (2) Inducing the expression and release of DAMP-related Molecular Patterns (DAMPs), activating specific immunity and triggering Immunogenic Cell Death (ICD) [14].

In the field of gynecology, PDT can be used not only as an alternative treatment or adjuvant treatment for gynecological cancer when other treatments fail, but also as a less invasive treatment for superficial lesions that are extensive or difficult to eradicate [15]. Currently, ALA PDT has been used in the treatment of cervical and vaginal HSIL and LSIL in China and other countries



[16,17]. LSIL lesions are limited to the epithelial thickness above the basement membrane of about 2 to 3 mm, which is within the effective depth of PDT, and PDT may be effective for LSIL treatment [18,19]. Many domestic and foreign studies have confirmed the efficacy of PDT in the treatment of LSIL [20-22].

The latest meta-risk study showed that the CRR for CIN1 was 57.1% to 83.3%, the overall CRR for CIN2 and CIN3 was 95% to 100%, and the CRR for HPV was 66.7% to 92.73%. The CRR of CIN 2/3 patients was higher than that of CIN1 patients. During a follow-up period of up to 2 years, the recurrence rate of the disease was only 3.3-8.9% [23]. The results showed that PDT had good short-term and long-term efficacy in treating CIN with HPV effect.

Studies have shown that Human Papillomavirus (HPV) infected cells can selectively absorb ALA, resulting in the accumulation of PpIX in infected cells, photosensitivities after light irradiation kill cells, and prevent viral replication through oxygen-dependent cytotoxicity, viral nucleic acid chain break or base site disappearance [18,24-26]. At the same time, PDT can also increase the number of local lymphocytes of CD4+ and CD8+T, enhance the activity of natural killer cells, regulate local immunity, and improve the antiviral ability of the body [27]. It can be seen that PDT can also clear high-risk HPV (hrHPV) infection while treating SIL [27,28], so as to prevent recurrence. A recent study suggests that repeated ALA PDT might enhance HPV antibody production in CIN patients [29].

In this study, the conversion rate of ALA-PDT in the treatment of LSIL was 85.84%, and the negative conversion rate of HPV was 76.41%, which was better than the expert consensus of 75% to 85.7% histological remission rate of 3 to 6 months. ALA-PDT is effective in LSIL treatment and HPV clearance. When colposcopy is low-grade impression and Transformation Zone (TZ3) type, the missed diagnosis rate of CIN2 and CIN3 (52.6%, 31.6%) is higher than that of TZ 1/2 type (27.5%, 18.8%) [30]. It can be seen that TZ3 patients have an increased risk of missed diagnosis of HSIL, so more attention should be paid to TZ3. Photodynamic therapy has a specific optical fiber that can penetrate into the cervical canal, so it has a unique therapeutic effect on cervical lesions in the type III transformation area. The good therapeutic effect of middle-aged and elderly women in this study is related to the good treatment of cervical canal. In this experiment, 45 postmenopausal women were included, and the LSIL conversion rate and HPV negative conversion rate reached more than 85%, which was far better than the therapeutic effect of other methods. The main reason was that the vaginal cervical epithelial tissue of postmenopausal women was about 1/3 thinner than that of women of reproductive age. Under the same concentration and dose of photosensitizer, the action time and scope were the same. Photosensitizers can fully penetrate the epithelium and adequately act on the lesion site, so the treatment effect is good. It opens up a promising treatment plan for elderly patients who have long been troubled by the clinic [31]. Due to the small number of cases in this group, further clinical verification is needed.

A study reported the follow-up results of 112 cases of CIN II-III women of childbearing age who received PDT treatment for a maximum of more than 4 years, indicating that the CRR of CIN patients reached 92.8%, and 88 cases of hrHPV infection existed before PDT treatment. The removal rate of HPV within 3 months was 53.4%, and 15 women became pregnant and recovered completely during follow-up. Therefore, PDT can be recommended for CIN treatment in women of childbearing age. In this study, 104 women of childbearing age had 86.53% LSIL conversion rate and 74.03% HPV negative conversion rate. The treatment cycle is short, the effect is satisfactory, the trauma of cervical surgery is avoided,

the adverse pregnancy outcome is avoided, especially the patient's concern about neonatal HPV infection is reduced, and it is the best choice for patients with LSIL with fertility requirements.

Based on the literature and preliminary test results, the author used 20% ALA for 3h to improve the absorption rate of ALA. The cylindrical optical fiber and point light source were used to irradiate the cervical canal and the external cervical opening at the same time, saving the irradiation time, so that the cervical canal and the entire cervical surface could get uniform and sufficient irradiation, and no serious adverse reactions were observed. The conversion rate of LSIL in this study was higher than that reported in the literature, considering that we paid full attention to the screening of vaginal wall lesions, a total of 6 cases of CINI complicated with VAIN, and the complete remission rate was 100%. For patients with VAIN, the coverage site of ALA was extended to the whole vagina, achieving a wide coverage of ALA. Therefore, the photosensitizer acts on the cervical canal, cervical surface and vaginal wall to achieve the maximum removal of virus and ensure the reversal rate of lesions.

In this group of 30 patients who failed to achieve LSIL reversal, the reason may be related to the longtime of HPV infection (3 years, 5 years), and one of them showed new lesions in the vaginal wall at the 12-month follow-up, suggesting that attention should be paid to vaginal lesions in the treatment follow-up. Some of them had one or more following comorbidity. Because the number of cases is not enough to explain the problem, medical records need to be accumulated for further study.

## CONCLUSIONS

In this study, by comparing the results of 3 months, 6 months and 12 months follow-up of ALA-PDT photodynamic treatment of LSIL, the LSIL reversal rate and HPV negative conversion rate were much higher than that of natural clearance, and there was no impact on the structure and function of the cervix. ALA-PDT treatment of cervical HR-HPV infection was highly selective and effective. Low toxicity, low recurrence rate, especially suitable for women with fertility requirements. For elderly patients, it has the advantages of good efficacy and small side effects, and is worth further research. This study has the defects of short follow-up time and lack of individualized detailed analysis of failure cases, and corresponding studies will be further conducted in the future.

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