Gynecology and Obstetrics Clinical Medicine 3 (2023) 213–219

Contents lists available at ScienceDirect

Gynecology and Obstetrics Clinical Medicine

journal homepage: www.keaipublishing.com/en/journals/gynecology-and-obstetrics-clinical-medicine

Review Article

Advances in ablative treatment for human papillomavirus related cervical pre-cancer lesions

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ARTICLE INFO

Keywords:
Ablative treatment
Thermal ablation
Cryotherapy
Cervical intraepithelial neoplasia
Human papillomavirus

ABSTRACT

HPV infection is the primary cause of cervical intraepithelial neoplasia (CIN), with persistent high-risk HPV infection being the leading factor in the development of cervical cancer. In addition to the application of large loop excision of the transformation zone (LLETZ) for the treatment of cervical pre-cancerous lesions, various ablative techniques, including thermal ablation, cryotherapy, carbon dioxide (CO_2) laser therapy, and focused ultrasound therapy also play significant roles in the management of cervical intraepithelial neoplasia. This review presents a comprehensive overview of the pathophysiology of cervical HPV infection and discusses the ablative methods commonly used in clinical practice, along with their indication and contradiction, especially in women with high-grade squamous intraepithelial lesions. The aim is to identify safe and effective treatment strategies for treating cervical intraepithelial neoplasia, thereby avoiding under- or over-treatment, which may reduce the incidence and progression of cervical cancer through timely diagnosis and treatment.

1. Introduction

According to the estimates from International Agency for Research on Cancer (IARC), there were about 604,000 new cervical cancer cases and 342,000 deaths worldwide in 2020. Notably, nearly 90 % of these cases occurred in low and middle-income countries (LMICs).[1] The primary contributing factor can be attributed to limited medical infrastructure and the fact that the majority of women have not undergone the standardized three-stage process of cervical cancer, which includes screening, diagnosis, and treatment. Consequently, cervical lesions often go undiagnosed and untreated within the required timeframe.

Based on this, in 2021, the World Health Organization (WHO) released the second edition of cervical cancer screening and treatment guidelines, which recommended the use of human papillomavirus (HPV) tests as a cervical cancer screening method.[2] Meanwhile, the guidelines advocate for both “screen-and-treat” and “screen-triage-treatment” strategies, aiming to enhance the treatment rate for individuals with cervical precancerous lesions. While the majority of HPV infections tend to clear spontaneously within one to two years without treatment,[3] it's important to emphasize that there is currently no effective method for rapidly clearing cervical HPV. In this review, our objective is to clarify HPV-induced cervical lesions and present a comprehensive overview of the current clinical practice of ablative treatment for cervical lesions. We aim to offer clear guidance by covering indications, contraindications, treatment outcomes, and relevant research data, ultimately reducing the likelihood of inadequate or excessive interventions.

2. High-risk HPV-related cervical lesions

Due to its strong affinity for epithelial tissues, HPV specifically targets the squamous epithelium in particular regions of the skin and mucous membranes.[4] High-risk HPV can infect either surface epithelial cells or basal cells particularly when they are exposed due to minor injuries. In cases where the infection occurs in surface differentiated epithelial cells, high-risk HPV is typically cleared as these cells mature and shed, without interfering with the normal differentiation process. Furthermore, viral

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Publishing services by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.gocm.2023.11.002
Received 15 August 2023; Received in revised form 13 October 2023; Accepted 5 November 2023
Available online 17 November 2023

particles may be released from the cell membrane surface and subsequently eliminated by the body's immune system, resulting in a temporary infection.

However, if the high-risk HPV virus infects basal cells and integrates its genes into the human genome, it can lead to abnormal cellular proliferation, disrupted cellular arrangement, and nuclear changes such as enlargement, hyperchromasia, and uneven chromatin distribution. This cascade of events results in nuclear atypia, a condition known as cervical squamous intraepithelial lesion (SIL), which has the potential to progress and invade the stroma, ultimately leading to cervical precancer lesions or invasive carcinoma.[5–7]

3. Ablative treatment for cervical disease

In accordance with the recommendations outlined in WHO guideline, women who screen positive in visual inspection with acetic acid (VIA) should undergo ablative treatment promptly following their screening, irrespective of whether a histological diagnosis has been established. For those who are not eligible for ablation, should receive either a large loop excision of the transformation zone (LLETZ) or the loop electrosurgical excision procedure (LEEP) on the same day. Furthermore, for patients who test positive for HPV DNA in the primary screening and subsequently in the second test, the "screen, triage, and treat" approach can be implemented.[2] In these cases, if visual inspection with acetic acid is eligible for ablation, the decision to treat also can be made without a histologically confirmed diagnosis (Fig. 1).[2]

Methods for treating cervical lesions may encompass either ablative techniques or excisional procedures, with the aim of either destroying or surgically excising the transformation zone of the cervix or removing areas of the cervix that have been identified as abnormal. In addition to excisional procedures such as LLETZ or cold knife cone (CKC), ablative methods, also known as physical therapy, play a crucial role in cervical lesion treatment. They are recommended in a screen-and-treat approach

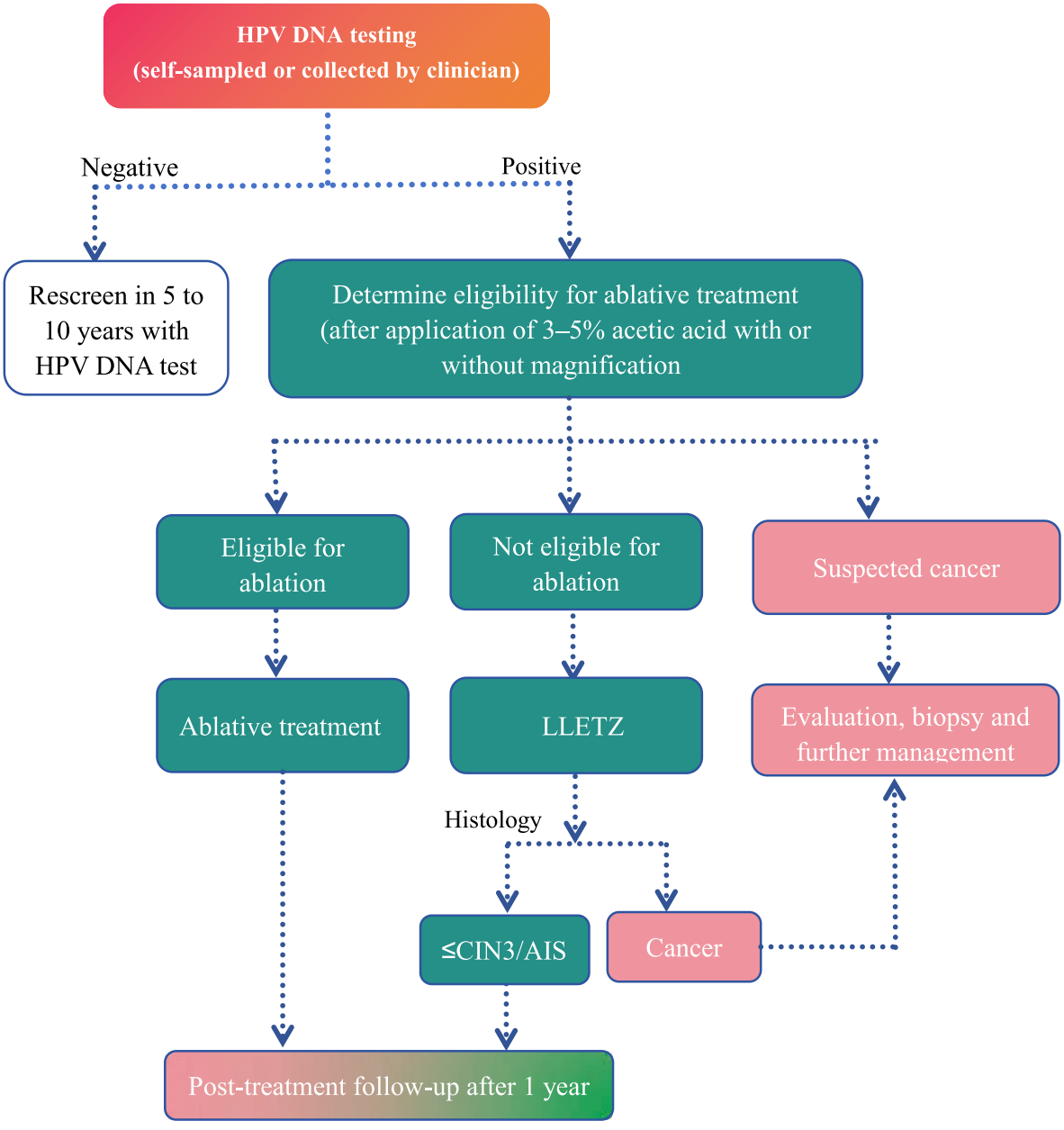

Fig. 1. Algorithm of primary HPV DNA test screening for the general population of women.

when the patient is eligible for ablative treatment. Currently, ablative methods primarily comprise thermal ablation and cryotherapy, both of which are recommended by the WHO as ablation treatment methods. In addition to these, in recent years, there have been numerous reports suggesting that other ablative techniques such as laser therapy, focused ultrasound, and photodynamic therapy have also demonstrated promising results. Fig. 2 illustrates the commonly used methods for cervical ablative treatment.

Based on the WHO guidelines for thermal ablation in cervical precancer lesions and the Chinese expert consensus on the management of high-grade cervical intraepithelial neoplasia,[8,9] Table 1 summarizes eligibility and non-recommended conditions for ablative therapy in cervical lesion patients. Table 2 provides a comprehensive overview of the advantages and disadvantages of different ablative treatments.

Table 1
Eligibility and non-recommended conditions for ablative treatment.

The prerequisites of ablative treatment
1 Lesion is fully visualized
2 The entire transformation zone can be visualized
3 No suspicion of microinvasive or invasive disease
4 No suspicion of glandular disease
5 All lesions are within a manageable treatment area
6 Cytology and histology result are consistent if available
Ablative methods are not recommended in the following situations
1 In cases of recurrence of CIN
2 Endocervical sampling shows CIN/lesion extending into the endocervical canal
3 Cytology or colposcopy suggests cancer
4 Histology is CIN 2 or CIN 3 and colposcopy is inadequate
5 Cervical lesion involves >75 % area of the cervix
6 Cryotherapy is not recommended when the lesion extends>2 mm beyond the tip of the cryotherapy probe

CIN: cervical intraepithelial neoplasia.

3.1. Cryotherapy

Cryotherapy, also known as cryoablation, usually creates an iceball that reaches a depth of 5–7 mm. This depth is adequate for treating cervical lesions, including cases of severe dysplasia or carcinoma in situ that extend into cervical crypts. Cryotherapy eliminating cervical by freezing, involves applying a highly cooled metal probe to the cervix and freezing the abnormal areas (along with normal areas) covered by it. This procedure may induce dehydration and desiccation of cervical cells, leading to their structural breakdown and damage to vascular endothelial cells, contributing to the eradication of diseased cervical tissue and the elimination of HPV.[10,11]

This technique offers several advantages, including simplicity, cost-effectiveness, minimal invasiveness, and low scarring.[12] It eliminates the need for preoperative anesthesia, causing only mild discomfort during the procedure, and removes the necessity for tissue excision, resulting in minimal intraoperative bleeding. Furthermore, it doesn't produce any smoke during the ablation process, thus preventing any unnecessary harm to the visual field. Additionally, there's no scarring at the treatment site after healing, and hospitalization isn't required. However, the main disadvantage of cryotherapy is the necessity for refrigerant gases like Nitrous Oxide (N_2O) or carbon dioxide (CO_2), which may not be consistently accessible, particularly in LMICs.[8] In addition, the regular refilling of freezing gas can lead to substantial expenses.

Cryotherapy is contraindicated in the following conditions: cervical lesions larger than the cryotherapy probe, lesions involving >75 % of the

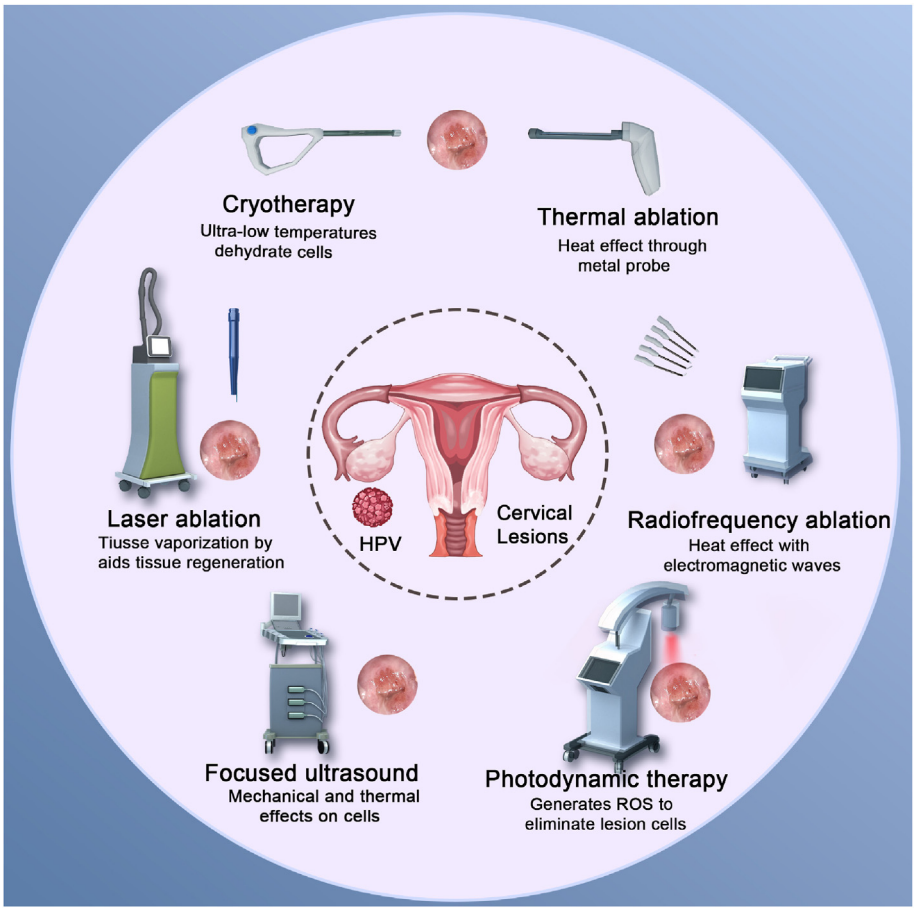

Fig. 2. Ablative treatment for human papillomavirus related cervical lesion.

Table 2
The advantages and disadvantages of different ablative treatment.

Treatment Method	Advantages	Disadvantages
Cryotherapy	Cost-effectiveness, minimal invasiveness, low scarring, no need for anesthesia, minimal intraoperative bleeding	Limited treatment depth and area, the necessity for refrigerant gases like N_2O or CO_2
Thermal Ablation	High efficacy rate, rapid and easy to learn, relatively low recurrence rate, minimal invasive, short recovery time	Possibility of under or overtreatment, risk of cervical stenosis, potential side effects such as pain, bleeding, and infection
Laser Therapy	High precision, minimal damage to surrounding tissues, minimal bleeding, fast recovery	Higher cost, limited availability, potential side effects such as pain, bleeding, and infection
Focused ultrasound	Minimally invasive, minimal bleeding, low risk of infection, reduced discharge and bleeding, no scar formation or cervical stenosis, no impact on cervical function, and suitable for fertility	Unclear tissue destruction boundaries, limited treatment depth, limited data on HSIL, especially CIN3, and inability to retrieve tissue for pathology
Photodynamic Therapy	High efficacy rate, non-invasive, outpatient procedure, short recovery time, no impact on cervical function, and suitable for fertility	Limited depth of treatment, potential side effects such as pain, sensitivity to light, and blistering, and require photosensitizer drug administration

cervix's area, or lesions extending >2 mm beyond the tip of the cryotherapy probe, as well as suspicion of invasive lesions. Moreover, cryotherapy may be contraindicated for women with the following conditions: cryoglobulinemia, Raynaud's disease, severe cold urticaria, uncontrolled diabetes, elderly individuals, and those in frail health who may not tolerate cryotherapy well. Additionally, individuals with acute vulvar, vaginal, cervical, or pelvic inflammation, or severe cervical inflammation should also be considered as contraindications for cervical cryoablation treatment.

Most studies suggest that cryoablation yields similar results in the treatment of HSIL when compared to other ablative treatments.[13] A recent randomized controlled study[14] found that at 4 and 8 months follow up after treatment, cryoablation and thermocoagulation showed no statistically significant differences in terms of HPV HPV-negative (4/8 months: 68.6 %/80.6 % vs. 72.5 %/86.2 %) and pathology-negative (94.3 %/92.3 % vs. 97.1 %/98.5 %). Nonetheless, thermocoagulation demonstrated a superior rate of pathology-negative results at 8 months (100 % vs. 88.7 %). Moreover, extensive findings from a retrospective study suggest that cryoablation for HSIL treatment carries a higher risk of failure, particularly in women aged 40 and above, where the failure rate can reach as high as 34 %.[15] As a result, the choice of ablative therapy should be influenced by the patient's age and clinical profile, with cryotherapy being less preferable for women over the age of 40 years.

3.2. Thermal ablation

Thermal ablation, also known as “cold coagulation” or thermocoagulation is a technique used to treat cervical lesions. It involves dehydrating the tissue using a heated metal probe, typically applied for 20–40 s (or more if necessary). The probe is electrically heated to reach temperatures of approximately 100 °C–120 °C,[16] resulting in the destruction of both epithelial and stromal tissue.

Thermal ablation has emerged as a highly effective approach for managing CIN lesions due to its swift, high efficacy, rapid, and easy to learn.[17] The equipment is straightforward, lightweight, and easily transportable to field clinics in LMICs. Typically, the procedure can be performed without anesthesia, and it offers rapid and highly effective results, with a relatively low recurrence rate and minimal invasiveness, leading to short recovery times. However, it's essential to recognize some limitations, including the potential for under or overtreatment, the risk of cervical stenosis, and limited data on long-term outcomes. Additionally, it is worth noting that pathological diagnosis is infrequently used as the gold standard for disease diagnosis in this context, and there is limited evidence from large sample sizes regarding long-term treatment outcomes.

In a retrospective study[18] involving 472 women who underwent either cold coagulation or LLETZ therapy, it was found that 85 % of those treated with LLETZ and 54.7 % of those treated with cold coagulation exhibited HSIL on pre-treatment biopsy. At the 6-month follow-up after treatment, 86.9 % of these women had negative cytology results and this percentage increased to 90.8 % at the 18-month follow-up. Specifically, for women with HSIL, negative cytology at the 18-month follow-up was observed in 89.4 % of those treated with cold coagulation and 91.1 % of those treated with LLETZ. These results suggest that cold coagulation achieves cure rates similar to LLETZ, not only in cytology but also in HPV testing as a measure of cure. Meta-analysis and other related studies[19,20] also suggest that the effectiveness of thermal ablation in treating HSIL is as high as 90 %, with a very low recurrence rate. It can be considered as an alternative method for treating SIL, especially in the context of the screen and treat strategy. Further research is needed to fully evaluate its long-term effectiveness and safety.

3.3. Laser ablation

Laser vaporization, also known as laser ablation, is a highly effective and precise tool for treating CIN lesions that extend onto the vagina. It provides controlled depth (0.1–0.5 mm) with minimal lateral thermal damage, ensuring safety and versatility. By precisely targeting CIN lesions in the vaginal area, laser vaporization effectively eliminates heat-sensitive HPV, resulting in carbonization and tissue shedding. This process promotes the regeneration of new squamous epithelium in clinical settings for cervical disease treatment. Furthermore, its power density can be adjusted to switch between vaporization and excision modes. Currently, the CO_2 laser is frequently used in clinical settings for treating cervical diseases.

Laser ablation offers several advantages, including simplicity, safety, precise targeting of smaller lesions, minimal bleeding, and the frequent avoidance of anesthesia. In the context of treating CIN, it demonstrates high clinical effectiveness, minimal harm to healthy tissue, favorable healing with minimal scarring, few complications, and the added convenience of being an outpatient procedure. Moreover, it is the preferred choice for ablative treatment when the lesion extends into the vaginal area. The limitations of laser ablation encompass its relatively high cost and limited availability. Moreover, the procedure often takes longer than other ablative treatments, requiring doctors to undergo a more extended learning curve. From the patient's perspective, there is typically a higher level of discomfort compared to alternative methods, and there is a potential for an increased risk of bleeding complications in certain cases.

A previous retrospective analysis[21] revealed that between 1977 and 1987, 4024 women diagnosed with cervical intraepithelial neoplasia through cytology, colposcopy, and biopsy examinations received CO_2 laser treatment. Among them, 3070 patients underwent laser vaporization, with 2881 of them showing no cervical lesions after a single laser treatment, resulting in an effectiveness rate of 93.8 %. The rates of cervical stenosis (1.1 %), incompetent cervix (0 %), and pelvic infection (0.05 %) were all very low. In another retrospective study,[22] 52 patients with CIN2 and CIN3 cervical lesions underwent CO_2 laser vaporization treatment. Following the initial colposcopy examination, it was noted that 17 patients still exhibited persistent cervical lesions. Among the remaining 35 patients, 4 experienced recurrences, and 2 were lost to follow-up, leaving only 29 patients without any recurrence. The study indicates that CO_2 laser vaporization treatment is most appropriate for specific high-grade exocervical lesions, but only after a thorough colposcopy examination. This treatment should be reserved for CIN1 and CIN2 lesions, as it appears

to be less effective for CIN3. Another study on laser ablation for CIN3 treatment also indicates that the long-term oncologic outcomes of cervical vaporization in CIN3 remain suboptimal.[23]

3.4. Focused ultrasound

In theory, focused ultrasound primarily eliminates cervical lesion tissue through the combination of heat production and cavitation effects, placing it technically within the category of thermal ablation.[24,25] In recent years, its widespread application has been particularly notable in China, where devices for focused ultrasound treatment of cervical lesions have been developed. Focused ultrasound is a promising new minimally invasive treatment modality by emitting low-intensity ultrasound from an external transducer, the focused ultrasound is directed with accuracy towards the target area (up to 4 mm deep subcutaneous tissue) to induce thermal, mechanical, and cavitation biological effects that elevate the temperature of target cells to the threshold temperature for protein denaturation (60 °C) or higher. This innovative approach not only has the potential to eliminate diseased tissues, viruses, pathogens, and their byproducts but also enhances local tissue microcirculation and boosts tissue resistance against diseases. Ultimately, it aims to accomplish the desired treatment outcome.

Focused ultrasound presents several distinct advantages, especially when compared to other ablative methods like laser treatment. These benefits include minimal intraoperative bleeding, the absence of acute tissue necrosis or scab detachment in postoperative patients, a low risk of infection, reduced postoperative discharge and bleeding, and the preservation of cervical structure and elasticity without complications such as cervical spasms, scar formation, or cervical stenosis. Additionally, focused ultrasound treatment is both safe and radiation-free, posing no risks to either the operator or the patient.

Focused ultrasound also has certain limitations, including unclear tissue destruction boundaries and the inability to retrieve tissue for pathology. Even with prior cervical smears, colposcopy, or biopsies, there's a risk of misdiagnosis. Thus, strict adherence to indications and close follow-up are crucial in HSIL treatment using focused ultrasound.

Currently, there is a lack of prospective randomized controlled studies on the use of focused ultrasound for HSIL/CIN2/CIN3. Only a few retrospective studies have shown promising results for HSIL. Recently, in a prospective one-arm study[26] that screened 287 consecutive CIN 2/3 patients, 29 women with fertility requirements underwent focused ultrasound treatment. Among them, there were 22 cases of CIN2 (75.9 %), 2 cases of CIN2/3 (6.9 %), and 5 cases of CIN3 (17.2 %). During the procedure, ultrasound power was typically set at 3.5–4.5 W, employing a working frequency of 10 MHz and a pulse rate of 1000 Hz. The treatment duration ranged from 1.5 to 5 min, with no reported incidents of bleeding or notable pelvic discomfort during the procedure. The outcomes revealed an impressive cure rate of 82.8 % at 7 months post-treatment and a remarkable 96.6 % within 1 year. Around 6 months after treatment, the HPV-negative rate reached 72.4 % (21 out of 29 cases). Notably, only three cases experienced minor wound infections as postoperative complications, with no other adverse events reported. Furthermore, there is limited research suggesting the safety and effectiveness of focused ultrasound therapy for HSIL.[27,28]

Further research is needed to establish the effectiveness of focused ultrasound in treating HSIL. In particular, conducting large-scale prospective randomized controlled studies across multiple centers is crucial for gaining a deeper understanding of the ideal patient population for this treatment.

3.5. Photodynamic therapy

Photodynamic therapy (PDT) is a conservative treatment modality using a photosensitizer and irradiation with laser or light energy at a low intensity which enables the selective destruction of cancerous or dysplastic cells while preserving the uterus. Photodynamic therapy involves three key components, including a photosensitizer, a light source, and oxygen.[29] The treatment strategy relies on the selective accumulation of photosensitizers in proliferating and structurally aberrant lesion tissues, which upon irradiation with a 630 nm wavelength light source, generate reactive oxygen species (ROS) in the presence of oxygen. These ROS can directly eliminate lesion cells, impair tumor neovascularization, and stimulate a local immune response.[30–32]

The advantage of PDT is that it does not induce cervical stenosis or scarring, making it particularly beneficial for managing CIN in young patients who wish to preserve their fertility. The main contraindications for PDT encompass patients with concurrent conditions such as systemic lupus erythematosus (SLE), diffuse photosensitivity disorders, skin photosensitivity, porphyria, and individuals with allergies to porphyrins. PDT is also not advisable for patients with allergies to 5-Aminolevulinic acid (5-ALA) or those taking photosensitizing medications. PDT can be employed for type I and type II lesions as determined by colposcopy. Although PDT has not been officially endorsed as a standard treatment method by the WHO for HSIL, numerous recent reports have showcased encouraging outcomes in the management of HSIL using PDT.

Recently, Ma et al.[33] conducted a prospective cohort study at a single center, involving 210 CIN_2 patients. Of these, 97 patients opted for PDT, while 101 patients chose cryotherapy based on their preferences. In the PDT group, the pathological regression rate was notably higher at 92.0 % compared to the cryotherapy group's rate of 81.4 %. The HPV clearance rates were similar between the two groups. This study suggests that PDT may be an effective and safe treatment option for CIN2 patients. The primary side effects of PDT included abdominal pain (24.1 %) and increased vaginal secretions (23.0 %). In another retrospective study,[34] 99 patients with cervical HSIL and high-risk Human Papilloma Virus (hr-HPV) infections were treated with ALA-PDT. Six months after treatment, the overall HPV clearance rate reached 64.6 %, with complete remission of lesions observed in 88.9 % of cases. At the one-year follow-up, the overall HPV clearance rate had increased to 81.3 %, and complete resolution of lesions was observed in 92.5 % of patients. These results robustly endorse ALA-PDT as a viable and safe treatment option for individuals with cervical HSIL and hr-HPV infections. Moreover, other pertinent studies also indicate the efficacy and safety of PDT in HSIL cases.

Although PDT has shown significant efficacy in achieving complete remission of CIN or cervical HPV infection, caution must be exercised. PDT should be avoided for type III lesions due to the lack of visual control during laser irradiation. Furthermore, its therapeutic safety may be compromised by the side effects of photosensitizers, which include mild headaches when administered intravenously, and mild to moderate erythema, pruritus, burning sensations, and occasional blistering when applied topically. Therefore, the quest for less toxic photosensitizers remains a top priority.[35]

3.6. Other ablative methods

In addition to the aforementioned ablation treatment methods, electrocautery, microwave, and infrared therapy have also been utilized in the treatment of cervical lesions associated with HPV.[36–38] Among these, electrocautery has been employed for many years to eliminate CIN and can be considered a form of thermal ablation therapy. It is generally well-tolerated with no major side effects. However, patients often experience significant pain during and after the procedure, requiring anesthesia. Dilatation and curettage should be performed during the same session to prevent cervical stenosis.

Although microwave and infrared therapy have been used in recent years for the treatment of cervical lesions and HPV, their application is less common, and the supporting evidence is limited. A deficiency of clinical research with substantial sample sizes hampers the substantiation of their efficacy.

4. Conclusion and future perspective

Cervical lesions, especially HSIL with high-risk HPV, are the main cause of cervical cancer. Ablative treatment is one of the key components of the 'screen-and-treat' approach. However, ablative treatments must be chosen carefully, following guidelines to prevent over-treatment and rule out invasive cancer or AIS beforehand. When ablative treatment is indicated, cryotherapy is the preferred choice for eligible women, particularly for ectocervix-confined, small-volume diseases. Laser ablation is valuable for extensive cervix or vaginal fornix involvement, and it is effective for treating vaginal and vulvar intraepithelial neoplasia. Thermal coagulation is appealing due to its minimal supply requirements, ease of use, and can be used in low-resource settings.

Guidelines have yet to endorse focused ultrasound for HSIL treatment, with unclear indications. LSIL or CIN2 patients concerned about fertility might explore focused ultrasound or PDT. More large-scale studies are required to identify applicable populations. Ablative treatment aligns with 'screen-and-treat' but lacks histological specimens, impeding pathological assessment. Women treated with ablation, especially without histopathology or for CIN2/3, require a 6–12 month follow-up test.

In the future, the focus should move towards personalized therapy, incorporating suitable methods such as ablative treatments, enhancing the effectiveness and safety of various ablative therapy techniques, conducting long-term follow-up studies, and exploring alternative approaches. These initiatives will contribute to the worldwide goal of reducing cervical cancer.

Funding

This work was supported by the Guangxi Health Technologies Promotion Program (Project number: S2020071).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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