Review Article

# Cryotherapy vs Laser for Genital Warts Management: A Systematic Review

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## ABSTRACT

The study compared cryotherapy and laser in managing external genital warts (EGW) using various databases. The research involved eleven studies with 92 patients, with follow-up durations ranging from 28 days to 39 months. One study found that CO2 laser therapy was two times more effective than cryotherapy in terms of clearance, recurrence, and complication rates. Six studies showed that laser was the best option for immunocompromised patients and those who did not respond to cryotherapy, with the lowest recurrence rates and complications. Cryotherapy is economical, effective, and safe, but it is painful, deformed, and requires multiple sessions. Current treatment approaches focus on the surface wart rather than the underlying viral infection, making them less successful in long-term effects. There is little evidence to support the idea that a specific therapy is not more successful than others. Future research should focus on extensive comparisons with larger sample sizes.

**Keyword:** External genital warts; Condylomata acuminata; Cryotherapy; Laser; Systematic review.

## Introduction

Condylomata acuminata (CA), commonly referred to as EGW, is one of the most prevalent STDs impacting the general public [1]. Between 500,000 and one million new instances are thought to be diagnosed annually in the United States alone, although only 1% of people who are sexually active present with clinically noticeable warts [2, 3]. When the direct medical expenses of treating genital warts and invasive cervical cancer are taken into consideration, the economic impact of the human papillomavirus (HPV) was estimated to be four billion dollars in 2004 [4].

Since genital warts are usually visible, a second biopsy is not necessary. Hyperplastic squamous epithelium exhibiting koilocytes— squamous epithelial cells have an acentric, a hyperchromatic nucleus displaced by a huge perinuclear vacuole—is the defining feature of these exophytic lesions [5]. The dermal papillae expand, which leads to their development. Regarding differential diagnosis, in cases of planar Facial warts, syringomas, and lichen nitidus should be taken into consideration; in cases of big verrucous lesions, such as those on the foot, Bowenoid papulosis, and condylomata lata should be taken into account.

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It is impossible to foresee how warts will emerge and spread, and each illness has a different history, so treatment should begin as soon as feasible. Treatment could be considered preventive if it can prevent the illness from becoming chronic or common in at least half of the afflicted patients [6]. As long as the warts are not too big, cryotherapy using liquid nitrogen, nitrous oxide, or carbon dioxide delivered by cryoprobe, cryospray, or cotton wool-tipped swabs is a safe and efficient treatment for most sites. It works by quickly freezing extracellular and intracellular fluid, which causes cell lysis and death when it thaws. According to the authors' experience, cryotherapy can be used to treat warts at any location as long as they are not too big, in which case surgical excision is the better option [7]. EGW warts have been treated with both CO2 and NdYAG lasers, which use light that is infrared or close to it. When it comes to minimizing damage to surrounding tissue, the CO2 laser is more accurate, but the NdYAG provides better hemostatic control. Expert operators are necessary. Under competent supervision, laser ablation is a safe procedure; the rare side effects include hemorrhage, recurrent infection, inexplicable fever, and one case of toxic shock syndrome [7]. The therapy aims to eradicate warts that are visible to the patient and to activate the immune system to identify the virus and stop its spread. Many aspects are considered when deciding which course of treatment is best for a patient. Patient preference is very important to us; instead of regular clinic visits, most patients who come to our clinic choose a therapy they can administer in the privacy and comfort of their own homes [6, 7]. The primary goal of this comprehensive research is to compare cryotherapy versus laser in the treatment of EGW.

## Methods

This systematic review was implemented in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards [8]. Study Design and Timeframe: January 2024 marks the beginning of this comprehensive review.

Search Approach: To find relevant material, a comprehensive search was undertaken across five major databases: PubMed, SCOPUS, and Web of Science. We focused our search on English and considered each database's unique requirements. The following keywords were converted into PubMed Mesh terms or topic terms in Scopus and utilized to discover the relevant studies: "condylomata acuminata," "External genital warts," "Cryotherapy," "Laser," "Treatment," and "Management." The Boolean operators "OR," "AND," and "NOT" all matched the needed criteria. The search results included publications in English language, freely available papers, and human trials.

Eligibility criteria: The PICOS-guided eligible criteria comprised the following:

1) Population (P): Patients with EGW.
2) Intervention (I): Treatment with cryotherapy or laser.
3) Outcomes (O): The outcome following the treatment modality.
4) Study design (S): Any study design conducted between 2010-2024.

Exclusion criteria: Our review did not include the following types of publications: unpublished data, letters, reviews, conference abstracts, case reports, and insufficient data. Disagreements were settled by discussion amongst all authors after the investigators completed the eligibility assessment.

Extracting data: Rayyan (QCRI) was utilized twice to validate the search method's findings [9]. The researchers applied inclusion/exclusion criteria to the combined search results to assess the relevancy of the titles and abstracts. The reviewers gave each paper that met the inclusion criteria a thorough inspection. The authors talked about ways to resolve conflicts. A previously prepared data extraction form was utilized to upload the authorized research. The authors gathered information on the trial titles, authors, study year, nation, participants, gender, follow-up length, population type, treatment technique, and primary outcomes. A second spreadsheet was built to analyze the risk of bias.

Strategy for data synthesis: Summary tables were developed by combining information from pertinent studies to offer a qualitative assessment of the study findings and components. Once the data for the systematic review had been collected, the most efficient manner to use the information from the included study articles was determined.

Assessing the risk of bias: Cochrane Collaboration's Risk of Bias (ROB) tool [10] was utilized to determine the risk of bias in the included randomized control studies. The results are presented as a table with several color schemes. Green implies low risk, red signals high risk, and yellow indicates an inability to assess the danger of bias owing to missing information. To evaluate the quality of non-randomized research, the Joanna Briggs Institute (JBI) [11] Critical assessment criteria for research giving prevalence data were applied. This technique employed nine questions to assess the research. If the response was in the affirmative, the question received a score of 1. A score of 0 was given to any response that was no, ambiguous, or not applicable. Ratings of $< 4$, 5 to 7, and $\geq 8$ for overall quality were considered low, moderate, and excellent quality in that order. Researchers evaluated the quality of the studies they conducted, and conflicts were resolved through debate.

## Results

Search results: The systematic search yielded 426 study papers, with 188 duplicates eliminated. A total of 238 papers were screened for titles and abstracts, with 198 removed. 40 reports were requested for retrieval, and two articles were obtained. Finally, 38 papers were screened for full-text evaluation; 14 were removed due to incorrect research results, 11 due to incorrect population type, and two were letters to the editors. The systematic review contained eleven eligible study papers. A synopsis of the study selection procedure is given in (Figure 1). Characteristics of the included studies (Table 1) shows the sociodemographic features of the study articles that were included. Our findings included eight trials including 925 people diagnosed with EGW. Seven studies were randomized controlled clinical trials (RCTs) [12, 13, 6, 8, 19, 21, 22], and four were retrospective Remove [14, 15, 18, 20]. Three studies were conducted in Iran [12, 13, 21], two in Italy [16, 17], one in Germany [14], one in Turkey [15], one in Egypt [19], one in Bosnia and Herzegovina [20], and one in the USA [22]. (Table 2) displays the clinical features. The follow-up time ranged between 28 days [21] and 39 months. [17]. One study compared cryotherapy to laser and reported that CO2 laser therapy is approximately two times more effective than cryotherapy in terms of clearance, recurrence, and complication rates. Other six studies applied laser treatment to EGW and demonstrated that laser is the best option for immunocompromised patients and those who did not respond to cryotherapy and with the lowest recurrence rates and complications [12, 14-18]. On the other hand, cryotherapy is an economical, effective, and safe option, but it is painful, deformed, and needs multiple sessions [19-22]. (Table 3) discussed the effectiveness and safety of the reported types of lasers and cryotherapy for managing EGW. The highest clearance response (95%) with the lowest recurrence rate (0.05%) was found in the Co2 laser [12]. Regarding cryotherapy, more complications such as pain, exudation, swelling, burning sensation, erythema, atrophy, and ulceration were reported [20, 21]. The greatest complete response was noted in the KOH solution (88.9%), while the lowest recurrence rate was found in liquid nitrogen (0.18%) [13].

## Discussion

Instead of curing the underlying viral infection, the majority of the current treatment approaches for EGW focus on removing the warty growth. There is insufficient data to conclude that current therapies are useful in permanently curing genital warts or that they significantly impede the development of potentially cancerous warts. There are currently many different medicines in use, all of which are rather varied and can differ significantly in terms of cost, side-effect profiles, dosage schedules, length of therapy, and overall effectiveness. CO2 laser and electrocautery: Ablative operations (physical annihilation) include the eradication of common warts and cutaneous warts. The CO2 laser is available over the counter and is frequently used in doctor's clinics for the treatment of warts. Primary care physicians usually use liquid nitrogen, which can freeze tissue up to 321°F (196°C), while over-the-counter CO2 laser devices can only get tissue as cold as 94°F (70°C). Liquid nitrogen can be administered with a cotton pad or a cryogen [23]. This review found that CO2 laser therapy is approximately two times more effective than cryotherapy in terms of clearance, recurrence, and complication rates. Laser treatment is the best option for immunocompromised patients and those who did not respond to cryotherapy and had the lowest recurrence rates and complications [12, 14-18]. Iranmanesh et al. reported that for quicker remission, it is advised to combine laser therapy with mechanical or topical keratolytic techniques before laser therapy. Additionally, immunosuppressed patients, genital warts, and recalcitrant lesions—particularly periungual warts—may benefit from the combination of lasers and immunomodulators [24]. It is possible to cause scarring using both CO2 Laser and electrocautery techniques. If the necessary tools are available, argon plasma coagulation may also be considered an ablative technique, particularly in the case of condyloma acuminate [25]. Regretfully, laser therapy is a costly and intricate form of treatment as well. To properly use specialized laser technology, doctors themselves must need additional training in addition to the equipment needing to be acquired and maintained regularly, laser therapy is a costly and intricate form of treatment as well. To properly use specialized laser technology, doctors themselves must need additional training in addition to the equipment needing to be acquired and maintained regularly. Moreover, HPV DNA may be released into the environment as a result of the vaporization of viral lesions. Thus, appropriate steps need to be made to guarantee that medical professionals and support staff are shielded against infection. This makes the examination room's vacuum ventilation system and the usage of certain virus-resistant masks necessary [26]. Thin skin, the degree of viral burden, and the treatment of malignant HPV subtypes are additional risk factors for the transmission of genital warts during vaporization. Moreover, HPV DNA may be released into the environment as a result of the vaporization of viral lesions. Thus, appropriate steps need to be made to guarantee that medical professionals and support staff are shielded against infection. This makes the examination room's vacuum ventilation system and the usage of certain virus-resistant masks necessary [26].

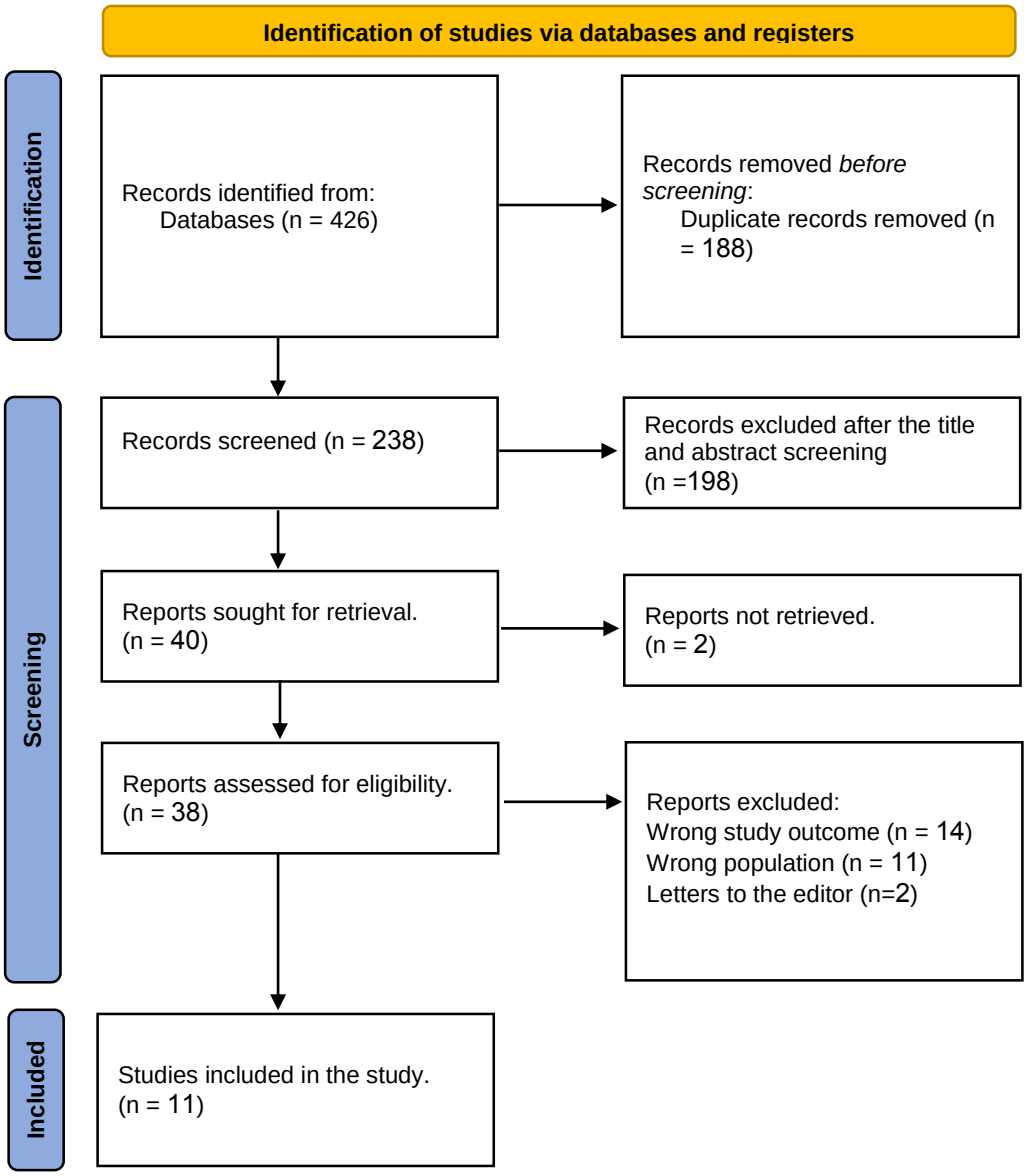


*Figure 1: PRISMA flowchart summarizes the study selection process.*

Table 1: Sociodemographic characteristics of the included participants.

| Study | Study design | Country | Participants | Mean age | Gender (Females) |
|---|---|---|---|---|---|
| **Asadi et al., 2016 [12]** | RCT | Iran | 70 | 28.6±7.9 | 70 (100%) |
| **Azizjalali et al., 2012 [13]** | RCT | Iran | 160 | NM | NM |
| **Alharbi et al., 2019 [14]** | Retrospective | Germany | 124 | 33 | 16 (12.9) |
| **Ogrinc & Senčar 2020 [15]** | Retrospective | Turkey | 133 | 39.6±12.9 | 133 (100%) |
| **Puviani et al., 2019 [16]** | RCT | Italy | 60 | 43±11 | 8 (14%) |
| **Del Zingaro et al., 2021 [17]** | RCT | Italy | 60 | 24-71 | 0 |
| **Ghiasy et al., 2019 [18]** | Retrospective | Iran | 101 | 31.2±9 | 101 (100%) |
| **Moubasher et al., 2021 [19]** | RCT | Egypt | 45 | NM | NM |
| **Jahic, 2019 [20]** | Retrospective | Bosnia and Herzegovina | 50 | 34.6 | 50 (100) |
| **Jahromi et al., 2022 [21]** | RCT | Iran | 80 | 32.2 ± 9 | 80 (100) |
| **On SC et al., 2014 [22]** | RCT | USA | 42 | NM | 42 (100) |

*NM=Not mentioned

Table 2: Clinical outcomes.

| Study | Follow-up period | Population type | Treatment modality | Main outcomes | JBI |
|---|---|---|---|---|---|
| **Asadi et al., 2016 [12]** | 6 | Female genital warts | CO2 laser | The majority of patients who received laser treatment (88.9%) showed full recovery. By the end of the third week of treatment, the lesions in patients receiving laser treatment had improved the most. In this investigation, recurrence rates were lower for CO2 laser than for KOH. | NA* |
| **Azizjalali et al., 2012 [13]** | 3 | Both females and males | CO2 laser vs cryotherapy | When treating external genital warts, CO2 laser therapy is approximately two times more effective than cryotherapy in terms of clearance, recurrence, and complication rates. | NA |
| **Alharbi et al., 2019 [14]** | 3 | Both females and males | Diode laser | Comparable cure rates between the two groups were obtained by dividing the laser therapy for many, extensive, and/or merging genital warts into two sessions, hence being less harmful to the surrounding tissue. According to this study, laser therapy is a useful therapeutic approach. | Moderate |
| **Ogrinc & Senčar 2020 [15]** | 6 | Female genital warts | YAG laser | When it comes to treating immunocompromised patients with large lesions who do not respond to TCA or cryotherapy, YAG laser therapy may be the best option. It can be considered a one-session therapy and has been shown to be especially effective for big-volume EGW or those situated in anatomical areas that are challenging to | Moderate |

| | | | | | |
|---|---|---|---|---|---|
| | | | | approach with other ablative procedures. | |
| **Puviani et al., 2019 [16]** | 3 | Both females and males | CO2 laser | When TS 10% was used as proactive sequential therapy (PST) following CO2 laser ablative treatment, the rate of new EGW lesions recurred less frequently in the short term compared to the control group (OR = 0.16). To assess this approach's role as PST, comparative larger trials are necessary. | NA |
| **Del Zingaro et al., 2021 [17]** | 12-39 | Male genital warts | YAG laser | For the treatment of EGW and urethral warts, holmium laser surgery appears to be a secure and reliable option. A positive outcome in dermatology contributes to increased patient satisfaction. | NA |
| **Ghiasy et al., 2019 [18]** | 6 | Female genital warts | Holmium laser and nitrous oxide | Among the various treatments in this study, Holmium laser treatment has the best clearance rate (92.2%) and lowest recurrence rate (14.3%). We may infer that the holmium laser has a low recurrence rate and is a safe and effective treatment for genital warts. | Moderate |
| **Moubasher et al., 2021 [19]** | 2-6 | Both females and males | Tuberculin purified protein derivative and cryotherapy | Warts that are present both locally and distantly can be efficiently cured with intralesional immunotherapy using a pure protein derivative. It is economical, effective, and safe. The most successful treatment method for genital warts was determined to be a combination of cryotherapy and pure protein derivative. | NA |
| **Jahic, 2019 [20]** | 3 | Female genital warts | Cryotherapy | Cryotherapy is a method with a high success rate in the healing of genital warts, and it | High |

| | | | | | |
|---|---|---|---|---|---|
| | | | | decreases the concentration of the HPV virus and removes the trigger that allows the development of cancer. | |
| **Jahromi et al., 2022 [21]** | 28 days | Female genital warts | Cryotherapy | In our investigation, we found that the clearance rate for cryotherapy was 88.7%, whereas the rate for formaldehyde was 58.7%, but with less cosmetic effect and more pain. | NA |
| **On SC et al., 2014 [22]** | 16 weeks | Female genital warts | Sinecatechins 15% and cryotherapy | When compared to cryotherapy alone, the reduction of EGW was significantly improved by using sinecatechins 15% ointment BID in conjunction with cryotherapy. | NA |

*NA=Not Applicable

Table 3: Types and effectiveness of laser and cryotherapy.

| Study | Laser | Effectiveness and complications | Cryotherapy | Effectiveness and complications |
|---|---|---|---|---|
| **Asadi et al., 2016 [12]** | $CO_2$ laser | 88.9% had the lesion completely cleared.<br><br>19% experienced complications, but no major negative events were reported.<br>7.9% recurrence rate. | *KOH solution* | 88.9% complete response.<br>24% complications rate.<br>11.7% recurrence rate. |
| **Azizjalali et al., 2012 [13]** | $CO_2$ laser | 95% complete clearance.<br>0.05% recurrence rate. | Liquid nitrogen - 196°C | 46.2% complete clearance.<br>0.18% recurrence rate. |
| **Alharbi et al., 2019 [14]** | Diode laser | 16% to 40% recurrence rate according to size and some warts. | NM | NM |
| **Ogrinc & Senčar 2020 [15]** | YAG laser | 64% complete clearance.<br>15.8% recurrence rate. | NM | NM |
| **Puviani et al., 2019 [16]** | $CO_2$ laser | 29% recurrence rate. | sinecatechins 10% after laser | 3.5% recurrence rate. |

| | | | | |
|---|---|---|---|---|
| **Del Zingaro et al., 2021 [17]** | YAG laser | 95% complete clearance. 13.3% recurrence rate. | NM | NM |
| **Ghiasy et al., 2019 [18]** | Holmium laser | 9.9±5.7 clearance 1.5±0.8 some lesion recurrence | Nitrous oxide | 3.6±1.8 clearance 2.8±1.4 some lesion recurrence |
| **Moubasher et al., 2021 [19]** | NM | NM | Liquid nitrogen -196°C with cryogun | 26.7% complete response. |
| **Jahic, 2019 [20]** | NM | NM | Liquid nitrogen (N-39) | 78% complete response. exudation, swelling, and pain were complications. 4% recurrence rate. |
| **Jahromi et al., 2022 [21]** | NM | NM | No type specified (cryotherapy courses) | 88.7% complete response. pain, burning sensation, erythema, atrophy, post-inflammatory hyper or hypopigmentation (PIH) and ulceration were complications. |
| **On SC et al., 2014 [22]** | NM | NM | Cryotherapy-sinecatechins ointment | 28.6% complete response. |

*NM=Not Mentioned

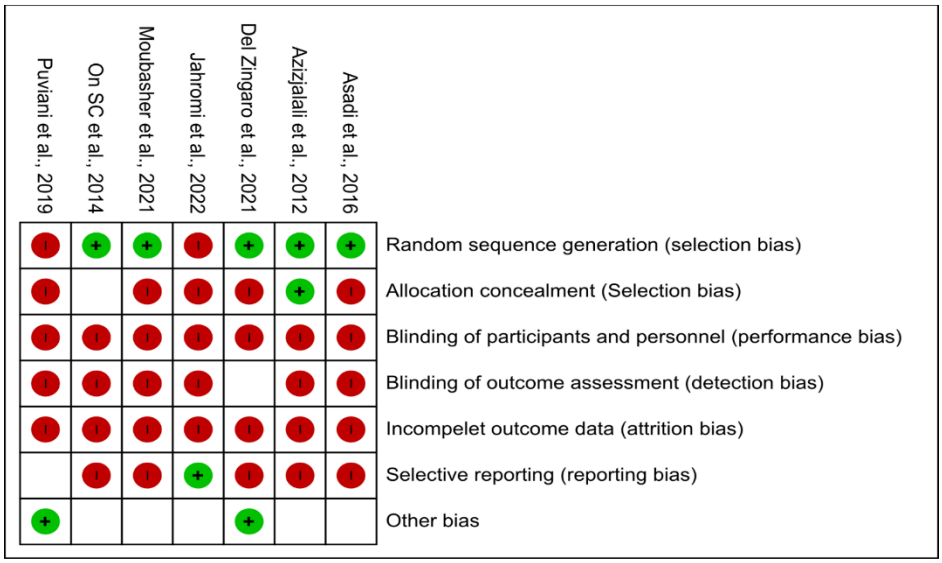


*Figure 2: Risk of bias summary.*

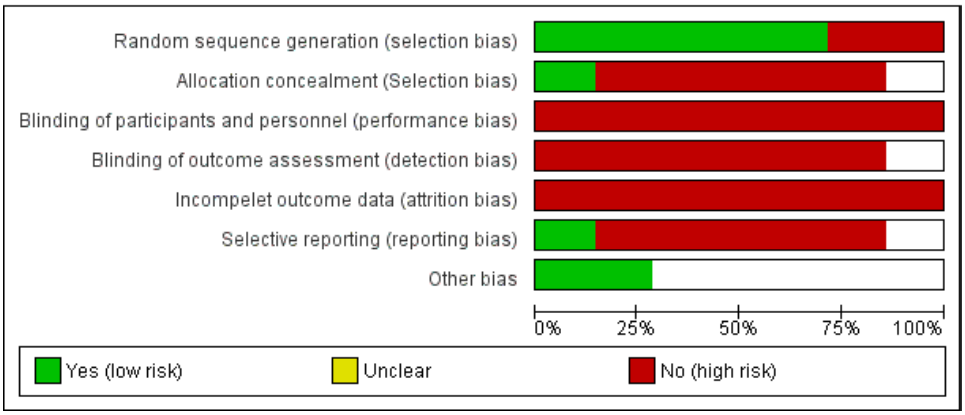


*Figure 3: Risk of bias results.*

Thin skin, the degree of viral burden, and the treatment of malignant HPV subtypes are additional risk factors for the transmission of genital warts during vaporization [27]. In contrast, an earlier review by Scheinfeld et al. reported that the effectiveness of CO2 treatment for CA is still debatable. With clearance rates ranging from 23 to 52 percent, laser therapy is generally regarded as less effective than other surgical treatments. Recurrence rates are also frequently high, sometimes as high as 77% [28]. The scorching of the tissue around the lesion is the only common, minor side effect [29]. Even with these seemingly adverse outcomes, a deeper and more thorough viral attack is frequently possible with the laser's deep penetrating action than with other surgical therapy approaches. This makes it the preferred course of treatment for patients with compromised immune systems and for expectant mothers with large lesions that do not respond to TCA or cryotherapy. The procedure of cryotherapy involves using a chilling substance, such as liquid nitrogen or nitrous oxide, to freeze the aberrant tissue. Extremely low temperatures are required to permanently harm skin and blood vessels. This triggers the immune system's healing reaction, which causes the damaged cells to necrotize and be cleared out. This treatment works best, generally speaking, when applied to several tiny warts on the vulva or penile shaft [30]. Our review also found that cryotherapy is an economical, effective, and safe option, but it is painful, deformed, and needs multiple sessions [19-22]. Scheinfeld et al. reported that with a 79–88% clearance rate in the first three sessions, cryotherapy is seen to be a reasonably priced and very effective therapy. There are some restrictions on cryotherapy. The period of contact and the temperature used during administration are two factors that affect how effective a treatment is. Local tissue degradation, including painful blistering, ulceration, infection, perhaps permanent scarring, and pigmentation loss, which can be significantly more severe than that of TCA, are common adverse effects of cryotherapy. Furthermore, cryosurgery does not treat subclinical lesions in the surrounding skin, similar to other lesion-directed therapies. It has been calculated that this provider-applied approach has a recurrence rate of 25–40 percent. Cryotherapy has various drawbacks, such as the need for numerous outpatient visits and the potential for pain during administration to prevent certain people from using it repeatedly [31].

This review is limited by its qualitative assessment as well as the small sample sizes. Additionally, we included different types of lasers (such as YAG laser, CO2 laser, and Holmium laser).

## Conclusion

The majority of current treatment approaches target the surface wart rather than the underlying viral infection, which has made them less successful in producing long-term effects. Currently, there is minimal evidence to support the concept a certain kind of therapy is not more successful than others, and one particular technique has not yet established itself as the gold standard for treatment. When selecting a therapy strategy, each patient's needs and preferences are typically taken into consideration. Future research should focus on extensive comparisons between these modalities with larger sample sizes.

## Conflict of Interest

None

## Funding

None

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