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Photodynamic therapy in the treatment of condyloma acuminata: A systematic review of clinical trials

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Abstract

Introduction: Condylomata acuminata (CA) is a sexually transmitted infection with a high prevalence associated with psychosexual morbidity in both men and women of various age. Up to now, treatment modalities yield low clearance and recurrence rate (RR) and are also deemed low quality evidence-wise. Photodynamic therapy (PDT) is a novel and promising therapy to effectively cure and prevent CA recurrence.

Method: This systematic review was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) and registered to the International Prospective Register of Systematic Review (PROSPERO) (CRD42022332760).

Results: Ten studies were included in this systematic review. A significant value of complete response (CR) ranging from 63–100% in patients with genital warts after receiving several sessions of PDT. A relatively low recurrence rate was seen in all 10 studies, with an RR of less than 17%. Quality assessment of included studies reported mostly high-quality research.

Conclusions: PDT therapy resulted in a higher CR with significantly lower RR compared to other therapies. Thus, PDT can be an alternative treatment of CA with low RR and minimal side effects. Additional research, especially randomized clinical trials in various countries, is needed to further substantiate this treatment and formulate definitive protocols.

Keywords

Genital warts, condylomata acuminata, photodynamic therapy, systematic review

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Strength and limitations

- To our knowledge, this is the first systematic review that assesses the effectiveness and potential benefits of PDT in CA treatment. Most of the studies included were critically appraised and deemed as high-quality studies.
- The main limitation of this study is the limited number of studies (especially RCTs, which are the best study design to evaluate interventions) and unvaried study locations which caused this study sample to be unrepresentative. Variety in the intervention used, such as type of photosensitizer, therapy wavelength, power, final dose, and administration frequency, may affect the effectiveness and safety of the therapy.
- Some differences in equipment specifications which may exist between urology/gynecology practice and dermatovenereology practice were not taken into account in the current study. Furthermore, degree of hyperkeratosis in the lesions were not reported in the included studies. As such, its effect in the depth of light penetrartion cannot be evaluated.

Key messages

- Presently, treatment for condylomata acuminata (CA) is backed by low quality evidence and yields unsatisfactory results. A search for novel and effective treatment modality is warranted.
- Treatment with photodynamic therapy (PDT) serves as a promising alternative in the management of CA.
- In this opportunity we conducted a systematic review of clinical trials to investigate the efficacy of PDT in clearing and preventing the relapse of CA. While we found that PDT therapy resulted in a higher complete response.

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Introduction

Condylomata acuminata (CA) or genital warts, is a sexually transmitted infection with a high prevalence. Around 500, 000 cases of CA are estimated to be diagnosed each year in the United States alone. In 2013, the global median annual incidence among males and females for CA is estimated to be 137 per 100,000 and 120.5 per 100,000 respectively. The global recurrence rate after initial remission was found to be as high as 163 per 100,000 and 110 per 100,000 in males and females respectively. In females, incidence of CA peaked before the age of 24 years and between 25 and 29 years in males.[1,2]

Although not commonly associated with mortality, CA is associated with psychosexual morbidity in both men and women of various age groups.[3,4] Although unlikely, CA may also culminate in obstetric complications such as labor difficulties in the presence of large genital warts and vertical transmission of the virus, putting the child at risk of juvenile-onset respiratory papillomatosis.[5,6] CA itself is mainly caused by human papilloma virus (HPV) subtypes 6 and 11, however the impact of HPV in CA is not limited to morbidity alone. In 2004, a study was conducted to calculate the financial burden in treating CA and invasive cervical cancer. The direct cost in the treatment of the two diseases was estimated at four billion dollars.[2]

Presently, there exists various treatment modalities for CA. However, no modalities yield a satisfactory clearance and recurrence rate. Topical and ablative treatments are currently the most used treatment modalities. Furthermore, existing studies in the literature are also deemed low quality evidence.[7] Treatment with photodynamic therapy (PDT) is a novel and promising therapy to effectively cure and prevent CA recurrence. Hence, we conducted a systematic review to investigate the efficacy of PDT in curing CA and preventing its relapse.

Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[8] This study has also been registered to the International Prospective Register of Systematic Review (PROSPERO) CRD42022332760.

Search strategy

The search was conducted for studies assessing photodynamic therapy as Condylomata Acuminata treatment on May 11th, 2022, with the following keywords: ((“Condylomata Acuminata”[Mesh]) OR (Genital warts) OR (anogenital warts) OR (Human Papillomavirus) OR (HPV)) AND (photodynamic) AND ((treatment) OR (therapy)). Detailed keywords for each database can be seen in Appendix A. Three investigators (SAP, HA, SC) independently searched for studies throughout several databases, including PubMed, EBSCOhost, Scopus, Cochrane, and Google Scholar. Any discrepancies will be consulted to the fourth reviewer (KDAI). Decisions were recorded through Microsoft Excel.[9]

Study eligibility criteria

In terms of studies eligibility, our inclusion criteria included: (1) type of study, Clinical trials; (2) study population, Adult Condylomata Acuminata patients (>18 years old) without any underlying conditions (e.g. immunodeficiency); (3) intervention, use photodynamic therapy (PDT) as intervention; and (4) outcomes, complete response (CR) and recurrence rate. Meanwhile, the exclusion criteria are set to: (1) irretrievable full text; (2) language other than English and Bahasa Indonesia.

Data extraction

A predetermined outcome sheet in tabular form (Microsoft Excel) was used to include the following data to be extracted: (1) author and year of publication; (2) study design; (3) study location; (4) time to follow up; (5) study population (number of population, gender distribution, mean age, number of lesions, and location of lesions); (6) Intervention (type of intervention and duration); (7) Comparison (type of other intervention); (8) Outcome (Complete response and recurrence rate). Complete response (CR), as our main outcome, is achieved when all patients’ lesions are successfully eliminated (100%). When the size of the wart decreased but did not disappear, a partial response is said to be reached. On the other hand, recurrence rate is defined by the presence of new warts after complete response is reached.

Two investigators (HA, SC) extracted the available data independently and two other reviewers (SAP, KDAI) further rechecked the accuracy of extracted data. If missing data was detected, reviewers will contact the author of study by mail and ask for the unreported data.

Quality assessment

Two different tools were used with regards to the type of study. The assessments were performed by three independent reviewers (SAP, HA, SC), and resolution would be discussed between all reviewers if there is any disagreement.

Cochrane Revised Risk of Bias (ROB 2.0) Tool[10] were used for Randomized Controlled Trials (RCTs) risk of bias assessment. Five domains, namely randomization bias, bias due to deviations from intended interventions, missing outcome data, outcome measurement, and bias in reporting results, were evaluated with this tool.

On the other hand, Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I)[11] tool of bias assessment were used for non-randomized clinical trials. Seven domains evaluated were grouped into pre-intervention (confounding, selection of participants), at intervention (classification of intervention), and post-intervention (deviations of indeed in interventions, missing data, measurement of outcomes, selection of reported results).

Results

Search selection and characteristics

Literature search flow details are depicted on Figure 1. The authors yielded a total of 1926 records upon initial search. After removing 554 duplicates, the authors performed title and abstracts screening and retrieved 64 articles. After excluding studies due to language barriers and unsuitable study designs, 10 studies[12–21] were included in this systematic review.

Studies included were performed ranging from 2004 to 2022 for 3–30 months of duration. With either randomized controlled trials (RCTs) or clinical trials study design, most of the studies were conducted in People's Republic of China, and one study was done in Brazil. A total of 819 patients were included, all with CA, and all aged in their thirties or forties. CA were described in various locations, including external genitalia, cervix, distal urethra, and perianal/anal region. All patients received photodynamic therapy with a variety of photosensitizers used (ALA 20%, ALA 5%, ALA 19.09%, and MAL 20%). Several photodynamic therapy specifications differed between studies, such as duration of incubation (3–5 h), wavelength (630–635 nm), power (20–100 mW/cm^3), and final dose (18–1000 J/cm^3) of PDT. Most of the studies gave the therapy weekly for a maximum of three weeks until a complete response was obtained. Five RCTs also compare PDT efficacy when compared to carbon dioxide (CO_2) laser therapy, Cryotherapy alone, or Trichloroacetic acid (TCA). Full characteristics study results can be seen in Table 1.

Study outcomes and quality assessment results

The summary of the outcome of each included study is listed in Table 2. Our systematic review found a significant value of CR ranging from 63–100% in patients with CA after receiving several sessions of PDT. Seven out of 10 studies reported CR ≥ 95%, while the other three studies had 63%, 70%, and 90% patients achieving complete response. All studies that used ALA as photosensitizer showed better efficacy compared to methyl aminolevulinate (MAL) with reported CR that is greater than 90% after patients underwent 4 sessions. Studies comparing PDT to other interventions also showed PDT superiority in their CR results, except in Du et al.[19] which suggested that carbon dioxide laser therapy had a slightly higher CR rate. However, this result was not significant ($p = 0.13$). In terms of recurrence rate (RR), a relatively low rate was shown in all 10 studies, with an RR of less than 17%. Six studies depicted a lower rate (RR ≤ 6.15%) and a remarkable rate was also obtained in all studies comparing PDT to other control group treatments.

Quality assessment of included studies reports mostly high-quality research (Appendixes B and C). Three RCTs assessed with Cochrane Revised Risk of Bias (ROB 2.0) Tool[10] had good overall quality; nevertheless, Chen et al.[13] and Liang et al.[15] did have some concern bias due to a lack of information regarding the randomization process. Furthermore, Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I)[11] for clinical trials gave an overall low risk of bias, except Sun et al.[18] that had a moderate bias due to unclear selection of participants method.

Discussions

Being a sexually transmitted infection with a high prevalence, effective treatments to tackle the problem of CA are called for. The disease itself also has some long-term consequences, some of which are deterioration in sexual quality of life, psychological vulnerability, anxiety, and fear of recurrence and malignancy.[22] Current available treatment modalities for CA, such as 80–90% trichloroacetic acid (TCA) for up to ten sessions has an efficacy of 70–81%, with high recurrence rate, i.e. about 46% in three months. Hence, patients need to return to the clinic to undergo re-treatment. Other modalities such as podophyllotoxin and imiquimod, while boasting a low recurrence rate, have a low rate of CR. On the other hand, surgical modalities such as cryotherapy and CO_2 laser therapy have a relatively high rate of CR. However, its frequent recurrence, especially in long-term follow up, is frustrating patients and physicians alike.[23,24]

Mechanism of 5-aminolevulinic acid photodynamic therapy

ALA-PDT eradicates warts by inducing cellular death via both apoptotic pathways and necrosis, also through induction of local immune responses (by activating T-cell lymphocytes and dendritic cells). In PDT, photosensitive agents interact with oxygen to generate singlet oxygen. This process is considered fundamental in ablative ability of PDT.[25] One study also concluded that the efficacy of PDT in genital warts may also be attributable to the increased levels of interferon (IFN)-α and IFN-β after the treatment.[26]

ALA itself is not a photosensitizer, but rather a prodrug. After administration, ALA will undergo enzymatic conversion to protoporphyrin IX (Pp IX) which functions as a photosensitive agent. As with all photosensitive agents, Pp

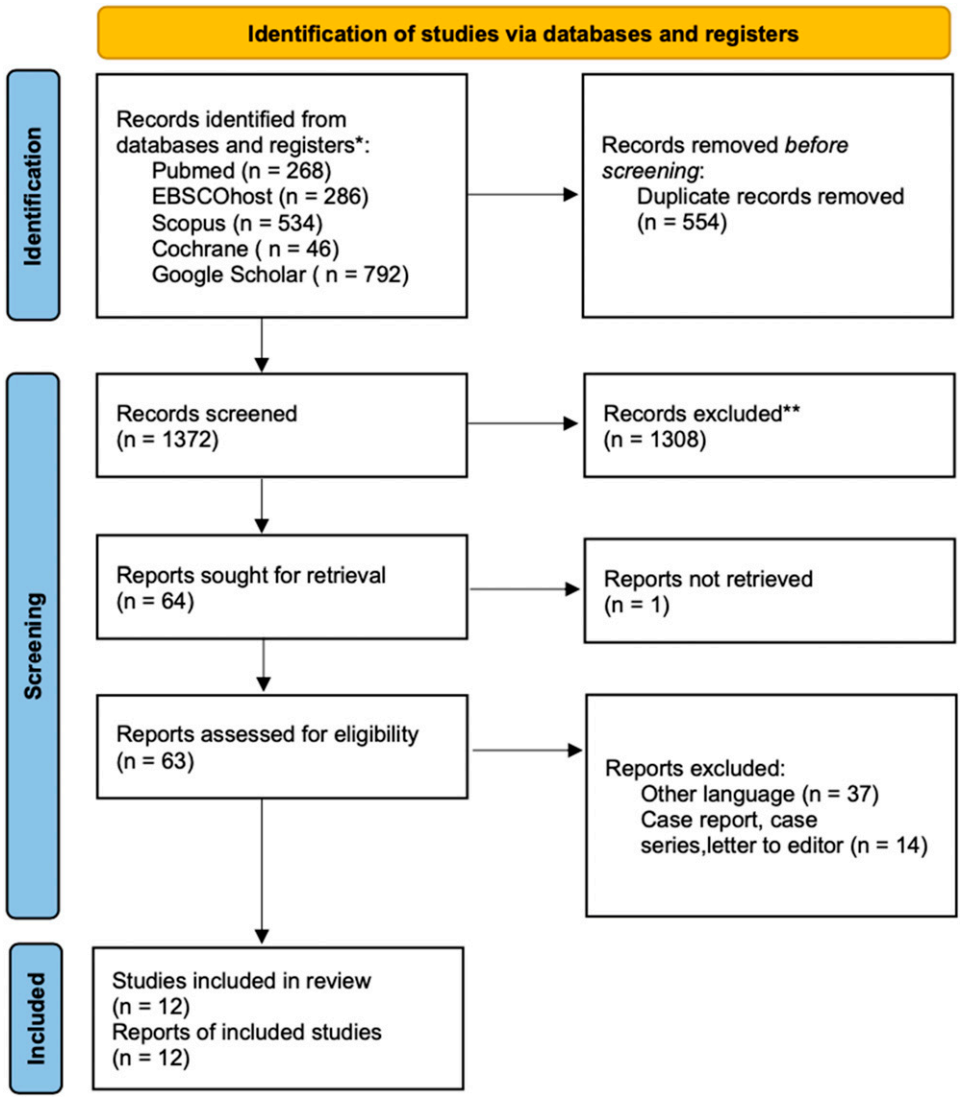

Figure 1. Literature search strategy based on PRISMA statement.[8]

IX becomes activated when energized by light and produces a photodynamic reaction. Pp IX also possesses fluorescent property and affinity towards abnormal lesions. Hence, treatment can be guided by the fluorescent Pp IX to detect and delineate lesions, including subclinical ones, in order to deliver a more precise therapy. This ability also sets ALA-PDT from other modalities such as TCA, as ALA-PDT can target subclinical and latent lesions, it can also lower viral load and recurrence rates.[21,25]

Complete response

According to 10 studies, the total CR in the ALA/MAL-PDT treatment had a high value (63–100%) based on both lesion and patient counts. Six of the 10 studies reported CR after the patients have received 3 sessions of ALA-PDT.[12,13,16–18,20] Comparison of ALA-PDT with CO2 laser, cryotherapy with placebo-PDT, or trichloroacetic acid (TCA) also showed higher CR values of ALA-PDT than the three controls.[13,15,17,19,21] ALA-PDT therapy in primary and recurrent lesions was reported to be equally effective (100%).[14] On the other hand, there was a study that reported significantly lower CR in ALA-PDT (95.93%) than CO_2 laser therapy (100%) ($p < 0.05$).[15]

Other modalities, such as cryotherapy, did not yield better CR than ALA-PDT. Reyna-Rodríguez et al.[27] studied the efficacy of cryotherapy with or without oral isotretinoin in the treatment of CA. The 46 Hispanic patients in the study were randomly assigned to either the cryotherapy group or cryotherapy and isotretinoin therapy group equally. Both groups in the study had a CR of 50% at the end of the 4 months follow up period. However, a combined treatment of cryotherapy with podophyllin 25%, followed by post-ablative immunomodulation with 15% sinecatechins

Table 1. Study characteristics of included studies.

				Population					Intervention and comparison							
										Specification of intervention						
										Photosensitizer	Photodynamic therapy (PDT)					
Author, year	Study location	Study design	Study duration	Subject (*n*)	Gender (%)	Age in years (mean ± SD.)	Number of lesion (*n*)	Location of lesion	Intervention	Type	Duration of incubation (hours)	Wavelength (nm)	Power (mW/cm^2)	Final dose (J/cm^2)	Frequency of Photosensitizer-PDT administration	Comparison
Wang et al. 2004	People's republic of China	Pre-post study	24 months	164	Male = 108 (66%) Female = 56 (34%)	35 (range: 23–66)	—	Distal urethra	Aminolevulinic acid-photodynamic therapy	ALA 10%	3	630	100	100	1 session weekly; 4 weeks maximum	—
Chen et al. 2007	People's republic of China	Randomized controlled trial	3 months	86 Treatment: 65 Control: 21	Treatment: Male = 44 (67.7%) Female = 21 (32.3%) Control: Male = 15 (71.43%) Female = 6 (28.57%)	Treatment: 35.2 ± 10.4 Control: 35.9 ± 9.3	Mean ± S.D Treatment: 1.5 ± 0.7 Control: 1.9 ± 0.9	Distal urethra, external genitalia	Aminolevulinic acid-photodynamic therapy	ALA 20%	3	632.8	100	100	1 session weekly; 3 weeks maximum	Carbon dioxide laser therapy
Liu et al. 2009	People's republic of China	Pre-post study	3 months	30	Female = 30 (100%)	Primary group: 28.5 (range 20–53) Recurrent group: 26.9 (range 20–39)	Primary group: 31 Recurrent group: 9	Cervix	Aminolevulinic acid-photodynamic therapy	ALA 20%	3	635	100	100	1 session weekly; 3 weeks maximum	—
Liang et al. 2009	People's republic of China	Randomized controlled trial	3 months	91 Treatment: 68 Control: 23	Treatment: Male = 61 (89.71%) Female = 7 (10.29%) Control: Male = 19 (82.61%) Female = 4 (17.39%)	Treatment: 33.84 ± 10.01 Control: 34.72 ± 10.74	Mean ± S.D Treatment: 1.84 ± 0.82 Control: 2.04 ± 0.93	Distal urethra, external genitalia	Aminolevulinic acid-photodynamic therapy	ALA 5%	3	632.8	100	100	1 session weekly; 3 weeks maximum	Carbon dioxide laser therapy
Chen et al. 2011	People's republic of China	Pre-post study	12 months	48	Female = 30 (100%)	26.5 (range 20–34)	Primary group: 39 Recurrent group: 9	Cervix	Aminolevulinic acid-photodynamic therapy	ALA 20%	3	635±5	100	100	1 session weekly; 3 weeks maximum	—
Mi et al. 2011	People's republic of China	Double-blind randomized controlled trial	3 months	80 Treatment: 40 Control: 40	Male = 53 (66.25%) Female = 27 (33.75%)	Treatment: 30.9 ± 7.70 Control: 28.8 ± 7.02	Treatment: 280 Control: 276	Anus, urethral meatus, external genitalia	Cryotherapy plus aminolevulinic acid-photodynamic therapy	ALA 20%	3	635	100	100	1 session weekly; 3 weeks maximum	Cryotherapy alone

(continued)

Table 1. (continued)

				Population					Intervention and comparison							
										Specification of intervention							
										Photosensitizer	Photodynamic therapy (PDT)						
Author, year	Study location	Study design	Study duration	Subject (*n*)	Gender (%)	Age in years (mean ± SD.)	Number of lesion (*n*)	Location of lesion	Intervention	Type	Duration of incubation (hours)	Wavelength (nm)	Power (mW/cm^2)	Final dose (J/cm^2)	Frequency of Photosensitizer-PDT administration	Comparison
Sun et al. 2012	People's republic of China	Pre-post study	3 months	86	Male = 75 (87.21%) Female = 11 (12.79%)	43.50 ± 24.97 (range 13–69)	Single: 67 Multiple: 19	Distal urethra	Aminolevulinic acid-photodynamic therapy	ALA 19.09%	3	635	-	100	1 session weekly; 3 weeks (1 cycle)	—
Du, et al. 2015	People's republic of China	Randomized controlled trial	3 months	161 Treatment: 89 Control: 72	Female = 161 (100%)	30.2 ± 9.0 (range 18–64)	Mean: 1.72 (range = 1–4)	Cervix	Aminolevulinic acid-photodynamic therapy	ALA 5%	3	635	100	1000	2 sessions every 2 weeks	Carbon dioxide laser therapy
Zhao et al. 2020	People's republic of China	Pre-post study	3 months	46	Male = 46 (100%)	18–30 = 30 (65.2%) 31–45 = 13 (28.3%) >45 = 3 (6.5%) (Range 18–67)	Mean ± S.D 6.07 ± 2.22	Intra anal-rectal, perianal	Aminolevulinic acid-photodynamic therapy	ALA 20%	3	635	20–40	18–36	1 session weekly; 4 weeks maximum	—
Buzza et al. 2021	Brazil	Single-blinded randomized controlled trial	30 months	31 Treatment: 16 Control: 15	Female = 31 (100%)	Treatment: ≤18 = 5 (33%) 19–55 = 10 (67%) Control: ≤18 = 1 (6%) 19–55 = 11 (69%) ≥56 = 4 (25%) (Range 16–70)	—	Mucosa, perianal region, vulva, mons pubis	Methyl aminolevulinate-photodynamic therapy	MAL 20%	3	630	80	100	1 session weekly; 10 weeks maximum	Trichloroacetic acid (TCA)

ALA: Aminolevulinic acid; MAL: Methyl aminolevulinate.

Table 2. Outcome of included studies.

	Outcome	
Author, year	Complete response	Recurrence
Wang et al. 2004	1 session: 44/164 patients (27%) 2 sessions: 75/164 patients (46%) 3 sessions: 30/164 patients (18%) 4 sessions: 7/164 patients (4%) Total = 156/164 (95%)	8/156 (5%)
Chen et al. 2007	Treatment versus Control 1 session: 95/100 lesions (95%) vs. 41/41 lesions (100%) 2 sessions: 5/100 lesions (5%) vs. - Total: 100/100 (100%) vs. 41/41 (100%)	Treatment versus control: 4/65 patients (6.15%) vs. 4/21 patients (19.04%); p <0.05
Liu et al. 2009	Primary group: 31/31 lesions (100%) Recurrent group: 9/9 lesions (100%)	Primary group: 1/31 lesion (3.23%) Recurrent group: 1/9 lesion (11.1%) Total = 2/40 lesions (5%)
Liang et al. 2009	Treatment versus Control: 95.93% vs. 100%; p >0.05	Treatment versus Control: 9.38% vs. 17.39%; p <0.05
Chen et al. 2011	46/48 patients (95.8%) after 3 sessions of therapy	2/46 (4.4%)
Mi et al. 2011	Treatment versus Control: 1 session: 140/280 lesions (50%) vs. 76/276 lesions (27.5%) 2 sessions: 57/280 lesions (20.4%) vs. 41/276 lesions (14.9%) Total: 197/280 lesions (70.4%) vs. 117/276 lesions (42.4%); p <0.05	Treatment versus Control: 35/280 lesions (12.5%) vs. 89/276 lesions (32.2%); p <0.05
Sun et al. 2012	1 cycle: 105/117 lesions (89.74%); 76/86 patients 2 cycles: 12/117 lesions (10.26%); 10/86 patients Total: 117/117 lesions (100%); 86/86 patients	14/86 patients (16.28%)
Du et al. 2015	Treatment versus Control: 90.20% vs. 96.2% lesions; p = 0.13	Treatment versus Control: 4.90% vs. 19.00% lesions; p = 0.006
Zhao et al. 2020	1 session: 4/46 patients (11.4%) 2 sessions: 11/46 patients (31.4%) 3 sessions: 12/46 patients (34.3%) 4 sessions: 8/46 patients (22.9%) Total: 35/46 patients (95%)	5/35 patients (14.3%)
Buzza et al. 2021	Treatment versus Control: 63% vs. 60%	Treatment versus Control: 0% vs. 33%

resulted in a significantly high clearance rate (96.3%) and low recurrence rate (7.4%), which makes this intervention combination promising.[28] This regimen has been only studied once in a retrospective analysis, hence it has limited evidence. Further clinical studies should be conducted to support this promising combination therapy.

A study by Anggraini et al.[29] also concluded that topical therapy of CA with 1% 5-fluorouracyl, 5% 5-fluorouracyl, nor 90% trichloroacetic acid was more efficacious than the other. The complete response rate at 7 weeks follow up was 67%, 63%, and 46% respectively. Of the three preparations, the study recommended 1% 5-fluorouracyl as alternative topical therapy for its milder adverse effects and convenience.

Recurrence

While CA is a curable condition, recurrence has become one of the main problems in treating CA. Limited information was available regarding factors that may contribute to this high recurrence. A cross-sectional study conducted in perianal CA patients underwent surgical intervention, found a significant correlation of age, which recurrence rate was found higher in reproductive age.[30] Another study by Kim et al. also suggest a significant association of high-risk HPV subtypes with anorectal CA.[31]

Apart from all risk factors, interventions are expected to capable in reducing the recurrence rate. Nonetheless, the only treatment option that has a clearance rate of nearly 100% is surgical excision. Other modalities showed around 20–30% of recurrence. For instance, topical podophyllotoxin treatment which results in 45–83% recurrence; imiquimod treatments with 35–68% recurrence; and cryotherapy with liquid nitrogen that has 21–42% recurrence rate.[32] The use of 5-ALA-PDT as an emerging treatment was obtained to be more effective, simple, and lower recurrence rate than CO_2 laser intervention.

This finding is proven in our results that showed a significant lower recurrence on ALA/MAL-PDT treatment

than controls (p <0.05) in studies comparing the recurrence of ALA/MAL-PDT with CO2 laser control, cryotherapy with placebo-PDT, or trichloroacetic acid (TAA).[13,15,17,19,21] A maximum recurrence rate of 16.28% (14/86 patients) was experienced by those who received two treatments.[18] Yet, after addition of the therapy, the patients were able to achieve 100% CR without the appearance of relapse during the 3 months follow-up period.[18] In addition, it was reported that the recurrence of ALA-PDT in primary lesions was lower (3.23%) than in recurrent lesions (11.1%).[14] A meta-analysis done by Zhu et al. also supported higher efficacy of CO_2 laser intervention when combined with ALA-PDT with recurrence rate of 10.29% ($p < 0.0001$).

Adverse effects

Eight out of 10 studies reported tolerable side effects from the ALA/MAL-PDT treatment, with the majority being pain.[12–15,17,18,20,21] Of these studies, several reported other patient experiences in the form of mucosal hyperemia,[18] edema, and mild erosions,[14–18] erythema,[13] and exudate.[18] However, one study that conducted a satisfaction survey of patients with ALA-PDT therapy found satisfaction rates of 100% at 1 month and 95% at 3 months after completing treatment.[33] Another study trying to screen for the side effects with modified ALA-PDT—ALA applied for 30 min without washing and followed by 630 nm 300 J/cm^2 irradiation—reported painless (VAS 0.3 ± 0.47, range 0–1) compared to conventional ALA-PDT (VAS 3.6 ± 0.94, range 3–6) with relatively similar efficacy.[34]

Similarly, pain was also observed in patients treated with other modalities such as cryotherapy and intralesional bleomycin (VAS 5.83 ± 1.80 and 6.95 ± 2.33 respectively) as reported by Shahidi-Dadras et al.[35] All patients treated with these modalities experienced dyspigmentation and bullae/ulcers, while 71% of patients treated with intralesional bleomycin experienced delayed ulcer. Furthermore, infection was also seen in more than half of the patients in bleomycin group while no infection occurred in those treated with cryotherapy. Likewise, Reyna-Rodríguez et al.[27] reported severe pain in around 60% of all subjects treated with cryotherapy.

Some studies have also revealed the immunosuppressive effects of PDT. High fluence rate PDT was found to cause significant dose-dependent immunosuppressive effects in healthy Mantoux-positive population sample. High fluence rate PDT (75 mW cm^{-2}) with a total dose of 37 J cm^{-2} using either MAL or 5-ALA as photosensitizer resulted in immunosuppression ($p < 0.05$). The research was continued with a lower fluence rate (15 mW cm^{-2} and 45 mW cm^{-2}) and found no immunosuppressive effects ($p < 0.05$).[36] A recent review also summarized 13 studies, showing PDT-induced immunosuppression effects, possibly involving cyclooxygenase-2 (COX-2), regulatory T cell (Tregs), and myeloid-derived suppressor cell (MDSCs) upregulation.[37]

Modification and combination

Several modifications or combinations of ALA-PDT were carried out to obtain more optimal results in overcoming CA. Some of them are modified ALA-PDT in the form of needleless injection which results in significantly higher CR (68.8%) than topical ALA-PDT (52.5%)[38] and the combination of ALA-PDT with effective DNA detection in determining the therapy session required by the patients.[39] A recent case series also found complete responses without any recurrence in 66 case of anogenital CA treated with ALA-PDT combined with tretinoin. Other combination of ALA-PDT, such as with laser ablation or carbon dioxide laser, still need further evaluation and comparison to ALA-PDT only treatment.

A modification of conventional PDT is daylight-PDT (d-PDT), which uses sunlight to energize the photosensitizer. Conventional PDT, like the one used by studies in our results, mainly utilizes narrowband red light while d-PDT utilizes the visible spectrum of daylight. PpIX absorbs blue light wavelength the most in the solar spectrum. As such, the therapeutic effects of d-PDT are mostly attributed to blue light, which also more shallow penetration compared to red light. This modification of PDT is gaining traction in the treatment of actinic keratosis. The utilization of daylight in PDT is promising as it is thought to contribute to a pain-free therapy with increased effectiveness.[40] However, d-PDT may not be practical in the context of CA considering the location of the lesions. Furthermore, as the irradiance delivered in d-PDT is comparatively lower than conventional PDT, d-PDT requires a longer irradiation time to achieve the same level of PpIX activation. Until modifications can be made to d-PDT delivery, application of d-PDT may be more appropriate in other types of warts.

The immunosuppressive effects of PDT can also be blocked by understanding the potential mechanism of PDT-induced immunosuppression. Theoretically, COX-2 inhibitors, such as diclofenac, are ideal in reversing the upregulation of COX-2, nonetheless; practicians should keep in mind with regards to possible side effects. Topical vitamin D, which has the capability to augment the production of tumor specific PpIX, is another promising agent. However, vitamin D receptor activation was discovered to have the ability in increasing Tregs, resulting in immunosuppressive condition. Up to now, a combination of calcipotriol (topical vitamin D agonist) and 5-fluorouracil was known to induce long-term remissions and is thus an interesting subject to be investigated in the future. In addition, topical and oral nicotinamide (vitamin B3) can reload cellular ATP after UV light irradiation. Hence, it can diminish the immunosuppression resulted by PDT. Lastly, simply decreasing the rate of irradiation may be another option in reducing immunosuppressive effects by PDT,[37] as it was previously reported that reduction in oxygen

consumption through the administration of lower levels of irradiation (e.g. 15 $mW{\cdot}cm^{-2}$, 45 $mW{\cdot}cm^{-2}$, and 50 $mW{\cdot}cm^{-2}$) can reduce the immunosuppressive effects of PDT.[41] The effectivity of low irradiation PDT in the management of CA should also be investigated in future studies.

Conclusion

PDT therapy resulted in a higher CR with significantly lower recurrence rate compared to other therapies. The main side effect of PDT, which is the sensation of pain, is still tolerated by patients. Thus, PDT can be an alternative treatment of CA with a low recurrence rate and minimal side effects.

To our knowledge, this is the first systematic review that assesses the effectiveness and potential benefits of PDT in CA treatment. Most of the studies included were critically appraised and deemed as high-quality studies. However, several limitations exist in the current review. First, this study did not consider the differences that may exist between PDT equipment used in urology/gynecology practice and dermatovenereology practice. The PDT equipment used between these fields may differ in specifications other than those already mentioned in this study, i.e. equipment wavelength, power, and dose. Second, the included studies did not report the degree of hyperkeratosis in the lesions. As such its effect towards the depth of light penetration cannot be evaluated.

We recommend doing further research, especially randomized controlled trials (RCTs) in various countries, to further substantiate and integrate this treatment to guidelines in the future. Further investigations with regards to the current protocol, such as the optimal photosensitizer concentration, PDT specifications (wavelength, power, and dose), and mitigation of adverse effects are also relevant for further exploration to improve outcomes and minimize unwanted effects. Additionally, long-term studies to assess the recurrence rate of PDT with longer follow-up periods are also demanded.

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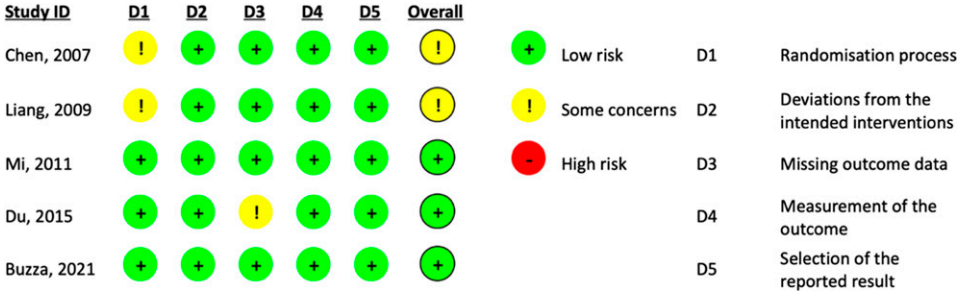
Appendix A. Search strategies on various databases.

Database	Keywords	Date searched	Hits
PubMed	((“Condylomata Acuminata”[Mesh]) OR (genital warts) OR (anogenital warts) OR (human papillomavirus) OR (HPV)) AND (photodynamic) AND ((treatment) OR (therapy))	11th May 2022	268
EBSCO	((“Condylomata acuminata”) OR (genital warts) OR (anogenital warts) OR (human papillomavirus) OR (HPV)) AND (photodynamic) AND ((treatment) OR (therapy))	11th May 2022	286
Google scholar	Photodynamic treatment “condylomata acuminata” OR “genital warts” OR “anogenital warts”-“*in vivo*”-“*in vitro*”-neoplasia-vaccine	11th May 2022	792
Scopus	TITLE-ABS-KEY ((Condylomata acuminata) OR (genital warts) OR (anogenital warts) OR (human papillomavirus) OR (HPV)) AND (photodynamic) AND ((treatment) OR (therapy))	11th May 2022	534
Cochrane	TITLE-ABS-KEY ((Condylomata acuminata) OR (genital warts) OR (anogenital warts) OR (human papillomavirus) OR (HPV)) AND (Photodynamic) AND ((treatment) OR (therapy))	11th May 2022	46

Appendix B. Risk of bias assessment with cochrane revised risk of bias (ROB 2.0).



Appendix C. Risk of bias assessment with risk of bias in non-randomized studies-of interventions (ROBINS-I).

	Pre-intervention		At intervention	Post-intervention				
Author (Year)	Confounding	Selection of participants	Classification of intervention	Deviations of intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Wang (2004)	Low	Low	Low	Low	Low	Low	Low	Low
Liu (2009)	Low	Low	Low	Low	Low	Low	Low	Low
Chen (2011)	Low	Low	Low	Low	Low	Low	Low	Low
Sun (2012)	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Zhao (2019)	Low	Low	Low	Low	Low	Low	Low	Low
Hua (2021)	Low	Low	Low	Low	Low	Low	Low	Low
Romero (2022)	Low	Low	Low	Low	Low	Low	Low	Low