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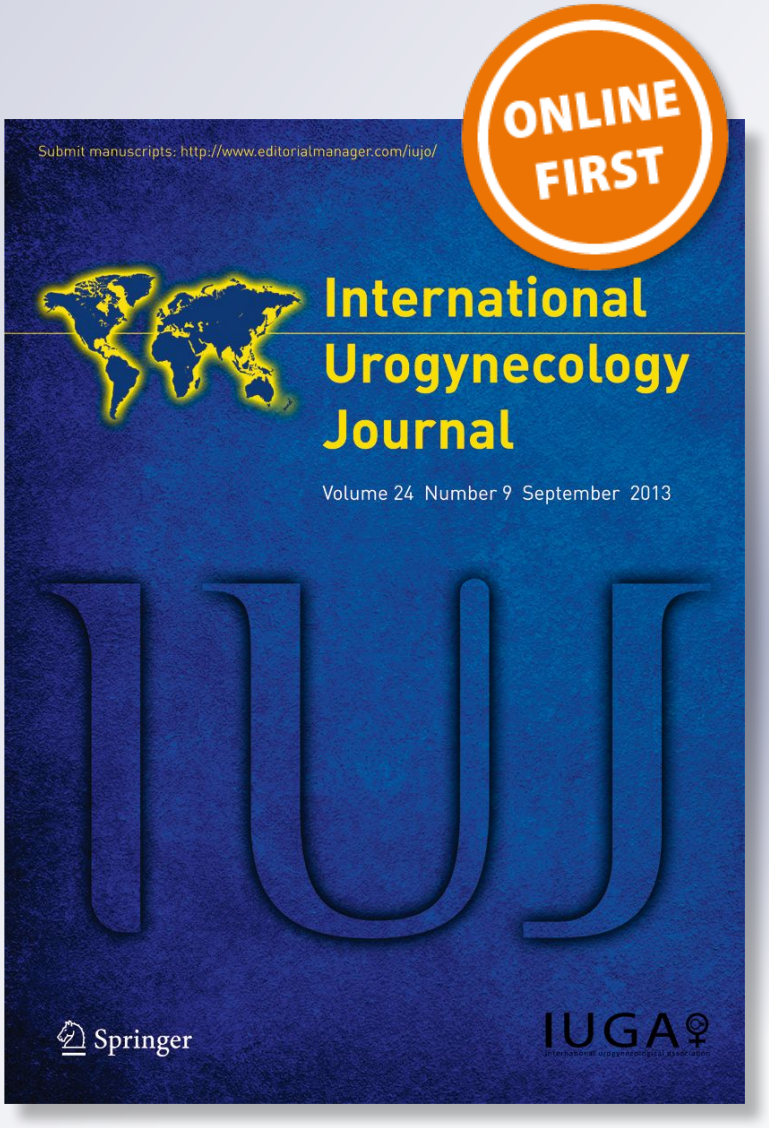


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ORIGINAL ARTICLE

# Laser treatment for the management of genitourinary syndrome of menopause after breast cancer. Hope or hype?

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## Abstract

**Introduction and hypothesis** Fractional $CO_2$ and vaginal erbium lasers have emerged as potential treatment options for genitourinary syndrome of menopause (GSM) in breast cancer (BC) survivors.

**Methods** We conducted a systematic review of the literature to ascertain whether available evidence supports the efficacy and safety of laser treatment for GSM in BC patients. MEDLINE, Scopus and Cochrane Library databases were systematically searched from inception until March 2019 for studies on laser treatment for GSM in BC patients.

**Results** We yielded six observational studies meeting the inclusion criteria. The studies were of moderate quality. Taken together, the studies suggest that laser treatment may significantly alleviate or resolve the GSM-related symptoms and improve sexual function. Furthermore, a significant increase of the vaginal health index was reported. Positive effect was maintained up to 12 months. The safety and tolerability profile is encouraging, given that no adverse effects were reported, while only few patients discontinued laser treatment, owing to reported discomfort.

**Conclusions** Our findings suggest that lasers appear to be effective and practical treatment options in BC survivors suffering from GSM. Evidence concerning long-term effects is lacking. The rationale for repeated treatment remains uncertain. Randomized controlled trials that collate different frequencies, intensities and durations are warranted to ascertain a dose-response relationship and adherence.

**Keywords** Genitourinary syndrome of menopause · Vaginal atrophy · Laser · Breast cancer

## Introduction

Breast cancer (BC) is the most common cancer in females worldwide, with an incidence peak between 55 and 64 years of age [1]. However, approximately 12.1% of patients with BC are diagnosed aged < 44 years [2]. Early stage diagnosis in addition to effective adjuvant systemic therapies has markedly improved the overall survival, but BC remains a disease with increased mortality, while treatment and survival are associated with significant effects on quality of life [3].

The genitourinary syndrome of menopause is characterized by vulvovaginal atrophy, vaginal elasticity and vascularity loss in addition to impaired pro-lubricative and pro-elastic functions [4, 5]. The most common symptoms consist of dyspareunia, burning sensation, itching, irritation, dryness and decreased lubrication, whilst urinary symptoms such as dysuria and urgency might also be present [6].

GSM affects 50% of post-menopausal women and up to 70% of BC survivors [6, 7]. The latter might present with early GSM onset as a result of chemotherapy (CT)-related gonadal insufficiency, prophylactic oophorectomy and hormonal treatment (HT) aiming at reducing the effect of oestrogen on breast tissue [8]. Over the last decade the use of aromatase inhibitors (AI), tamoxifen (TMX) or gonadotropin-releasing hormone agonists has significantly increased [9], while therapy duration has been extended from 5 to 10 years [10].

Anastasios Tranoulis, Dimitra Georgiou and Lina Michala contributed equally to this work.

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GSM management remains challenging, owing to poor compliance to treatment modalities and side effect concerns in addition to contraindications to systematic treatment [11, 12]. In BC patients, systematic HT is currently contraindicated, whilst vaginal topical treatment with low-dose oestrogens remains controversial [11, 12]. A growing body of evidence suggests that laser treatment is an effective and safe option for GSM symptoms [13, 14]. However, there is a paucity of data concerning its efficacy amongst BC survivors suffering from GSM. The present systematic review aims to synthetize all available evidence that stems exclusively from breast cancer case series to ascertain the efficacy and safety of treatment for GSM.

## Materials and methods

We systematically searched MEDLINE, Scopus and Cochrane Database for relevant references from inception until March 2019, in line with the PRISMA guidelines [15]. Eligible studies were yielded based upon the Boolean search strategy (PICO) to describe the patient population (P: women with GSM and breast cancer history), the intervention [I: fractional ablative $CO_2$ laser OR vaginal erbium laser (Er: YAG laser)] and the outcome [O: GMS symptom intensity OR vaginal health index score (VHIS) OR female sexual function index (FSFI) OR female sexual distress scale (FSDS-R) OR adherence] without defining any comparison (C:/) or study design (S:/). For the MEDLINE search the following MeSH terms and keywords were combined: 'genitourinary syndrome of menopause'; 'GSM'; 'vulvovaginal atrophy';' vaginal atrophy'; 'vulval atrophy'; 'breast cancer'; 'fractional $CO_2$ laser'; 'vaginal erbium laser'. A similar modified search strategy was carried out for subsequent databases. In case of repeated publications by the same team, the most recent or complete data were retained.

### Inclusion criteria

The inclusion criteria consisted of the following: (1) menopausal status; (2) confirmed GSM diagnosis; (3) women with previous or current BC; (4) laser treatment; (5) negative cervical cytology; (6) randomized controlled trials (RCTs); (7) observational studies (OSs); (8) reported data on pre- and post-treatment clinical data); (9) English language.

### Exclusion criteria

Exclusion criteria consisted of the following: (1) studies irrelevant to GSM treatment with laser; (2) population other than BC patients or survivors; (3) combination treatment; (4) use of other treatment within 30 days before inclusion in the study; (5) active lower genital tract infection; (6) case reports, reviews and small case series of five or fewer patients; (7) repeated or overlapped data.

### Study selection and quality assessment

Study selection was conducted in parallel by two co-authors (DG, AT). The study selection was performed in two stages. Full titles and abstracts were initially screened and articles meeting the predefined criteria were obtained. These articles were assessed in full text to make the final selection. A hand search for missed articles after the electronic search was also carried out. For duplicates, the most recent or complete publication was chosen. Any discrepancy was resolved by consensus with a third reviewer (LM). Quality assessment and data synthesis were carried out independently (AT, DG). MINORS (Methodological Index for Non-Randomized Studies) was used to evaluate the OS quality [16]. Any conflicts were resolved by discussion with a third reviewer (LM). Figure 1 illustrates the search strategy and results. The methodological quality assessment of the included OSs is summarized in Fig. 2. The outcome data were analysed qualitatively owing to the heterogeneity among study interventions,

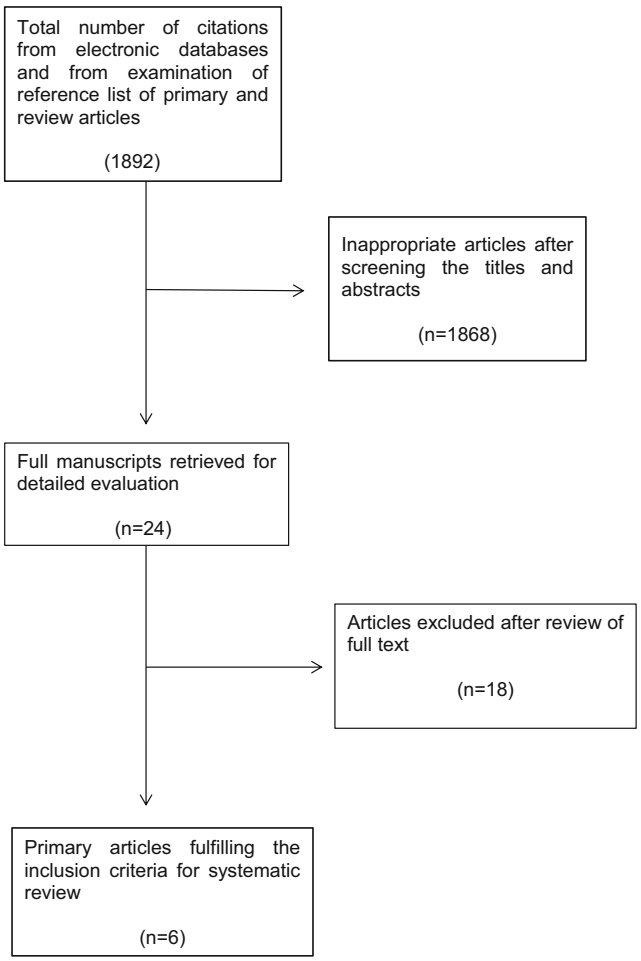


**Fig. 1** Flowchart of literature selection process

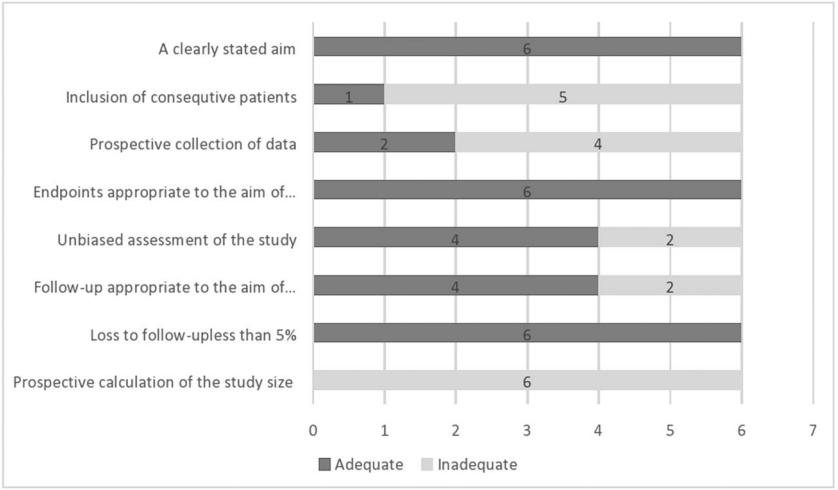


**Fig. 2** Quality assessment of the observational studies (MINORS criteria)

outcomes and participants. The yielded studies are tabulated in structured Table 1. Data were extracted using a standardized data extraction form. We extracted data on the following: name of authors, year of publication, study design, sample size, age, adjuvant or neoadjuvant treatment, laser treatment, pre- and post-treatment clinical data and follow-up.

### Assessment of changes

Several validated questionnaires were used to subjectively assess the changes in GSM symptoms including the Female Sexual Function Inventory (FSFI), the Wong-Baker Faces Scale (WBFS) and the FSDS-R. Different visual analogue scales (VAS) were used to rate symptom severity (Table 1). Some authors evaluated the appearance of vaginal mucosa using the VHIS. It consists of five parameters (elasticity, pH, vaginal discharge, mucosal integrity and moisture). Each parameter is rated from one to five. If the total score is ≤ 15, the vagina is considered atrophic [17].

## Results

The search strategy identified 1892 citations, of which 1868 were excluded, as they did not fulfil the selection criteria. The remaining 24 full articles were reviewed, and a further 18 were excluded. Finally, 6 studies encompassing 192 BT patients or survivors were included in the review [18–23]. Figure 1 depicts the selection process.

We identified four fractional ablative $CO_2$ laser studies and two Er: YAG laser studies. The OSs were of moderate quality (Fig. 2). The sample size varied across studies and ranged between 8 and 77 patients. The median menopause duration ranged between 6.6 and 9 years. All procedures were performed in an outpatient setting without local anaesthesia or any other preparation. Four studies reported on the safety and tolerability of laser treatment [18, 20–22]. No severe adverse effects were reported.

### Fractional ablative $CO_2$ laser

Our literature search identified four cohort studies—one retrospective and three prospective observational studies—on the effect of the fractional ablative $CO_2$ laser on GSM in BC women [18–20, 22].

Gittens et al. evaluated the efficacy and safety of the $CO_2$ laser in eight BC women treated with HT [18]. The treatment consisted of three laser cycles at 40-day intervals and demonstrated significant improvement in every domain of the FSFI between treatment sessions and after treatment. Correspondingly, significant improvement was noted with respect to pain, dyspareunia and vaginal dryness, whilst a significant decrease in sexual distress was reported (Table 1).

Similar findings were reported by Becorpi et al. [19]. Twenty BC patients were treated with two $CO_2$ laser cycles at 30-day intervals. Amongst those, 16 were treated with HT, 3 with radiotherapy (RT) and 1 with combined RT and CT respectively. A significant FSFI and VHI improvement from baseline was reported, yet no significant FSDS-R improvement was found (Table 1). Interestingly, the authors noted significant changes in inflammatory and modulatory cytokines, while no change in the vaginal microbiome was identified after treatment.

In a retrospective study, enrolling 82 BC women, Pagano et al. assessed the WBFS improvement from baseline following three laser sessions at 30 to 40-day intervals [20]. Three women discontinued treatment after two cycles, owing to procedure-related pain, and another two after the first session, for unknown reasons. Following three $CO_2$ laser cycles, the authors noted a significant improvement with respect to sensitivity during sexual intercourse, vaginal dryness, itching/stinging, dyspareunia, dysuria and bleeding. In addition, there

**Table 1** Studies selected for inclusion into the systematic review concerning the efficacy and safety of laser treatment for GSM amongst breast survivors

| Reference | Study design | No. of pts | Age | Menopause duration (years) | Adjuvant treatment | Laser type | No. of cycles | FSFI | FSDS-R | WBFS | VHIS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gittens, 2018 | RS | 8 | NR | NR | HT | FM $CO_2$ | 3 (40-day interval) | $12.48 \pm 7.7^b$ ($p = 0.003$) (Improvement from T0 to T3) | $18.7 \pm 9.25^b$ ($p = 0.002$) (Improvement from T0 to T3) | VAS (0–10)<br>Improvement from T0 to T4:<br>Pain: $4.14 \pm 2.6^b$ ($p = 0.006$)<br>Vaginal itching: $1.75 \pm 3.06^b$ ($p = 0.15$)<br>Dyspareunia: $4.25 \pm 3.45^b$ ($p = 0.01$)<br>Vaginal burning: $2.75 \pm 3.58^b$ ($p = 0.06$)<br>Vaginal dryness: $3.25 \pm 3.33^b$ (0.02)<br>Dysuria: $0.25 \pm 0.71^b$ ($p = 0.35$) | NR |
| Becorpi, 2018 | PS | 20 | 58.2 | $8.85 \pm 5.4$ [b] | 16 HT<br>3 RT | | 2 (30-day interval) | T0: 27.5 (4–54.5) [a] | T0: 21(10–28) [a] | NR | T0: 12 (11–13)[a] |
| | | | | | 1 CT + RT | FM $CO_2$ | | T3: 43 (20.25–70.5)[a] ($p = 0.03$) | T3: 15 (8–24)[a] ($p = 0.074$) | | T3: 16 (15.25–18)[a] ($p < 0.001$) |
| Pagano, 2018 | RS | 77 | NR | NR | 52 CT<br>61 HT (37 AI, 23 TMX)<br>42 CT + HT | FM $CO_2$ | 3 (30–40-day interval) | NR | NR | VAS (0–100)<br>Improvement from T0 to T4:<br>Reduced sensitivity during sexual intercourse: $3\ (2–4)^c$ ($p < 0.001$)<br>Vaginal discharge: $1\ (0–2)^c$ ($p = 0.08$)<br>Vaginal dryness: $5(4–5)^c$ ($p < 0.001$)<br>Vaginal itching: $4(3–4)^c$ ($p < 0.001$)<br>Vaginal bleeding: $2(1–3)^c$ ($p = 0.001$)<br>Dyspareunia: $4(3–5)^c$ ($p < 0.001$) | NR |

**Table 1** (continued)

| Reference | Study design | No. of pts | Age | Menopause duration (years) | Adjuvant treatment | Laser type | No. of cycles | FSFI | FSDS-R | WBFS | VHIS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Dysuria: 2(1–2)[c] ($p < 0.001$) Probe insertion-related pain: 10(5–10)[c] ($p = 0.001$) Probe movement-related pain: 10(0–10)[c] ($p = 0.011$) | |
| Gambacciani, 2017 | PS | 37 | 50.8 ± 8.1[b] | 9 ± 4[b] | NR | Er: YAG laser | 3 (30-day interval) | NR | NR | VAS (0–10) Vaginal dryness: T0: 8.5 ± 1[b] 12 months: 4.4 ± 1.2[b] ($p < 0.01$) 18 months: 7.5 ± 1.8[b] (N/S) Dyspareunia: T0: 7.5 ± 1.5[b] 12 months: 4.2 ± 0.9[b] ($p < 0.01$) 18 months: 6.5 ± 1.8[b] (N/S) | T0: 8.1 ± 1.3[b] 12 months: 21 ± 1.4[b] ($p < 0.01$) 18 Months: 14.8 ± 1.5[b] (N/S) |
| Pieralli, 2016 | PS | 50 | 53.3[a] (41–66) | 6.6[a] (1–17) | 22 HT (2 AI, 20 TMX) | FM $CO_2$ | 3 (30-day interval) | NR | NR | VAS (1–5) Dyspareunia: T0: 5(1–5) T4: 3(1–5) | T0: 8.9 ± 1.7[b] T4: 21.6 ± 1.6[b] ($p < 0.0001$) |
| Mothes, 2018 | RS | 16 | 71 ± 7[b] | NR | NR | Er: YAG laser | Single course | NR | NR | NR | T0: 16 ± 4.6[b] 6 weeks: 20 ± 3[b] ($p = 0.01$) |

No.: number; pts: patients; VHIS: Vaginal Health Index Score; FSFI: Female Sexual Function Index; FSDS-R: Revised Female Sexual Distress Scale; WBFS: Wong-Baker Faces Scale; VAS: visual analogue scale; HT: hormonal treatment; CT: chemotherapy; RT: radiotherapy; FM $CO_2$ laser: fractional micro-ablative $CO_2$ laser; Er: YAG laser: vaginal erbium laser; NR: not reported; T0: baseline; T3: 60 days from baseline; T4: 90 days from baseline; N/S: not significant

[a] Data are expressed as median (range)

[b] Data are expressed as median ± standard deviation

[c] Data are expressed as mean (95% confidence interval)

was a significant reduction in probe insertion- and movement-related pain. Adjuvant therapies significantly affected the probe movement-related pain in women treated with both HT and CT (Table 1).

Pieralli et al. included 50 BC women treated with three $CO_2$ laser cycles at 30-day intervals [22]. Twenty-two out of 50 women were receiving HT—2 AI and 20 MTX—as adjuvant treatment. The authors only assessed the VHI score for the first 36 included patients and they demonstrated a significant improvement from baseline. None of the patients required lubricants during sexual activity (Table 1). Approximately 75% of the women were very satisfied or satisfied at the end of the three courses. Of note, approximately 50% of participants reported long-term satisfaction with a mean time follow-up of 11 (3–25) months; 22% of the patients commenced a new cycle of laser treatment.

### Non-ablative vaginal erbium YAG laser

Two observational studies reporting on the effect of VEL met the inclusion criteria [21, 23]. Gambacciani et al. included a relatively younger population (median age 50.8 years) treated with three Er: YAG laser cycles at 30-day intervals. The authors prospectively assessed symptoms and VHIS improvement at 1, 3, 6, 12 and 18 months, respectively, following treatment completion. The vaginal dryness, dyspareunia and VHIS were significantly improved during the first year after treatment, although there was no significant difference at 18 months (Table 1). No adverse events related to the procedure were reported.

Mothes et al. retrospectively assessed the effect of the Er: YAG laser on 16 BC survivors with GSM symptoms following only one course [23]. The median age of the patients was 71 years, while the mean follow-up interval was 8.3 weeks. The authors reported a significant increase in VHI from 16 to 20 ($p = 0.01$) and non-significant decrease of pH from 5 to 4.8 ($p = 0.14$) (Table 1). The overall satisfaction concerning the symptom relief was 94%, while there were neither complications nor need for analgesic medication.

## Discussion

The fractional ablative $CO_2$ laser and the new generation Er: YAG laser have emerged as potential alternative treatment options for women suffering with GSM. Our findings suggest that laser devices appear to be an efficient, safe and comfortable intervention in the treatment of GSM in BC women. To the best of our knowledge, this is the first systematic review on the topic.

GSM has a debilitating impact on women's health. In addition to the profound negative impact on wellbeing and sexual function, it is associated with a worsened psychological profile and quality of life. It is difficult to critically outline the optimal treatment of GSM in BC patients. There are well-documented barriers to GSM treatment in general population post-menopausal women, whilst the paucity of evidence in BC women poses an additional barrier for this sub-group. BC patients suffering from GSM symptoms are often prescribed non-hormonal remedies, yet these usually offer short-term or inadequate symptom relief [24]. Although systematic HRT is contraindicated in BC survivors, low-dose vaginal oestrogen can be offered to women who are unresponsive to non-hormone treatment, following a thorough informative consultation with respect to the fine equilibrium between potential risk of disease relapse and symptomatic relief from GSM [11, 12]. Their use though is associated with poor patient compliance, because of the need for repeated self-applications, while women often complain of increased vaginal discharge.

The fractional ablative $CO_2$ laser has been proposed as a promising alternative option for GSM symptoms in healthy post-menopausal women [13, 14]. There is also a growing basis of evidence further supporting its efficacy in reducing GSM symptoms in BC patients [18–20, 22]. Although the precise action mechanism is unclear, it seems to induce collagen and elastic fibre production, in addition to remodelling of connecting tissue [25]. Shock proteins, in particular HSP-43-47-70, are activated by heat, thus inducing a local regulation in inflammatory and modulatory cytokines as part of the remodelling status [18]. The final effect is characterized by increased permeability of the connective tissue, which, in turn, translates into improved vaginal wall turgor, hence leading to GSM symptom alleviation [17].

According to our findings, although GSM symptoms were not completely resolved in many BC patients, nearly all symptoms were significantly ameliorated. There was significant improvement in GSM symptoms, including vaginal dryness, dyspareunia, itching and dysuria, in addition to a significant improvement in sexual function. Two studies also reported significant VHIS improvement [19, 22]. The objective evaluation of VHIS indicates a more realistic favourable effect of the $CO_2$ laser on GSM symptoms. The treatment effect was usually discernible after three laser sessions. The procedure tolerability was relatively high, while an improvement was noted with consecutive treatment cycles [20]. Therefore, more than three cycles may be needed to increase treatment efficacy. Interestingly, the symptom intensity reduction was related to a great extent to the baseline VAS, thus indicating that treatment should be introduced when the symptoms are less intense. Becorpi et al. noted an absence of modifications in the vaginal microbiome following completion of laser sessions, which further supports its safety profile. Data on long-term effects are hampered by the limited follow-up of the included studies. Therefore, the long-term efficacy of the $CO_2$ laser is still questionable. Cruz et al., in a recent RCT, aimed to evaluate the

efficacy of the $CO_2$ laser and compare it with local oestriol treatment and the combination of both modalities in the treatment of GSM amongst post-menopausal women. The authors demonstrated significantly higher VHI in all arms at week 8. However, despite the higher VHI score compared with baseline, the VHI score in the laser arm was significantly lower compared with other treatment arms at week 20. The latter raises concerns regarding the long-term effect of laser treatment [26]. Future research should seek to address these shortcomings by developing RCTs that focus on the dose-response relationship and long-term outcomes.

The Er: YAG laser operates through production of low-frequency pulses that are absorbed at the tissue surface, causing a transient heat increase of the vaginal mucosa. This induces collagen production in addition to microvascularization and new vessel formation [27]. We only identified two studies reporting on the Er: YAG laser outcomes in BC patients with GSM symptoms [21, 23]. Both studies noted a significant increase in VHIS, further supporting its efficacy, as well as a long-lasting positive effect on vaginal tissues, up to 12 months after Er: YAG laser treatment [21]. One RCT has suggested that the Er: YAG laser has comparable effectiveness to low-dose vaginal oestrogens in healthy postmenopausal women. Notably, the Er: YAG laser-treated arm positive effects were maintained up to 6 months, while the oestrogen effects diminished 12 weeks post-treatment [27]. Given that the Er: YAG laser allows heat to progressively dissipate to depths of approximately 200 μm, there is minimal mucosal damage risk. This contributes to a lower risk of infection, scarring, necrosis and other side effects [28]. However, no substantial evidence currently exists to support this hypothesis. An ongoing RCT directly comparing the Er: YAG and $CO_2$ laser will possibly enable clinicians to draw more robust conclusions with respect to the efficacy and safety of both laser types [28].

In addition to laser effectiveness, our study provides some evidence for its safety profile. No severe adverse effects were reported. Generally, the laser treatment was well tolerated by most women and only few studies reported discontinuation of the treatment owing to related pain [20, 22]. Furthermore, the tolerability to the treatment appears to improve over the course of time [20]. Nevertheless, none of the studies had safety as a primary end point and, although no adverse effects were reported in the vast majority of studies, the number of patients is too small to allow for firm conclusions. This is one of the issues that needs to be addressed in future studies.

Despite the fair number of publications thus far, there is a lack of clarity over the optimal laser protocol and it is unlikely that additional case series will add sufficient evidence to direct a change in current practice. Robust RCTs that collate and manipulate different frequencies, intensities and durations are warranted to ascertain a dose-response relationship and adherence. RCTs comparing the laser treatment with placebo are also needed. The limited follow-up in the published studies makes it difficult to assess the true long-term outcome of laser treatment. This should be a priority for future research. A number of practical and financial barriers also exist, particularly in low- and middle-income countries, further limiting laser availability. Financial analyses are warranted. Finally, an attempt should be made at standardizing outcome measures, which could improve comparability amongst studies.

The findings of the present systematic review are based on a thorough literature search. No date restriction was applied. We included all studies meeting the inclusion criteria, regardless their design, hence partly reducing the selection bias risk. We assessed the yielded studies' quality using a widely known and used tool. We thoroughly assessed the short- and long-term laser effects. We focused on short-term outcomes, as evidence on long-term outcomes is lacking. None of the included studies were sponsored.

Nonetheless, some limitations should be acknowledged. Only six OSs were identified; hence our review contributes moderate-quality evidence. There were no RCTs comparing different treatment modalities or differences in laser treatment forms in BC women. Meeting abstracts were not included. The findings of the review are limited by the small study sizes, lack of control group and limited follow-up. The heterogeneity of studies and differences in outcome measures made this unsuitable for meta-analysis. Few studies reported on long-term outcomes and there was no measure of a placebo effect.

## Conclusions

This is the first systematic review of the efficacy and safety of laser devices for the treatment of GSM in BC patients. Our findings suggest that laser treatment is an effective and practical treatment option in BC patients suffering from GSM. It appears to be a well-tolerable treatment modality. Only few patients discontinued treatment owing to procedure-related pain, while no severe side effects were reported. Although some studies indicate that positive effects could be maintained up to 12 months post-treatment, convincing data on long-term effects are lacking. Further studies are required to determine the ideal treatment frequency and duration to achieve better long-term results, with improved efficacy and patient compliance.

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## Compliance with ethical standards

**Conflicts of interest** None.

**Details of ethics approval** None needed, as this is a systematic review.

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