Original Study

The Impact of Vaginal Laser Treatment for Genitourinary Syndrome of Menopause in Breast Cancer Survivors: A Systematic Review and Meta-analysis

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Abstract

Vaginal laser is effective in treating genitourinary syndrome of menopause in survivors of breast cancer. There is an improvement in vaginal health index and Visual Analogue Scale Score for dyspareunia and vaginal dryness. Sexual function is improved following treatment. Side effects were infrequent and of mild severity.

Introduction: Genitourinary syndrome of menopause (GSM) is caused by hypo-estrogenism, resulting in vaginal dryness, pain, dyspareunia, and urinary tract infection. It is more severe and common in breast cancer (BC) survivors owing to the severity of induced menopause following treatment (ie, chemotherapy, GnRH agonists/anti-estrogen therapy). It has a detrimental effect on quality of life. The gold standard therapy is topical estrogen, which is highly effective; however, it is contraindicated in patients with BC owing to concerns with recurrence. Recently, vaginal laser therapy has been used to restore vaginal mucosal thickness, lubrication, and elasticity with good effect in menopausal women with GSM. The aim of this study is to assess the impact of vaginal laser therapy on BC-associated GSM. **Materials and Methods:** This study is a systematic review and meta-analysis. **Results:** A total of 48 papers were identified, revealing 10 observational studies of GSM symptoms before and after vaginal laser therapy with no randomized trials. Vaginal laser was effective in treating GSM in BC survivors with improvement in the Vaginal Health Index and the Visual Analogue Scale score for dyspareunia and vaginal dryness, sexual function, and overall satisfaction in the short term with minimal adverse events. **Conclusion:** Vaginal laser may be effective in treating GSM in BC survivors in the short term, but there are no long-term data on safety and efficacy. More research is needed looking at longer term follow-up, health economic costs, and sub-group analysis as well as the complex interplay between GSM and the other negative impacts of BC therapy on intimate relationships.

Clinical Breast Cancer, Vol. 19, No. 4, e556-62 © 2019 Elsevier Inc. All rights reserved.
Keywords: Breast cancer, CO_2 laser, Erbium YAG laser, GSM, Vaginal atrophy

Background

Breast cancer (BC) is the most commonly diagnosed cancer in women, and each year in the UK, 50,000 women are diagnosed with the condition. Up to 25% of women develop BC pre-menopausally, and many of these women will undergo treatment-induced premature menopause.[1] Many more patients with BC who are already post-menopausal at diagnosis will suffer a worsening of menopausal symptoms owing to prolonged antiestrogen therapies (tamoxifen or an aromatase inhibitor [AI] for 5 or, increasingly, 10 years). As survival rates at 5 years are now ~90%,[2] there are many millions of BC survivors globally, many of whom have their quality of life significantly impaired by ongoing menopausal symptoms.

One of the most distressing symptoms of menopause is genitourinary syndrome of menopause (GSM).[3] GSM is a result of a lack of estrogenic stimulus to the vulva and vagina, causing atrophy of the vaginal wall, loss of elasticity, and loss of the normal moisture and pH balance. This results in pain, irritation, burning, vaginal discharge, dyspareunia, and repeated urinary tract infections and may significantly impact on intimate relations with their partner.

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Submitted: Jan 26, 2019; Revised: Mar 16, 2019; Accepted: Apr 7, 2019; Epub: Apr 19, 2019

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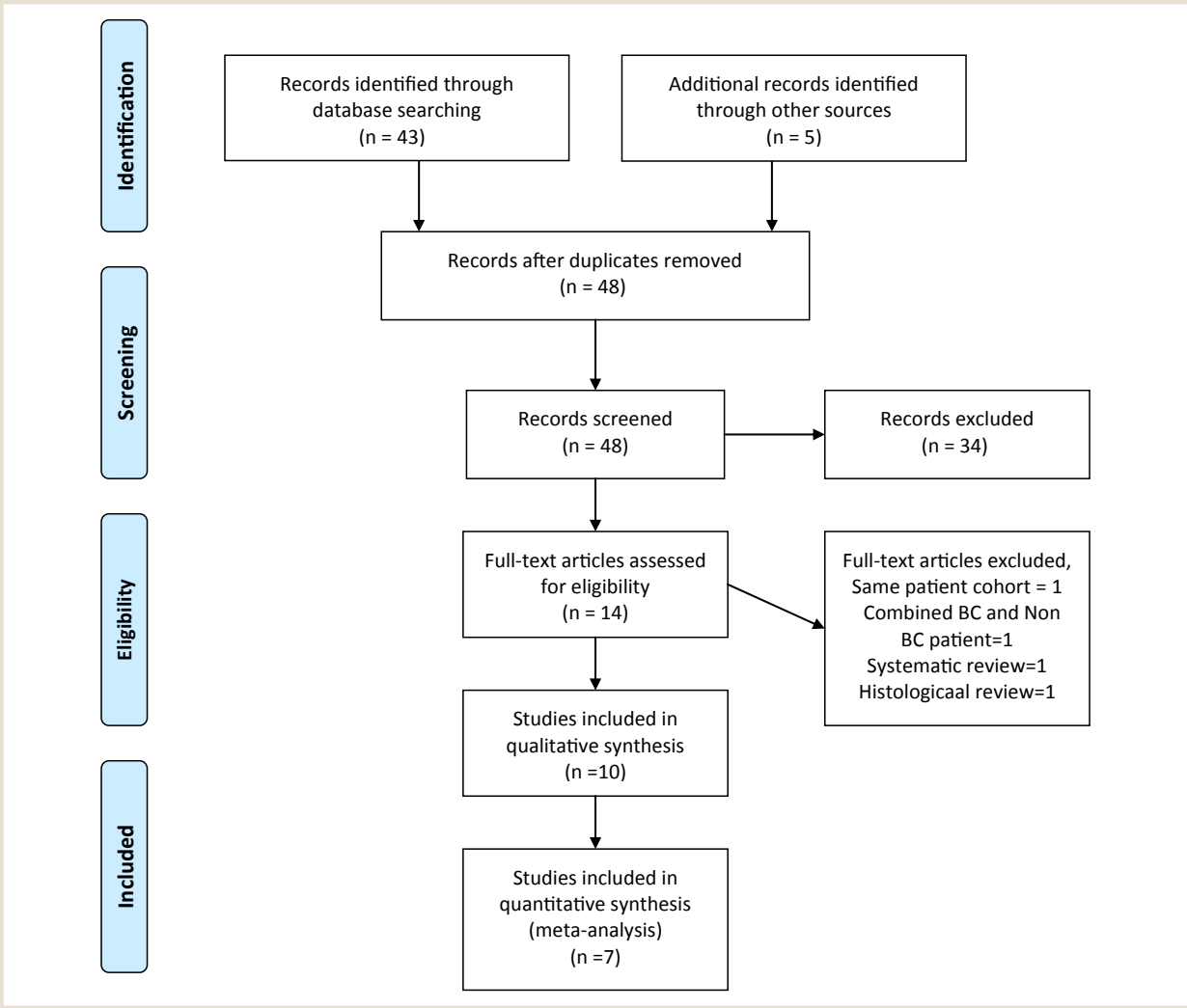
https://doi.org/10.1016/j.clbc.2019.04.007

Figure 1 Study Selection Criteria



Abbreviation: BC = breast cancer.

GSM affects 20% to 50% of women after menopause.[4-6] In patients with BC, who undergo menopause at an accelerated rate (eg, drug-induced such as with chemotherapy, or use of chemical ovarian suppression with GnRH agonists) or undergo a more severe degree of hypo-estrogenic state owing to use of aromatase inhibitor therapy, symptoms of GSM can occur sooner and be more severe than those found among women with a normal-paced menopause.[7-9] Symptoms are often not disclosed by patients because of embarrassment. It has an adverse emotional and physical impact on women and can be detrimental to relationships through unsatisfactory sexual relationships.[10] A premature menopause in young patients with BC (eg, less than 40 years of age) can have a profoundly negative impact on quality of life secondary to sexuality and intimacy changes.[11] Women of all ages wish to preserve their sexual function and improve their sexual quality of life.[12,13] Thus, GSM impacts women of all ages as a survivorship issue.

Unlike the vasomotor symptoms of menopause, which settle with time, GSM worsens with time and is unlikely to resolve without intervention.[8,14] The diagnosis of GSM is confirmed through patient-reported symptoms and gynecological examination of external structures, introitus, and vaginal mucosa. Lifestyle modifications can be helpful but are insufficient to significantly improve symptoms, and non-hormonal vaginal therapies may provide some relief by reducing vaginal dryness. However, the single treatment that would alleviate symptoms (ie, estrogen) is contraindicated in BC survivors. Systemic hormone replacement therapy may have an adverse effect on BC survival (HABITs trial [Hormonal replacement therapy After Breast cancer–Is It safe?]) and is contraindicated. However, there is little data about the BC recurrence risk associated with use of topical antiestrogen creams, with several small series showing no adverse effect on BC but a marked improvement in GSM. However, women and their clinicians are rarely comfortable using topical estrogen in the post-BC setting.

In recent years, 2 types of laser therapy, microablative fractional CO_2 (SmartXide^2 V^2 LR, Monalisa Touch, DEKA, Florence, Italy) and non-ablative photothermal Erbium YAG-laser (Fotona Smooth XS, Fotona, Ljubljana, Slovenia) have been used in postmenopausal

Table 1 Summary of Included Studies

Study Reference	Location	No. Treatment Cycles	No. Patients	Average Age of Patients, y	Time Period	Follow-up Period	Outcomes	Type of Laser
Becorpi (2017)[21]	Florence, Italy	2	20	58.2	December 2015-February 2015	4 weeks post final treatment	VHI, FSFI, VAS	CO_2 Microablative
Gamabacciani (2017)[22]	Pisa, Italy	3	37	50.8	Not stated	24 months post final treatment	VHI, VAS	Erbium YAG
Guerette (2017)[23]	Virginia, US	3	57	49.6	July 2017-December 2017	4 weeks post final treatment	FSFI, VAS	Erbium YAG
Joris (2015)[24]	Brussels, Belgium	3	7	–	January 2014-July 2014	30 days post final treatment	VHI, VAS, VMI	CO_2 Microablative
Maggiori (2015)[25]	Milan, Italy	5	40	–	Not Stated	4 weeks post final treatment	VHI, FSFI, QoL (SF12)	CO_2 Microablative
Mothes (2018)[26]	Jena, Germany	1	16	71	September 2016-June 2017	6 weeks post final treatment	VHI	Erbium YAG
Pagano (2018)[27]	Naples, Italy	3	82	44	April 2015-May 2017	30 days post final treatment	VAS	CO_2 Microablative
Pearson (2017)[28]	Sydney, Australia	3	25	55	February 2016-May 2017	4 weeks post final treatment	VAS	CO_2 Microablative
Pieralli (2016)[29]	Florence, Italy	3	50	53.3	June 2013-June 2015	11 months post final treatment	VHI, VAS	CO_2 Microablative
Scibilia (2017)[30]	Catania, Italy	3	20	–	Not Stated	3 months post final treatment	VHI, VAS, ICIQ	CO_2 Microablative

Abbreviations: FSFI = Female Sexual Function Index; ICIQ = International Consultation on Incontinence Questionnaire; QoL = Quality of Life; VAS = Visual Analog Scale; VHI = Vaginal Health Index; VMI = Vaginal Maturation Index.

women with GSM. This has the advantage of being non-hormonal and therefore carries no risk of worsening BC survival outcomes. They have been shown to be equivalent in efficacy.[15] In the non-BC setting, GSM in women who have undergone a normal menopause is significantly improved, and the treatment seems to have equivalence to use of topical estrogen, the gold standard.[16]

The treatment works by inducing collagen remodeling and increased vascularization in ex-vivo studies.[17] Its microablative effects improve vaginal health by restoring vaginal flora to the premenopausal state with predominant lactobacilli.[18] These effects are long-lasting, persisting up to a 1-year follow-up.[19] However, the efficacy in women made iatrogenically menopausal by their cancer treatment has not been widely or rigorously studied. GSM in this setting may be relatively more refractory to therapy. The purpose of this systematic review is to assess the impact of vaginal laser therapy on BC-associated GSM.

Materials and Methods

This systematic review of the literature followed the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines for the reporting of meta-analysis of observational studies.[20] It was registered prospectively on the PROSPERO database (registration number: CRD42018089610).

Eligibility Criteria, Search Strategy, and Data Extraction

Ovid Medline (1996-, March 2018), Embase, PubMed, the Cochrane register of controlled trials (CCTR), the Cochrane database of systematic reviews (CDSR), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Google Scholar were searched for studies that analyzed the effect of vaginal laser treatment on women with GSM in BC survivors using medical subject heading (MeSH) themes. For each database, a range of search strategies were performed. A manual search of reference lists of all known and included studies was conducted to identify studies not captured by electronic searches to ensure complete coverage of literature. Conference abstracts were included if data could be extracted. Unpublished work was excluded. No language restrictions were applied. The title and abstracts were screened by 2 independent reviewers (S.J. and P.K.). Full articles of all citations that were likely to meet the predefined selection criteria were obtained. Data was extracted independently by 2 authors (S.J. and P.K.) and recorded on a data collection form. Any discrepancies were settled by discussion with the senior author (L.W.). The search output is shown in Figure 1.

A protocol was developed with explicitly defined objectives, criteria for selection and quality assessment of studies, primary and secondary outcomes, and statistical methods. The following data were extracted: first author, year of publication, type of laser used, therapeutic protocol, duration of follow-up, baseline characteristics of participants, the symptoms of GSM being analyzed, the tools used for assessment, any objective measurements of vaginal pathophysiology, adverse events, and dropouts owing to these adverse effects. All studies included in the systematic review are shown in Table 1.

Study Selection

The study population included women with BC who had completed preliminary treatment for their cancer and suffered from GSM as a consequence. Any study that assessed the effect of vaginal laser treatment on GSM in this cohort of women were included. Where data were incomplete, the authors were contacted by email, and if no response was received after 2 weeks, a further email was sent.

Methodological Quality Assessment

The risk of bias assessment based on the quality of the studies was performed using the Modified Newcastle Ottawa Scale (NOS). The

Table 2 Summary of the Quality of Included Studies for Risk of Bias (Newcastle Ottawa Scale)

	Selection (5 Stars)				Comparability (2 Stars)	Outcome (3 Stars)		
	Representation*	Sample Size*	Ascertainment of Exposure**	Non Respondents*	Comparability**	Assessment of Outcome**	Statistical Test*	Total Stars, n/10
Becorpi (2017)[21]	*	—	**	—	**	—	*	6
Gambacciani (2017)[22]	*	*	**	—	**	**	*	9
Guerette (2017)[23]	*	*	*	—	*	*	*	6
Joris (2015)[24]	*	—	*	—	*	*	*	5
Maggiori (2015)[25]	*	*	*	—	*	**	*	7
Mothes (2018)[26]	*	—	**	—	*	**	*	7
Pagano (2018)[27]	*	*	**	—	**	**	*	9
Pearson (2017)[28]	*	—	*	—	*	**	*	6
Pieralli (2016)[29]	*	*	**	—	**	**	*	9
Scibilia (2017)[30]	*	—	*	—	—	*	*	4

NOS is a scale designed to assess the quality of non-randomized epidemiologic research. Stars are assigned for a study's design characteristics. Studies that garner more stars are deemed to be of higher quality. Using the tool, each study is judged on 6 items, categorized into 3 groups: the selection of the study groups, the comparability of the groups, and the ascertainment of either the outcome of interest. Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies are awarded up to 9 stars.

Quality assessment of all studies included in the review is shown in Table 2.

Data Extraction and Synthesis

The meta-analysis was performed using Review Manager 5.3 (RevMan). This was performed if more than 3 studies reported on data. Heterogeneity was assessed by examining the characteristics of the included studies. The outcomes included in the meta-analysis included the Vaginal Health Index (VHI), a Visual Analogue Scale (VAS) for dyspareunia, and the Female Sexual Function Index (FSFI). Overall improvement in symptoms was reported and estimated for the different studies. For continuous variables, inverse variance estimates were used with a random effects model to calculate mean values and 95% confidence intervals (CIs). For categorical variables, Mantel-Haenszel estimates were used with a random effects model to calculate odds ratios and their 95% CIs.

Results

Study Selection

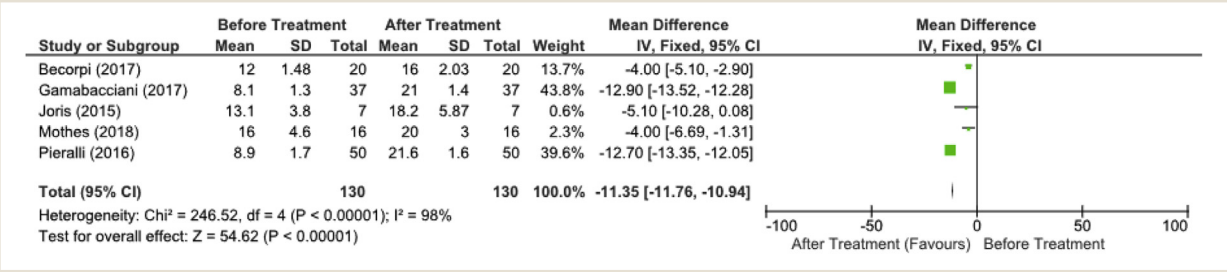
The search strategy revealed 48 references that were assessed for eligibility. Thirty-eight studies were excluded. Ten studies involving 522 women undergoing vaginal laser treatment following breast neoplasia treatment were considered eligible and were included in this systematic review: all were cohort studies as there have been no randomized trials to date. The search strategy is summarized in Figure 1, and details of studies included are in Table 1.

Study Characteristics

Ten studies were identified as being suitable for inclusion. Five were observational studies, and the remaining 5 were conference abstracts with limited data. Of these studies, 7 used the CO_2 laser, and 3 used the Erbium YAG. All studies were observational cohort studies reporting on the effects of laser treatment before and after completion of treatment on the same cohort of patients. The time elapsed since the last laser treatment was the follow-up interval and varied from 4 weeks to 24 months. There was one study that duplicated data, and it was excluded from the analysis. There were no randomized controlled trials. The treatment protocol varied in the different studies, ranging from 3 to 5 treatment sessions in the CO_2 laser treatment and 1 to 3 in the Erbium YAG laser treatments.

There was significant heterogeneity of the studies with respect to women undergoing the laser treatment. The time elapsed since the completion of active treatment for BC varied, and the age of the participants as well as time elapsed since menopause was variable. Most studies did not comment on the type of endocrine therapies the patients were on. In all studies, outcomes were reported before and after laser treatment.

Figure 2 Forest Plots Show Improvement in the Vaginal Health Index Following Vaginal Laser Treatment



Abbreviations: CI = confidence interval; SD = standard deviation.

Risk of Bias of Included Studies

The Newcastle Ottawa Scale (NOS) was used to assess the quality of studies. A 'star system' has been developed, in which a study is judged on 3 broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest. This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies to perform a quality assessment of cross-sectional studies for the purposes of this systematic review. This modified scale has been used by several other studies that have felt the need to adapt the NOS scale to appropriately assess the quality of cross-sectional studies.[31]

The risk of bias assessments are summarized in Table 2.

Synthesis of Results

A meta-analysis was undertaken for all outcomes that were represented in more than 3 studies. Seven studies analyzed the VHI, 4 studies analyzed the VAS for dyspareunia, 5 studies analyzed the VAS for vaginal dryness, 3 studies reported on the FSFI, and 6 studies reported on satisfaction/improvement rates.

VHI. Seven studies reported on the VHI, all of which reported an improvement, but only 5[21,22,24,26,29] were used for the meta-analysis as they gave pre- and post-treatment scores. There was a significant improvement in VHI scores post-treatment (mean difference, −11.35; 95% CI, −11.76 to −10.94). Two further studies[25,30] reported a significant improvement ($P < .01$) but could not be used for the meta-analysis as the individual scores pre- and post-treatment were not provided. Results are shown in Figure 2.

VAS: Dyspareunia. Four studies were used for this analysis,[22-24,27] all of which showed an improvement (mean difference, 2.22; 95% CI, 1.98-2.46). Results are shown in Figure 3.

VAS: Dryness. Five studies were used for this analysis,[22-24,27,28] all of which showed an improvement (mean difference, 2.72; 95% CI, 2.50-2.93). Results are shown in Figure 4.

Sexual Function. Three studies[21,23,25] used the FSFI to assess sexual function before and after treatment, and all studies showed an improvement in sexual function.

Overall Satisfaction. Of patients undergoing treatment, 83.53% experienced improvement/satisfaction following treatment (Table 3).

Adverse Events

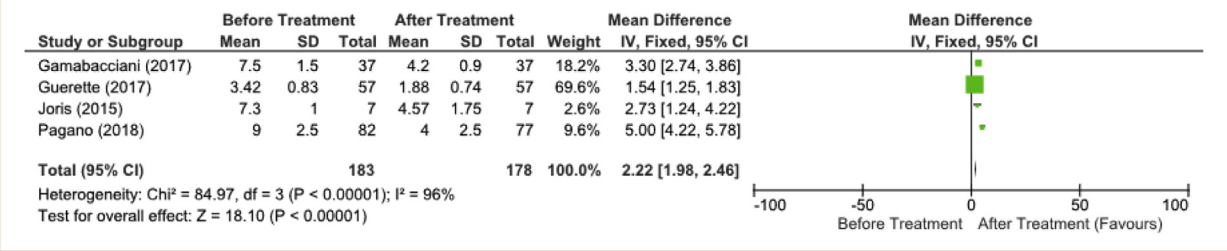
Nine studies reported no adverse effects from treatment. Pagano et al[27] reported adverse effects in 3 of 82 patients who discontinued treatment owing to discomfort after 2 cycles.

Conclusion

Principal Findings

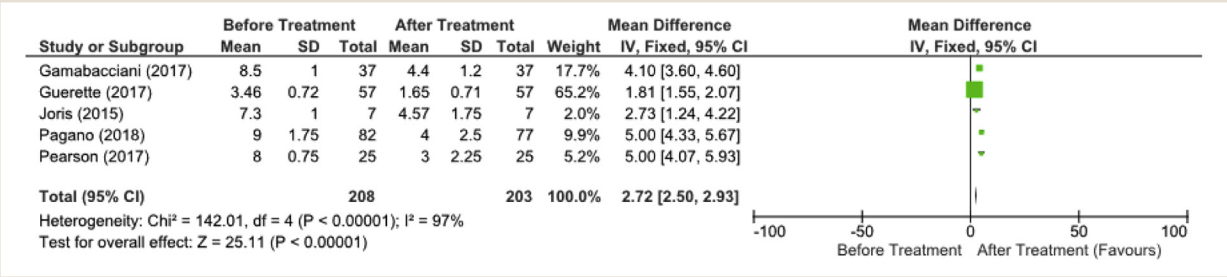
This systematic review shows that vaginal laser treatment may result in objective and symptomatic improvement in vaginal health

Figure 3 Visual Analog Scale: Dyspareunia. Forest Plots Show Improvement in Dyspareunia Following Vaginal Laser Treatment



Abbreviations: CI = confidence interval; SD = standard deviation.

Figure 4 Visual Analog Scale: Vaginal Dryness. Forest Plots Show Improvement in Vaginal Dryness Following Vaginal Laser Treatment



Abbreviations: CI = confidence interval; SD = standard deviation.

in BC survivors in the short term. There appeared to be an improvement in VHI and the VAS scores for dyspareunia and vaginal dryness following treatment. Sexual function appeared to improve, and overall satisfaction was in excess of 80%. Very few adverse events were reported. These included transient irritation and discharge that was generally mild and self-limiting. The procedure was well-tolerated, with few patients unable to complete the course of treatment. The duration of effect was, however, mainly limited to short-term follow-up (4-12 weeks), with one study reporting on 24-month outcomes. There are no reports of major long-term complications such as vaginal stenosis or ulceration, but patient follow-up was limited.

The majority of women included in these studies were on some form of antiestrogen therapy, either tamoxifen or an AI. AIs are linked to more marked vaginal changes than tamoxifen, which has a partial estrogen agonist effect on gynecologic tissues, whereas the AIs reduce circulating estrogen levels to almost undetectable levels. It was not possible to undertake subgroup analysis to assess whether vaginal laser is equally effective in both groups of women.

To date, no randomized controlled trial comparing topical estrogen cream with vaginal laser has been undertaken in BC survivors. The feasibility of conducting such a trial needs to be explored. However, such studies have been performed in the non-BC/normal menopausal setting and have shown equivalent efficacy.

Strengths and Weaknesses of the Study

There are several limitations to this systematic review, and these relate to the lack of robust studies or well-conducted trials that could be included in the review. Although the data from this review and meta-analysis support the use of vaginal laser therapy in the post-BC setting for GSM, more data is needed about longevity of effect and cost-effectiveness before this can be implemented in clinical practice.

None of the studies included in the systematic review were randomized control trials, and blinding of results was not performed in any of the studies. Five of the 10 studies were conference abstracts with limited data available. Follow-up was limited to the short term, with only one study reporting on 24-month outcomes.[32] In addition, none of the studies carried out a formal sample size calculation; therefore, it is difficult to know if the studies were adequately powered to answer the research question.

Lastly, none of the studies included in this review examined in detail the complex underpinnings of sexual dysfunction post-BC. GSM will have a significant negative impact on sexual intimacy for these women and their partners, but BC affects sexuality and relationships much more widely, with lack of confidence, body image concerns, fatigue, and depression all contributing. Dealing with the GSM for these women and their partners may help them to restore their intimate relationship but may not, in isolation, be enough to restore them to their pre-BC state.

Table 3 Percentage Improvement in Symptoms or Satisfaction Following Vaginal Laser Therapy

Study	Percentage Improvement/ Satisfaction
Gambacciani (2017)[22]	96.1
Maggiori (2015)[25]	77.5
Mothes (2018)[26]	93.7
Pearson (2017)[28]	85
Pieralli (2016)[29]	58.9
Sciblia (2017)[30]	90

Strengths and Weaknesses Related to Other Studies

Pitsouni et al[33] and Salvatore et al[34] carried out a systematic review of vaginal laser treatment in menopausal women with GSM in the absence of a diagnosis of BC. In their reviews, the number of patients included was greater, and the outcomes amenable to a meta-analysis included sexual function, vaginal maturation index (VMI), and urinary symptoms including urinary incontinence and burning. They also carried out a subgroup analysis of the CO_2 laser, which was not possible with our review. Similar to our review, both these studies showed an overall improvement in all parameters with minimal adverse events reported.

None of the studies report consensus on the number of treatment sessions recommended. In addition, there are no studies comparing the 2 types of vaginal laser.

Future Research

More research is needed to assess the wider impact on different BC survivor subgroups (age, degree of GSM, and type of antiestrogen therapy) and to assess the health economic impact of therapy before it can be made available more widely. Vaginal laser therapy may have the potential to improve the quality of life for the many BC survivors who struggle with GSM. However, there are no

studies with long-term follow-up; hence, this should not be introduced into clinical practice until more robust evidence is available.

There are currently no studies comparing the 2 types of lasers, CO_2 and Erbium YAG, to establish if one is better than the other, although there appears to be equivalence. There is also no consensus on the number of treatments required for the different types of laser, need for repeat and top-up treatments, or adverse events in women undergoing top-up treatments, and research into all aspects of treatment is urgently required. A study using the Erbium laser found that the positive effects were maintained for up to 12 to 18 months after completion of treatment but may require repeat treatment as it is not a definitive cure of GSM.

A randomized trial to compare laser with no treatment or with topical estrogen in this group of patients, with subgroup analysis for different degrees of severity and with a detailed assessment of the psychological and quality of life impacts, is urgently needed. Detailed assessment of the health economic costs is needed to enable health funders to assess whether this technique is likely to be cost-effective.

Clinical Practice Points

- Vaginal laser therapy may be effective at improving the symptoms of GSM in women with a past history of BC with a potential response in the short term. This may be a useful, nonhormonal method of ameliorating this distressing symptom complex for BC survivors.
- However, patients need to be informed of the lack of long-term data on the procedure particularly after the recent United States Food and Drug Administration[35] guidance pertaining to vaginal rejuvenation. Laser treatment would be a last resort and only where other modalities have failed.

Disclosure

The authors have stated that they have no conflicts of interest.

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