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Title page

Title: The impact of vaginal laser treatment for genitourinary syndrome of the menopause in breast cancer survivors: a systematic review and meta-analysis

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Running Title: Systematic Review of Vaginal Laser for GSM in Breast cancer survivors.

Contribution to authorship

SJ and LW: Project conception and development, Data Analysis, Manuscript write up

PK: Data collection and analysis, Manuscript write up

Conflicts of Interest: None of the authors have any conflicts to declare

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Title: The impact of vaginal laser treatment for genitourinary syndrome of the menopause in breast cancer survivors: a systematic review and meta-analysis

Abstract (250 words)

Introduction: Genitourinary syndrome of the menopause (GSM) is caused by hypo-oestrogenism resulting in vaginal dryness, pain, dyspareunia and urinary tract infection. It is more severe and common in breast cancer (BC) survivors due to the severity of induced menopause following treatment i.e. chemotherapy, GnRH agonists/ antioestrogen therapy. It has a detrimental effect on quality of life. The gold standard therapy is topical oestrogen which is highly effective however is contraindicated in BC patients due 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 breast cancer associated GSM.

Methods: A systematic review and meta-analysis.

Results: 48 papers were identified revealing 10 observational studies of GSM symptoms before and after vaginal laser therapy with no randomised trials.

Vaginal laser was effective in treating GSM in BC survivors with improvement in vaginal health index, 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 is no long term data of 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.

Background

Breast cancer 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 breast cancer patients who are already post-menopausal at diagnosis will suffer a worsening of menopausal symptoms due to prolonged antioestrogen therapies (tamoxifen or an aromatase inhibitor for 5 or, increasingly 10 years). As survival rates at 5 years are now ~90%[2], there are many millions of breast cancer 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 the menopause (GSM) [3]. Genitourinary syndrome of the menopause is due to lack of oestrogenic stimulus to the vulva and vagina, causing atrophy of the vaginal wall, loss of elasticity, loss of the normal moisture and pH balance. This results in pain, irritation, burning, vaginal discharge, dyspareunia, repeated urinary tract infections and may significantly impact on intimate relations with their partner.

GSM affects 20-50% of women after the menopause [4-6]. In breast cancer patients, who undergo menopause at an accelerated rate (e.g., drug-induced such as with chemotherapy, or use of chemical ovarian suppression with GnRH agonists), or undergo a more severe degree of hypo-oestrogenic state due to use of aromatase inhibitor therapy, symptoms of GSM can occur sooner and be more severe than is found among those with a normal, paced menopause [7-9]. Symptoms are often not disclosed by patients due to 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 breast cancer patients (e.g., 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 the 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 gynaecological 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 which would alleviate symptoms i.e. oestrogen, is contraindicated in breast cancer survivors. Systemic hormone replacement therapy may have an adverse effect of breast cancer survival (HABITs Trial) and is contraindicated. However there is little data about the breast cancer recurrence risk associated with use of topical antioestrogen creams, with several small series showing no adverse effect on breast cancer but a marked improvement in GSM. However, women and their clinicians are rarely comfortable using topical oestrogens in the post breast cancer 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 (Er: Yag-laser) (Fotona Smooth^{TM} XS, Fotona, Ljubljana Slovenia) have been used in postmenopausal women with GSM. This has the advantage of being non hormonal and therefore carries no risk of worsening breast cancer survival outcomes. They have been shown to be equivalent in efficacy [15]. In the non-breast cancer setting, GSM in women who have undergone a normal menopause is significantly improved and the treatment seems to have equivalence to use of topical oestrogen, the gold standard[16].

The treatment works by inducing collagen remodelling 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 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 breast cancer associated GSM.

Materials and Methods

This systematic review of the literature followed the 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, Cochrane register of controlled trials (CCTR), Cochrane database of systematic reviews (CDSR), CINAHL and Google scholar were searched for studies that analysed the effect of Vaginal Laser treatment on women with GSM in breast cancer 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 two independent reviewers (SJ and PK). Full articles of all citations that were likely to meet the predefined selection criteria were obtained. Data was extracted independently by two authors (SJ and PK) and recorded on a data collection form. Any discrepancies were settled by discussion with the senior author (LW). 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 analysed, the tools used for assessment, any objective measurements of vaginal pathophysiology, adverse events and drop outs due to these effects. All studies included in the systematic review are shown in Table 1.

Study selection

The study population included women with breast cancer who had completed preliminary treatment for their cancer and suffered from GSM as a consequence. Any study which 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 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 six items, categorized into three 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. For categorical variables Mantel-Haenszel estimates were used with a random effects model to calculate odds ratios and their 95% confidence intervals (CIs).

Results

Study Selection

The search strategy revealed 48 references which were assessed for eligibility. 38 studies were excluded. 10 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 randomised 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 five 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 which duplicated data so was excluded from the analysis. There were no randomised controlled trials. The treatment protocol varied in the different studies ranging from 3-5 treatment sessions in the CO_2 laser treatment and 1-3 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 breast cancer varied and the age of the participants as well as time elapsed since the 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.

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 three 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 so as to appropriately assess the quality of cross-sectional studies [21].

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. 7 studies analysed the VHI, 4 studies the VAS for dyspareunia, 5 studies VAS for vaginal dryness. 3 studies reported on the FSFI and 6 studies reported on satisfaction/ improvement rates.

Vaginal Health Index: 7 studies reported on Vaginal health index, all of which reported an improvement but only 5 [22-26] 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, -10.94). Two further studies [27;28] reported a significant improvement ($p< 0.01$) 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.

Visual Analogue Scale (VAS) Dyspareunia: 4 studies were used for this analysis [22;24;29;30] all of which showed an improvement (Mean Difference 2.22; 95% CI 1.98, 2.46).

Results are shown in Figure 3

Visual Analogue scale (VAS) Dryness: 5 studies were used for this analysis [22;24;29-31]all of which showed an improvement (Mean Difference 2.72; 95% CI 2.50, 2.93).

Results are shown in figure 4.

Sexual Function: 3 Studies [23;27;29] used the Female Sexual Function Index (FSFI) to assess sexual function before and after treatment and all studies showed an improvement in sexual function.

Overall satisfaction: 83.53 % of patients undergoing treatment experienced improvement/satisfaction following treatment (Table 3).

Adverse events

Nine studies reported no adverse effects from treatment. Pagano [30] reported adverse effects in three out of 82 patients who discontinued treatment due 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 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 which 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 weeks to 12 weeks) with 1 study reporting on 24 months 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 antioestrogen therapy, either tamoxifen or an aromatase inhibitor. Aromatase inhibitors are linked to more marked vaginal changes than tamoxifen, which has a partial oestrogen agonist effect on gynaecological tissues whereas the AIs reduce circulating oestrogen 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 randomised controlled trials comparing topical oestrogen 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-breast cancer/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 which could be included in the review. Though the data from this review and meta-analysis support the use of vaginal laser therapy in the post breast cancer 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 randomised control trials and blinding of results was not performed in any of the studies. Five of the ten 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 breast cancer. Genitourinary syndrome of the menopause will have a significant negative impact on sexual intimacy for these women and their partners, but breast cancer 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 breast cancer state.

Strengths and Weaknesses related to other studies:

Pitsouni [33] and Salvatore [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 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 breast cancer survivor subgroups (age, degree of GSM, and type of antioestrogen 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 breast cancer survivors who struggle with GSM, however there are no studies with long term follow up hence this should not be introduced into clinical practice till more robust evidence is available.

There are currently no studies comparing the two types of laser, CO_2 and Erb: Yag to establish if one is better than the other, though 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 Erbium laser found that the positive effects were maintained for up to 12-18 months after completion of treatment but may require repeat treatment as it is not a definitive cure of GSM.

A randomised trial to compare laser with no treatment or with topical oestrogen 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 breast cancer with a potential response in the short term. This may be a useful, non-hormonal method of ameliorating this distressing symptom complex for breast cancer survivors. However patients need to be informed of the lack of long term data on the procedure particularly after the recent FDA[35] guidance pertaining to vaginal rejuvenation. Laser treatment would be a last resort and only where other modalities have failed.

Reference List

(1) Maddams J, Utley M, Moller H. Projections of cancer prevalence in the United Kingdom, 2010-2040. *Br J Cancer* 2012;107:1195-1202.

(2) DeSantis CE, Lin CC, Mariotto AB et al. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin* 2014;64:252-271.

(3) Portman DJ, Gass ML. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Maturitas* 2014;79:349-354.

(4) Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *N Engl J Med* 2007;357:762-774.

(5) Santoro N, Komi J. Prevalence and impact of vaginal symptoms among postmenopausal women. *J Sex Med* 2009;6:2133-2142.

(6) Mac Bride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. *Mayo Clin Proc* 2010;85:87-94.

(7) Chin SN, Trinkaus M, Simmons C et al. Prevalence and severity of urogenital symptoms in postmenopausal women receiving endocrine therapy for breast cancer. *Clin Breast Cancer* 2009;9:108-117.

(8) Lester J, Crosthwaite K, Stout R et al. Women with breast cancer: self-reported distress in early survivorship. *Oncol Nurs Forum* 2015;42:E17-E23.

(9) Nappi RE, Kokot-Kierepa M. Women's voices in the menopause: results from an international survey on vaginal atrophy. *Maturitas* 2010;67:233-238.

(10) Nappi RE, Palacios S. Impact of vulvovaginal atrophy on sexual health and quality of life at postmenopause. *Climacteric* 2014;17:3-9.

(11) Rosenberg SM, Partridge AH. Premature menopause in young breast cancer: effects on quality of life and treatment interventions. *J Thorac Dis* 2013;5 Suppl 1:S55-S61.

(12) Kingsberg S, Kellogg S, Krychman M. Treating dyspareunia caused by vaginal atrophy: a review of treatment options using vaginal estrogen therapy. *Int J Womens Health* 2010;1:105-111.

(13) Lester JL, Bernhard LA. Urogenital atrophy in breast cancer survivors. *Oncol Nurs Forum* 2009;36:693-698.

(14) Lester J, Pahouja G, Andersen B, Lustberg M. Atrophic vaginitis in breast cancer survivors: a difficult survivorship issue. *J Pers Med* 2015;5:50-66.

(15) Karcher C, Sadick N. Vaginal rejuvenation using energy-based devices. *Int J Womens Dermatol* 2016;2:85-88.

(16) Cruz VL, Steiner ML, Pompei LM et al. Randomized, double-blind, placebo-controlled clinical trial for evaluating the efficacy of fractional CO2 laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women. *Menopause* 2018;25:21-28.

(17) Salvatore S, Leone Roberti MU, Athanasiou S et al. Histological study on the effects of microablative fractional CO2 laser on atrophic vaginal tissue: an ex vivo study. *Menopause* 2015;22:845-849.

(18) Athanasiou S, Pitsouni E, Antonopoulou S et al. The effect of microablative fractional CO2 laser on vaginal flora of postmenopausal women. *Climacteric* 2016;19:512-518.

(19) Sokol ER, Karram MM. Use of a novel fractional CO2 laser for the treatment of genitourinary syndrome of menopause: 1-year outcomes. *Menopause* 2017;24:810-814.

(20) Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-2012.

(21) McPheeters ML, Kripalani S, Peterson NB et al. Closing the quality gap: revisiting the state of the science (vol. 3: quality improvement interventions to address health disparities). *Evid Rep Technol Assess (Full Rep)* 2012;1-475.

(22) Gambacciani M, Levancini M. Vaginal erbium laser as second-generation thermotherapy for the genitourinary syndrome of menopause: a pilot study in breast cancer survivors. *Menopause* 2017;24:316-319.

(23) Becorpi A, Campisciano G, Zanotta N et al. Fractional CO2 laser for genitourinary syndrome of menopause in breast cancer survivors: clinical, immunological, and microbiological aspects. *Lasers Med Sci* 2018;33:1047-1054.

(24) Joris A, Rozenberg S. A New Fractionated CO2 laser to treat vulvovaginal atrophy in breast cancer patients. *Maturitas* 2015;81:159-160.

(25) Mothes AR, Runnebaum M, Runnebaum IB. Ablative dual-phase Erbium:YAG laser treatment of atrophy-related vaginal symptoms in post-menopausal breast cancer survivors omitting hormonal treatment. *J Cancer Res Clin Oncol* 2018;144:955-960.

(26) Pieralli A, Fallani MG, Becorpi A et al. Fractional CO2 laser for vulvovaginal atrophy (VVA) dyspareunia relief in breast cancer survivors. *Arch Gynecol Obstet* 2016;294:841-846.

(27) Leone Roberti MU, Parma M, Candiani M, Salvatore S. Microablative Fractional CO2 Laser for Vulvovaginal Atrophy in Women With a History of Breast Cancer. *J Minim Invasive Gynecol* 2015;22:S100.

(28) Scibilia G, Scollo P et al. CO2 Laser as a treatment option for genito urinary syndrome of menopause (GSM) in oncologogical patients: Preliminary results. American Society for Laser Medicine and Surgery Abstracts; 2017.

(29) Gueretta N. Novel Hybrid Fractional Erbium Yag Laser: Short Term outcomes for treatment of Genito urinary syndrome of menopause and Dyspareunia. IUGA academy. 2017.
Ref Type: Report

(30) Pagano T, De RP, Vallone R et al. Fractional microablative CO2 laser in breast cancer survivors affected by iatrogenic vulvovaginal atrophy after failure of nonestrogenic local treatments: a retrospective study. *Menopause* 2017;25:1-6.

(31) Pearson A, Booker A et al. Symptomatic improvment of vulvovaginal atrophy in breast cancer patients using vaginal laser therapy: report from LAAVA pilot study. COSA 44th Annual Scientific Meeting; 2017.

(32) Gambacciani M, Levancini M, Russo E, Vacca L, Simoncini T, Cervigni M. Long-term effects of vaginal erbium laser in the treatment of genitourinary syndrome of menopause. *Climacteric* 2018;21:148-152.

(33) Pitsouni E, Grigoriadis T, Falagas ME, Salvatore S, Athanasiou S. Laser therapy for the genitourinary syndrome of menopause. A systematic review and meta-analysis. *Maturitas* 2017;103:78-88.

(34) Salvatore S, Pitsouni E, Del DF, Parma M, Athanasiou S, Candiani M. Sexual Function in Women Suffering From Genitourinary Syndrome of Menopause Treated With Fractionated CO2 Laser. *Sex Med Rev* 2017;5:486-494.

(35) FDA. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm615130.htm. 30-7-2018.

Ref Type: Online Source

Reporting Checklist for Meta-analyses of Observational Studies (MOOSE) for PLoS Medicine

	Reported?	MS page
Reporting of background should include:		
Problem definition	Yes	4-5
Hypothesis statement	Yes	5
Description of study outcome(s)	Yes	7
Type of exposure or intervention used	Yes	6
Type of study designs used	Yes	6
Study population	Yes	6
Reporting of search strategy should include:		
Qualifications of searchers (eg, librarians and investigators)	Yes	6
Search strategy, including time period included in the synthesis and keywords	Yes	6
Effort to include all available studies, including contact with authors	Yes	6
Databases and registries searched	Yes	6
Search software used, name and version, including special features used (eg, explosion)	Yes	6
Use of hand searching (eg, reference lists of obtained articles)	Yes	6

List of citations located and those excluded, including justification	Yes	Prisma
Method of addressing articles published in languages other than English	Yes	6
Method of handling abstracts and unpublished studies	Yes	6
Description of any contact with authors	Yes	6
Reporting of methods should include:		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	8
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	8
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	8
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Yes	8
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	7
Assessment of heterogeneity	Yes	7
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	7
Provision of appropriate tables and graphics	Yes	Attached Tables and Figures
Reporting of results should include:		
Graphic summarizing individual study estimates and overall estimate	Yes	Table 1
Table giving descriptive information for each study included	Yes	Table 1
Results of sensitivity testing (eg, subgroup analysis)	No	NA
Indication of statistical uncertainty of findings	No	NA
Reporting of discussion should include:		
Quantitative assessment of bias (eg, publication bias)	No	NA
Justification of exclusion (eg, exclusion of non-English-language citations)	Yes	Figure 1
Assessment of quality of included studies	Yes	Table 2
Reporting of conclusions should include:		
Consideration of alternative explanations for observed results	Yes	11
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	13
Guidelines for future research	Yes	13

Disclosure of funding source	Yes	1

Figure 1: Study selection criteria

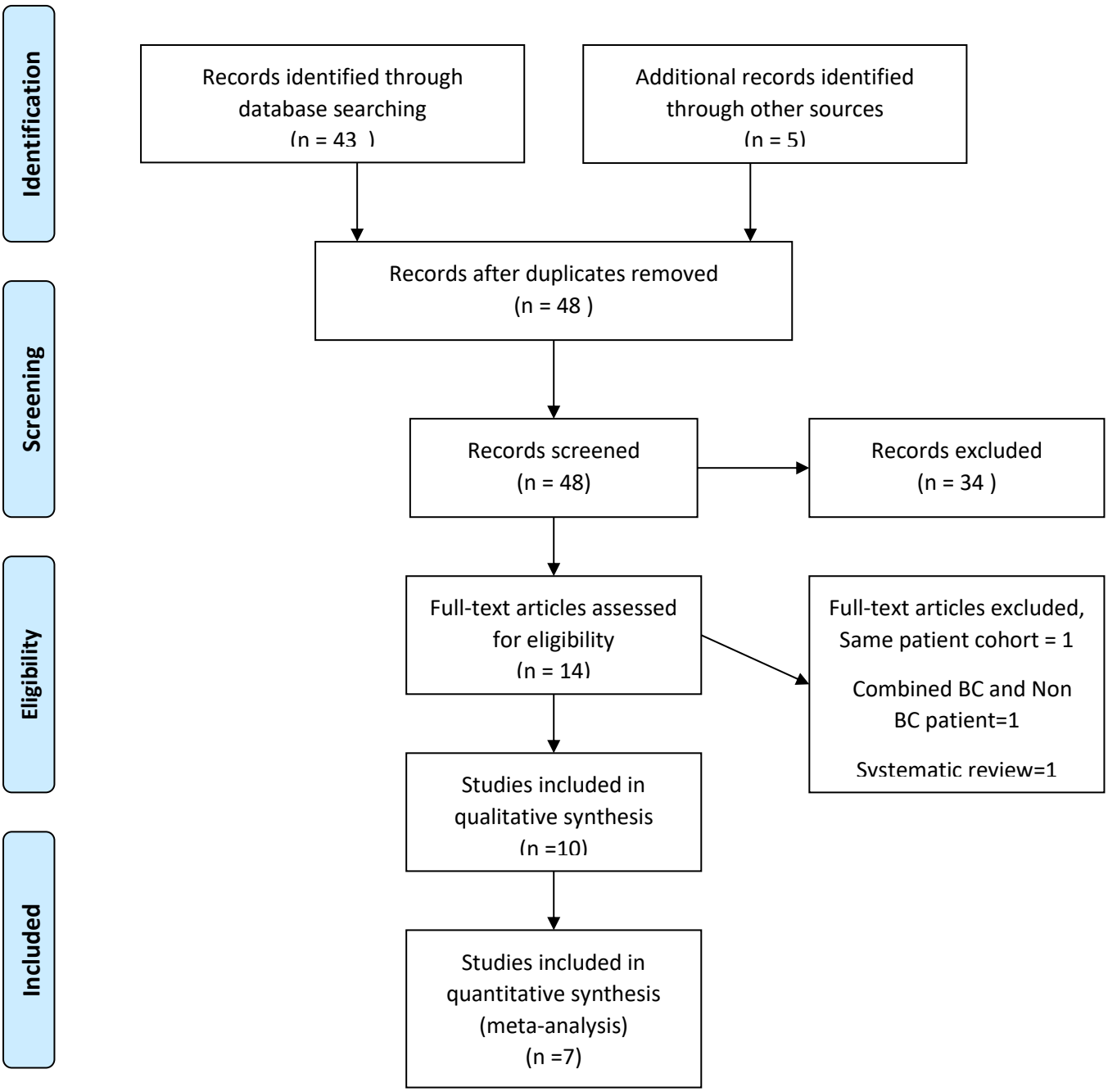


Table 1. Summary of included studies

Study Reference	Location	No of treatment Cycles	No of Patients	Average age of patients	Time period	Follow Up Period	Outcomes	Type of Laser
Becorpi (2017)[23]	Florence, Italy	2	20	58.2	December 2015-February 2015	4 weeks post final treatment	VHI, FSFI, VAS	CO_2 Microablative
Gamabaccciani (2017)[22]	Pisa, Italy	3	37	50.8	Not Stated	24 months post final treatment	VHI,VAS	Erbium YAG
Guerette (2017)[29]	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)[27]	Milan, Italy	5	40	-	Not Stated	4 weeks post final treatment	VHI, FSFI, QoL (SF12)	CO_2 Microablative
Mothes (2018)[25]	Jena, Germany	1	16	71	September 2016-June 2017	6 weeks post final treatment	VHI	Erbium YAG
Pagano (2018)[30]	Naples, Italy	3	82	44	April 2015-May 2017	30 days post final treatment	VAS	CO_2 Microablative
Pearson (2017)[31]	Sydney, Australia	3	25	55	February 2016-May 2017	4 weeks post final treatment	VAS	CO_2 Microablative

Pieralli (2016)[26]	Florence, Italy	3	50	53.3	June 2013-June 2015	11 months post final treatment	VHI, VAS	CO_2 Microablative
Scibilia (2017)[28]	Catania, Italy	3	20	-	Not Stated	3 months post final treatment	VHI, VAS, ICIQ	CO_2 Microablative

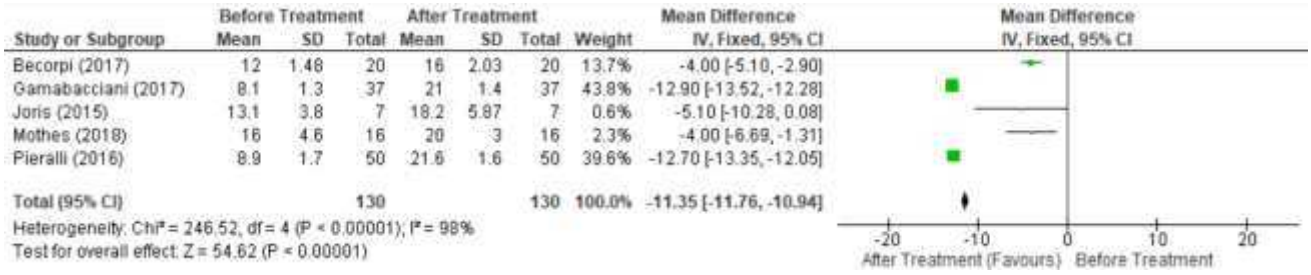
Table 2. Summary of the quality of included studies for risk of Bias (Newcastle Ottawa Scale)

	Selection (5 stars)				Comparability (2 Stars)	Outco (3 Sta	
	Representation *	Sample Size *	Ascertainment of Exposure **	Non Respondents *	Comparability **	Assessment of outcome **	S
Becorpi (2017)	*	-	**	-	**	-	
Gamabacciani (2017)	*	*	**	-	**	**	
Guerette (2017)	*	*	*	-	*	*	
Joris (2015)	*	-	*	-	*	*	
Maggiori(2015)	*	*	*	-	*	**	
Mothes (2018)	*	-	**	-	*	**	
Pagano (2018)	*	*	**	-	**	**	
Pearson (2017)	*	-	*	-	*	**	
Pieralli (2016)	*	*	**	-	**	**	
Scibilia (2017)	*	-	*	_	-	*	

Table 3. Table showing the percentage Improvement in symptoms or satisfaction following vaginal laser therapy.

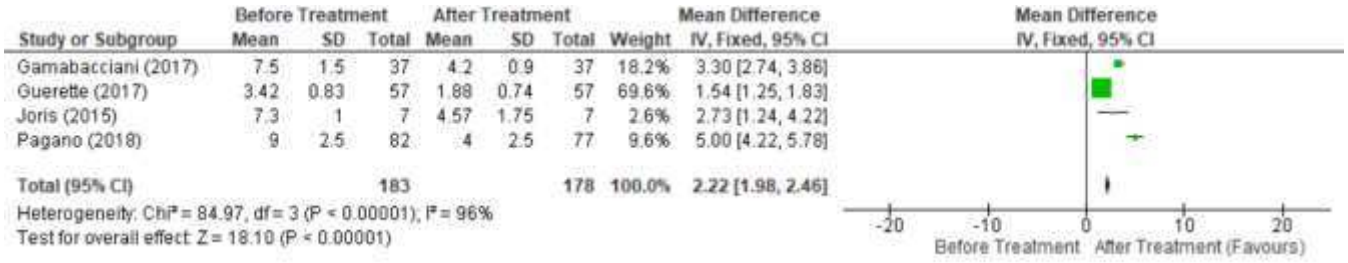
Study	Percentage improvement/satisfaction
Gambacciani (2017)	96.1
Maggiori (2015)	77.5
Mothes (2018)	93.7
Pearson (2017)	85
Pieralli (2016)	58.9
Sciblia (2017)	90

Figure 2: Vaginal Health Index (VHI)



Forest plots show improvement in the Vaginal health index following vaginal laser treatment.

Figure 3: VAS: Dyspareunia



Forest plots show improvement in the Dyspareunia following vaginal laser treatment.