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REVIEW ARTICLE

# Intravaginal energy-based devices and sexual health of female cancer survivors: a systematic review and meta-analysis

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## Abstract

A systematic review and meta-analysis was undertaken to assess the efficacy and safety of intravaginal energy-based therapies (laser and radiofrequency) on sexual health of cancer survivors (CS) (breast cancer (BCS) and/or gynecological cancer (GCS)). PubMed, Scopus, Web of Science, and Cochrane Library were searched until 21/02/2019. Quality of reporting, methodology, and body of evidence were assessed using STROBE, MINORS, and GRADE. Primary outcomes were dyspareunia, dryness, and sexual health (FSFI, FSDS-R). Secondary outcomes were burning, itching, dysuria, incontinence, Vaginal Health Index Score (VHIS), microbiome-cytokine evaluation, and adverse events. Main analyses, subgroup analyses, and sensitivity analyses were performed. Eight observational studies ($n = 274$) were eligible for inclusion. None of the studies evaluated radiofrequency. BCS and BCS-GCS were included in 87% and 13% of studies, respectively. All primary outcomes improved significantly with the exception of FSDS-R (dyspareunia (5 studies ($n = 233$), standardized mean difference (StdMD) (− 1.17), 95%CI [− 1.59, − 0.75]; $p < 0.001$; $I^2 = 55\%$), vaginal dryness (4 studies ($n = 183$), StdMD (− 1.98), 95%CI [− 3.31, − 0.65]; $p = 0.003$; $I^2 = 91\%$), FSFI (2 studies, $n = 28$, MD (12.79), 95%CI [7.69, 17.89]; $p < 0.001$; $I^2 = 0\%$). Itching, dysuria, and VHIS increased significantly, while burning was not improved. Serious adverse events were not observed by any of the studies. Intravaginal laser therapies appear to have a positive effect on dyspareunia, vaginal dryness, and FSFI of CS. However, the quality of evidence is "very low," with no data on intravaginal radiofrequency therapy. Further research with high-quality RCTs and long-term follow-up is needed to evaluate the value of energy-based devices as a therapeutic option for CS with sexual problems.

**Keywords** Laser · RF · Dyspareunia · Sexual distress · Vaginal atrophy · Menopause

## Introduction

Breast and gynecological cancer are among the most frequent types of female cancer [1]. Although modern therapies have increased the 5-year survival rates up to 98% (depending on cancer type, stage, etc.) [2], these may influence sexual function and affect significantly quality of life [3–7]. Surgery for gynecologic malignancies may cause anatomic and or neurologic disruption or rapid decline of estrogen levels or even psychological impact leading to sexual dysfunction. Pelvic radiotherapy may result in stenosis and fibrosis of the vagina, while chemotherapy may cause premature ovarian failure [4–7]. Long-term hormonal therapies (HT) with estrogen blockers in patients with hormone-responsive cancers may induce iatrogenic menopause in patients receiving the therapy, resulting in severe atrophic vaginitis [4–7]. It has been estimated that sexual dysfunction affects ≥ 50% of CS [4–6]. Moreover, young women or women who are sexually active at time of cancer diagnosis may experience even more stressful sexual problems [6].

Dyspareunia, vaginal dryness and decreased desire, arousal, and orgasm are among the most frequent sexual problems

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of CS [4–6]. Other symptoms of the genitourinary syndrome of menopause (GSM), such as lower urinary tract symptoms, may also occur [7]. Treatment of such sexual problems in CS includes the use of local moisturizers, vaginal dilators, and therapy with vaginally administered estrogens [8], although evidence for the efficacy of the treatments is grade C [6]. There are limited data on nonhormonal therapies and sexual function of menopausal women [9]. Vaginal estrogens were found to be superior to lubricants in studies evaluating sexuality scores [9]. Nevertheless, women are reluctant to use vaginal estrogens due to safety concerns [10], while only 15% of oncologists consider hormonal therapies to be safe [11]. Patients with history of estrogen-dependent tumors should be offered the choice of therapy with vaginal estrogens only when nonhormonal therapies have failed, considering the risk-benefit ratio, at the lowest dose and only till symptom cessation [12].

During the last years, intravaginal energy-based devices (laser and radiofrequency) appear to deliver promising positive results on sexual health and GSM symptoms of healthy postmenopausal women [13–23]. In fact, there is evidence that energy-based therapies improve significantly sexual function and GSM symptoms and restore vaginal health to premenopausal status [13–25]. However, the efficacy on sexual health of CS has not been systematically analyzed yet.

The objective of this study was to systematically summarize and critically appraise evidence regarding efficacy of intravaginal energy-based devices on female CS (breast cancer survivors (BCS) and/or gynecological cancer survivors (GCS)) with sexual dysfunction. In particular, we aimed to qualitatively and quantitatively synthesize data of sexual function, GSM symptoms severity, and vaginal health before and after the intravaginal administration of energy-based devices or compare intravaginal energy-based therapies to other available therapies or placebo.

## Methods

PubMed, Scopus, Web of Science, and Cochrane library were searched until 21/02/2019 by two reviewers independently (EP, AD) using the following keywords: laser dyspareunia, laser vaginal dryness, laser sexual function, laser orgasm, laser vulvovaginal atrophy, laser vaginal atrophy, laser genitourinary syndrome of menopause, radiofrequency dyspareunia, radiofrequency orgasm, radiofrequency vaginal dryness, radiofrequency sexual function, radiofrequency vaginal atrophy, radiofrequency vulvovaginal atrophy, radiofrequency genitourinary syndrome of menopause. Eligible studies were those published in full text in peer-reviewed journals with impact factor, that evaluated the efficacy of intravaginal laser or radiofrequency on dyspareunia and/or vaginal dryness and/or sexual dysfunction of BCS and/or GCS (ovarian/endometrial/cervical). Studies that included both healthy postmenopausal women and CS were eligible to be included in this review as long as they provided data for CS separately (i.e., subgroup analyses). Older versions of studies were eligible to be included if they provided data that were not included in updated published studies. The study design or methodological quality or language of publication were not considered as exclusion criteria. A hand search of the references of all eligible articles was also performed to ensure complete coverage of the literature. "Gray" literature, such as reports (i.e., pre-prints, technical reports, preliminary progress and advanced reports, technical reports, market research reports), theses, conference proceedings, commercial documentations, and official documents not published commercially, was not searched. PRISMA guidelines were followed for conducting and reporting the present review.

Data extraction was performed by two independent reviewers (EP, AD) for the following aspects: First author, year of publication, study design, funding, type and settings of energy-based devices, therapeutic protocol, follow-up period, number and baseline characteristics of participants, tools of assessing sexual function, measurements of GSM symptoms (dyspareunia, dryness, vaginal bleeding, leukorrhea, burning, itching, dysuria, frequency, urgency, urinary incontinence(UI)) and vaginal health, patients satisfaction with therapy, adverse events and drop outs due to adverse events. Evaluation of dyspareunia and dryness intensity as well as sexual function were considered primary outcomes. All other outcomes were defined as secondary.

Two reviewers (EP, AD) independently evaluated quality of reporting, methodological quality of the included studies, and body of evidence of meta-analyzed outcomes using Strengthening the Reporting of Observational studies in Epidemiology (STROBE) [26], Methodological Index for Non-randomized studies (MINORS) [27], and GRADE system [28], respectively. The ideal score of MINORS for uncontrolled studies is 16 [27]. Any discrepancies were resolved by consensus of all authors. All studies that provided relevant data for each outcome were included in the meta-analyses regardless of study design or methodological quality. PRISMA guidelines were followed for conducting and reporting this review.

Heterogeneity and publication bias were assessed using $I^2$ statistics and funnel plots, respectively. Mean difference (MD) or standardized mean difference (StdMD) was used as summary statistic when the same outcome was assessed with the same or a variety of ways, respectively. RevMan version 5.3 was the statistical program that was used for all analyses using generic inverse variance as statistical method, random effects model, and differences in means or standardized means as effect measure. Meta-analysis was performed when $\geq 2$ studies were involved. Data transformation was performed wherever median values were reported [29]. The main analyses included the efficacy of energy-based devices on outcomes regardless of the type of energy-based device. Subgroup

analyses were performed based on type of energy-based device. Sensitivity analysis was performed based on number of applied therapies with and without considering the type of energy-based device.

## Results

Initially, 3272 articles were retrieved, while 8 studies ($n = 274$) [30–37] were eligible for inclusion in this systematic review and meta-analysis (Fig. 1).

Characteristics of studies included in this review are presented in Table 1. None of the studies were controlled trials; 5 ($n = 184$) were prospective [30, 33–36] and 3 ($n = 116$) retrospective [31, 32, 37] studies. None of the studies evaluated radiofrequency; 6 studies ($n = 242$) evaluated microablative fractional $CO_2$ laser (SmartXide$^2$ V$^2$LR, Monalisa Touch, DEKA, Florence, Italy) [30–32, 34, 36, 37], 1 study ($n = 15$) Fractional Pixel $CO_2$ laser (Femilift, Alma Lasers) [33] and 1($n = 43$) study Er:YAG laser (Fotona Smooth™ XS, Fotona, Ljubljana Slovenia) [35]. BCS and BCS-GCS were included in 7/8 (87%) [30, 31, 34–37] and 1/8 (13%) [33] of studies, respectively. Three- and two-therapy protocols were included in 7/8 (87%) [31–37] and 1/8 (13%) [30] of studies, respectively. Applied energy was not mentioned in 1/8 (13%) study [31] while it was the same, increased, or decreased compared to first application in 4/8 (50%) [30, 34–36], 2/8 (25%) [32, 37], and 1/8 (13%) [33] studies, respectively. Blinding of outcomes assessors and sample size calculation was not reported by any of the studies. Score of methodological quality of the studies ranged from 6 to 12.

Outcomes of included studies are presented in Table 1. Studies assessed outcomes using the following measurements: (1) Female Sexual Function Index (FSFI) [38, 39] and Female Sexual Distress Scale-Revised (FSDS-R) [40] for sexual health: FSFI includes six domains corresponding to sexual desire, arousal, pain, lubrication, orgasm, and satisfaction. Synthesis of these domains calculates a total score ranging from 2 to 36. Higher score indicates better sexual function. A cut-off score of 26.55 distinguishes women with normal sexual function from those with sexual dysfunction. FSDS-R provides a total score ranging from 0 to 52 with higher score indicating higher sex related distress. (2) Visual Analogue Scales (ranges 0–10 cm, 0–3 cm, and 0–5 cm) and Wong–Baker Faces Scale for GSM symptoms intensity and (3) International Consultation on Incontinence modular Questionnaire short form (ICIQ-UI) for urinary incontinence (UI) [41]: total score ranges from 0 to 20 with higher scores

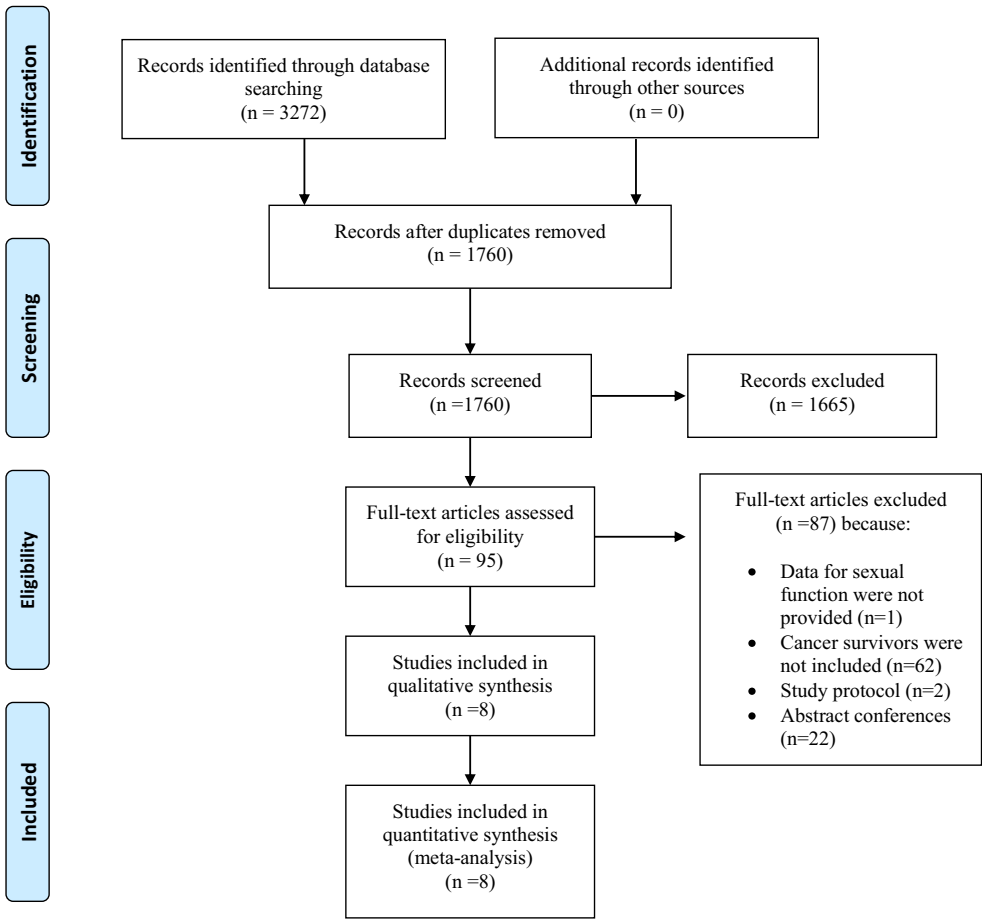


**Fig. 1** Identification process of studies included in this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram

**Table 1** Characteristics and outcomes of studies included in this review and meta-analysis

| First author/year/study design/funding [Ref] | Laser type/settings | Therapeutic protocol/ follow-up | No. | Baseline characteristics of participants | STROBE, MINORS | FSFI (total score) | FSD-R |
|---|---|---|---|---|---|---|---|
| Becorpi 2018<br>PUBA<br>Italian Ministry of Health [30] | MFCO2<br>(MonaLisa Touch) P: 30 W,<br>DT: 1000 μs<br>DS: 1000 μm<br>SmartStack:1 (same energy) | 2 therapies/1 month | 20 | Postmenopausal BCS with VVA diagnosis, average age 58.2, duration of menopausal status 8.85 ± 5.4 years. 16/20 (80%) received HT | 19/6/9,<br>10/16 | B: 27.5<br>[4–54.5]<br>A: 43<br>[20.25–70.50]† | B: 21<br>[10–28]<br>A: 15<br>[8–24] |
| Gittens 2018<br>RU<br>None [31] | MFCO2<br>(MonaLisa Touch)/NR | 3 therapies<br>(at 6 weeks intervals)/approx 1 month | 8 | Menopausal BCS with GSM, mean age 55.2 ± 9.5, average duration of symptoms 9.4 ± 7.6 years. 8/25 (32%) received HT | 20/5/9,<br>9/16 | Improve<br>12.48 ± 7.7† | Improve<br>18.7 ± 9.25† |
| Pagano 2018<br>RU<br>None [32] | MFCO2<br>(MonaLisa Touch) P: 30 W,<br>DT: 1000 μs<br>DS: 1000 μm<br>SmartStack:1–3<br>(increased energy) | 3 therapies<br>(at 30–40 days intervals)/1 month | 82 | Menopausal BCS with VVA, median age 44 years. 37/61(61%) received AIs and 23/61 (38%) Tamoxifen and 1/61 (1%) NR | 29/2/3,<br>6/16 | NR | NR |
| Pagano 2017<br>PUBA<br>NR [33] | FPCO2<br>(Femilift)<br>30 W, 6–100 mJ/ppxl, higher laser mode, 0.5 Hz with 81 pixels (decreased energy) | 3 therapies<br>(at monthly intervals)/3 months | 15 | Menopausal (surgical) cancer survivors (20% ovarian, 27% cervical, 7% breast, and 46% endometrial) with VVA, mean age 46.1 ± 6.6, mean years since menopause 5.4 ± 5.1 | 24/3/7,<br>11/16 | NR | NR |
| Pieralli 2017 PUBA<br>NR [34] | MFCO2<br>(MonaLisa Touch) P: 30 W,<br>DT: 1000 μs<br>DS: 1000 μm<br>SmartStack:1 (same energy) | 3 therapies<br>(at 4 weeks intervals)/up to 24 months | 56 | Menopause induced by chemotherapy or surgery in BC patients (current or with a history) with VVA, mean age 53.76 and mean years since menopause onset 6.3 | 24/4/6,<br>10/16 | NR | NR |
| Gambacianni 2017<br>PUBA<br>None [35] | Er:YAG<br>(XS Fotona Smooth)<br>Fluence 6.0 J/cm$^2$, frequency 1.6 Hz, spot size 7 mm (same energy) | 3 therapies<br>(at 30 days intervals)/up to 18 months | 43 | Postmenopausal BCS with GSM, mean age 50.8 ± 8.1, duration of menopause 9.0 ± 4.0 years | 22/6/7,<br>12/16 | NR | NR |
| Pieralli 2016 PUBA<br>NR [36] | MFCO2<br>(MonaLisa Touch) P: 30 W,<br>DT: 1000 μs<br>DS: 1000 μm<br>SmartStack:1 (same energy) | 3 therapies<br>(at 4 weeks intervals)/up to 25 months | 50 | Menopausal (oncologic) BC patients (current or with a history) with VVA, mean age 53.3, mean years of menopause 6.6. 2/50 (4%) received AIs and 20/50 (40%) tamoxifen | 20/6/8,<br>12/16 | NR | NR |
| Pagano 2016<br>RU<br>None [37] | MFCO2<br>(MonaLisa Touch) P: 30 W,<br>DT: 1000 μs<br>DS: 1000 μm<br>SmartStack:1–3 (increased energy) | 3 therapies<br>(at 30–40 days intervals)/1 month | 26 | Menopausal (oncologic) BCS with VVA due to CT/HT-related menopause. 1/26 (4%) received AIs and 25/26 (96%) tamoxifen | 21/4/9,<br>9/16 | NR | NR |

| First author/year/study design/funding [Ref] | Dyspareunia | Dryness | Itching, burning, dysuria | VHIS | Patients satisfaction with therapy | Adverse events |
|---|---|---|---|---|---|---|
| Becorpi 2018<br>PUBA | B: 2 [2–3]<br>A: 2 [1–2]† | B: 2 [2–3]<br>A: 2 [1–2]† | B: 1 [0–2.75]<br>A: 1 [0–1]†, | B:12<br>[11–13] | NR | NR |

**Table 1** (continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| Italian Ministry of Health [30] | | | B: 1 [0–3]<br>A: 1 [0–1]†,<br>B: 0 [0–1.75]<br>A: 0 [0–0.75] | A: 16<br>[15.25–18]† | | |
| Gittens 2018<br>RU<br>None [31] | Improve<br>4.25 ± 3.45† | Improve<br>3.25 ± 3.33† | Improve<br>1.75 ± 3.06†,<br>Improve<br>2.75 ± 3.58†,<br>Improve<br>0.25 ± 0.71 | NR | NR | None |
| Pagano 2018<br>RU<br>None [32] | B: 9 (0–10)<br>A: 4 (0–10) † | B: 9 (3–10)<br>A: 4 (0–10)† | B: 7 (0–10)<br>A: 3 (0–10)†,<br>NR,<br>B: 3 (0–10)<br>A: 2 (0–8) | NR | NR | Discomfort related to procedure |
| Pagano 2017<br>PUBA<br>NR [33] | B: 7.6 ± 0.7<br>A: 3.8 ± 0.7† | NR | NR,<br>NR,<br>NR | B: 8.0 ± 3.0<br>A: 15.2 ± 4.4† | 100% of patients were satisfied | None |
| Pieralli 2017 PUBA<br>NR [34] | NR | NR | NR,<br>NR,<br>NR | NR | 93%, 80%, 86%, and 50% of patients were satisfied at 6, 12, 18, and 24 months, respectively | NR |
| Gambacianni 2017<br>PUBA<br>None [35] | B: 7.5 ± 1.5<br>A: 4.2 ± 1.5† | B: 8.5 ± 1.0<br>A: 4.7 ± 1.2† | NR,<br>NR,<br>NR | B: 8.1 ± 1.3<br>A: 20.0 ± 1.0† | NR | None |
| Pieralli 2016 PUBA<br>NR [36] | B: 5(1–5)<br>A: 3 (1–5)† | NR | NR,<br>NR,<br>NR | B: 8.9 ± 1.7<br>A: 21.6 ± 1.6† | 76% and 52% of patients were very satisfied or satisfied at 1 and up to 25 months, respectively | NR |
| Pagano 2016<br>RU<br>None [37] | B: 9 (5–10)<br>A: 2 (0–5)† | B: 10 (7–10)<br>A: 0 (0–5)† | B: 8 (2–10)<br>A: 2 (0–6)†,<br>NR,<br>B: 5 (0–10)<br>A: 0 (0–6) | NR | NR | None |

STROBE checklist was used for the quality of reporting of studies [26]. Each item of the STROBE checklist could take one of the following values: yes/no/not applicable. The numbers presented are the sum for each of these values. MINORS checklist was used for the assessment of the risk of bias of the included studies. Scores of 0, 1, or 2 are applied when the items are not reported, inadequately reported, or adequately reported, respectively. The numbers presented are the sum of these scores [27]. Patients satisfaction with therapy was assessed using 5-point Likert Scale; Becorpi 2018 [30]: Visual rating scale from 0 to 3 was used for the evaluation of symptoms intensity. Data are presented as median (25th–75th percentile range); Gittens 2018 [31]: Wong–Baker Faces Scale from 0 to 10 was used for the evaluation of symptoms intensity. Data are presented as mean ± SD; Pagano 2018 [32]: Visual Analogue Scale from 0 to 10 cm was used for the evaluation of symptoms intensity. Data are presented as mean (min-max). Percentages in parentheses describe the proportion of patients presenting with symptom; Pagano 2017 [33]: Visual Analogue Scale from 0 to 10 cm was used for the evaluation of symptoms intensity. Data are presented as mean ± SD; Gambacianni 2017 [35]: Visual Analogue Scale from 0 to 10 cm was used for the evaluation of symptoms severity. Data are presented as mean ± SD; Pieralli 2016 [36]: Visual Analogue Scale from 1 to 5 was used for the evaluation of symptoms intensity. Data are presented as median (min-max) and as mean ± SD; Pagano 2016 [37]: Visual Analogue Scale from 0 to 10 cm was used for the evaluation of symptoms intensity. Data are presented as median (min-max)

*PUBA* prospective uncontrolled before (the initiation of laser therapies) and after (the completion of laser therapies) study, *RU* retrospective uncontrolled study, *MFCO2* microablative fractional $CO_2$, *FPCO2* fractional pixel $CO_2$, *P* power, *DT* dwell time, *DS* dot spotting, *NR* not reported, *No.* number of patients, *BCS* breast cancer survivors, *VVA* vulvovaginal atrophy (*VVA* diagnosis included symptom of vaginal dryness, pH > 5, and at least a sign of vaginal atrophy), *GSM* genitourinary syndrome of menopause, *HT* hormone therapy, *AIs* aromatase Inhibitors, *FSFI* Female Sexual Function Index total score [38, 39], *FSD-R* Female Sexual Distress Scale-Revised [40]

† Statistically significant differences ($p < 0.05$)

indicating more severe UI. (4) Vaginal Health Index Score (VHIS) [42] and microbiome-cytokine analysis for vaginal health: VHIS evaluates vaginal tissue elasticity, epithelial integrity, moisture, volume, and pH of vaginal fluid. Total score ranges from 5 to 25, while > 15 defines non-atrophic status.

### Primary outcomes

In the main analyses (including 2- and 3-therapy protocols) 1 month following the last laser therapy, all outcomes improved significantly with the exception of FSDS-R (Figs. 2 and 3). The proportion of patients with dyspareunia and dryness before and after laser therapy was 98% and 100% versus 80% and 83%, respectively [32]. The significant improvement of symptom intensity at short term remained unchanged at 3-month (Fig. 2) and up to 12-month follow-up [35]. In the sensitivity analyses of 3-therapy protocol, a significant decrease of dyspareunia and dryness was also found ((StdMD (− 1.33), 95%CI (− 1.85, − 0.81); $p < 0.001$, $I^2 = 47\%$; $n = 178$) [30, 31, 35, 36] and (StdMD (− 2.51), 95%CI (− 3.76, − 1.26); $p < 0.001$, $I^2 = 80\%$; $n = 128$) [30, 31, 35], respectively). The quality of evidence rated "very low" for dyspareunia/dryness/sexual health (Supplemental Table 1).

### Secondary outcomes

In the main analyses (including 2- and 3-therapy protocols), 1-month following the last laser therapy, itching/dysuria/VHIS improved significantly, while burning was not improved (Fig. 2, Supplemental Fig. 1). The significant improvement of VHIS at short-term (MD (9.65), 95%CI [5.53, 13.77]; $p < 0.001$; $I^2 = 99\%$; $n = 113$ [30, 35, 36]) remained unchanged at 3-month (MD (9.3), 95%CI [4.99, 13.61]; $p < 0.001$; $I^2 = 86\%$; $n = 58$ [33, 35]) (Supplemental Fig. 1) and 12-month follow-up [35]. Sensitivity analysis for the 3-therapy protocol was not performed due to lack of studies. The body of evidence rated "very low" for itching/burning/dysuria/VHIS (Supplemental Table 1).

The proportion of patients with vaginal bleeding related to sexual intercourse and leukorrhea before and after 3-therapy protocol was 60% and 68% versus 45% and 45%, respectively [32].

Data for urinary frequency/urgency/urge incontinence were not provided by any of the studies. ICIQ-UI score decreased significantly from 10 ± 4 (mean ± SD) to 7.2 ± 5.1 in women with surgical-oncologic menopause and stress UI [33].

The proportion of bacteria in vaginal fluid as assessed by molecular and conservative (Gram staining) techniques was not improved after 2-therapy protocol [30]. Higher levels of cytokines were found after 2-therapy protocol for IL-18, CTACK, LIF, M-CSF, and IL-17, while lower levels for IL-1ra, IL-2, IL-7, IL-9, IL-13, eotaxin, GM-CSF, and RANTES [30].

Data regarding adverse events were provided by 63% (5/8) of the studies ($n = 148$) [31–33, 35, 37]. In these studies, no serious adverse events were observed. Patients discontinued therapies due to "persistent procedure-related discomfort" ($n = 3/148$ (2%)) and unknown reasons ($n = 2/148$ (1%)) [32].

### Subgroup analyses

Subgroup analyses for $CO_2$ laser (including 2- and 3-therapy protocols) confirmed the improvement of dyspareunia, dryness, and VHIS ((StdMD (− 0.97), 95%CI [− 1.28, − 0.67]; $p < 0.001$; $I^2 = 0\%$ ($n = 136$) [30–32, 36]), (StdMD (− 1.41, 95% [− 2.56, − 0.27]; $p = 0.02$; $I^2 = 80\%$ ($n = 110$) [30–32]) and (MD (8.51), 95%CI [0.27, 16.74]; $p = 0.04$; $I^2 = 100\%$; $n = 70$ [30, 36]), respectively) (Fig. 4, Supplemental Fig. 1). In the sensitivity analyses of 3-therapy protocol ($CO_2$ laser), a significant decrease was found for dyspareunia and dryness (StdMD (− 1.08), 95%CI [− 1.44, − 0.72]; $p < 0.01$; $I^2 = 0\%$ ($n = 116$)) [31, 32, 36] and StdMD (− 2.07, 95% [− 2.81, − 1.33]; $p < 0.001$; $I^2 = 10\%$ ($n = 90$) [31, 32], respectively). Subgroup analyses was not performed for the Er:YAG laser due to lack of studies.

## Discussion

Intravaginal energy-based devices have recently been proposed as a non-pharmacological therapeutic alternative for the management of GSM. Although they have not yet obtained FDA approval for this indication, data on effectiveness and safety in healthy postmenopausal women with GSM have already been published [13–23]. Various authors investigating intravaginal energy-based devices in healthy postmenopausal women with GSM extrapolate their results to CS with GSM. They advocate the hypothesis that most CS might benefit from these therapies, especially when estrogen-based HT is contraindicated. However, there are few studies with small number of participants evaluating the efficacy and safety of energy-based devices in CS, while there are no studies comparing the effect of therapies on healthy postmenopausal and cancer survivors. The majority of studies assessed BCS using $CO_2$ laser, while data regarding GCS or radiofrequency were scarce. The findings of the present meta-analysis indicate that dyspareunia, dryness, itching, dysuria, VHIS, and FSFI may improve significantly following the last laser therapy but the body of evidence is of "very low" quality. In addition, RCTs have not yet been published, the therapeutic protocols (number of therapies, level of applied energy) have not yet been standardized, and studies with long-term follow-up as well as assessment of quality of life are lacking.

Two laser technologies have been evaluated in CS: the $CO_2$ and the Er:YAG. These two lasers have different mode of actions as wavelength, penetration depth, emission mode,

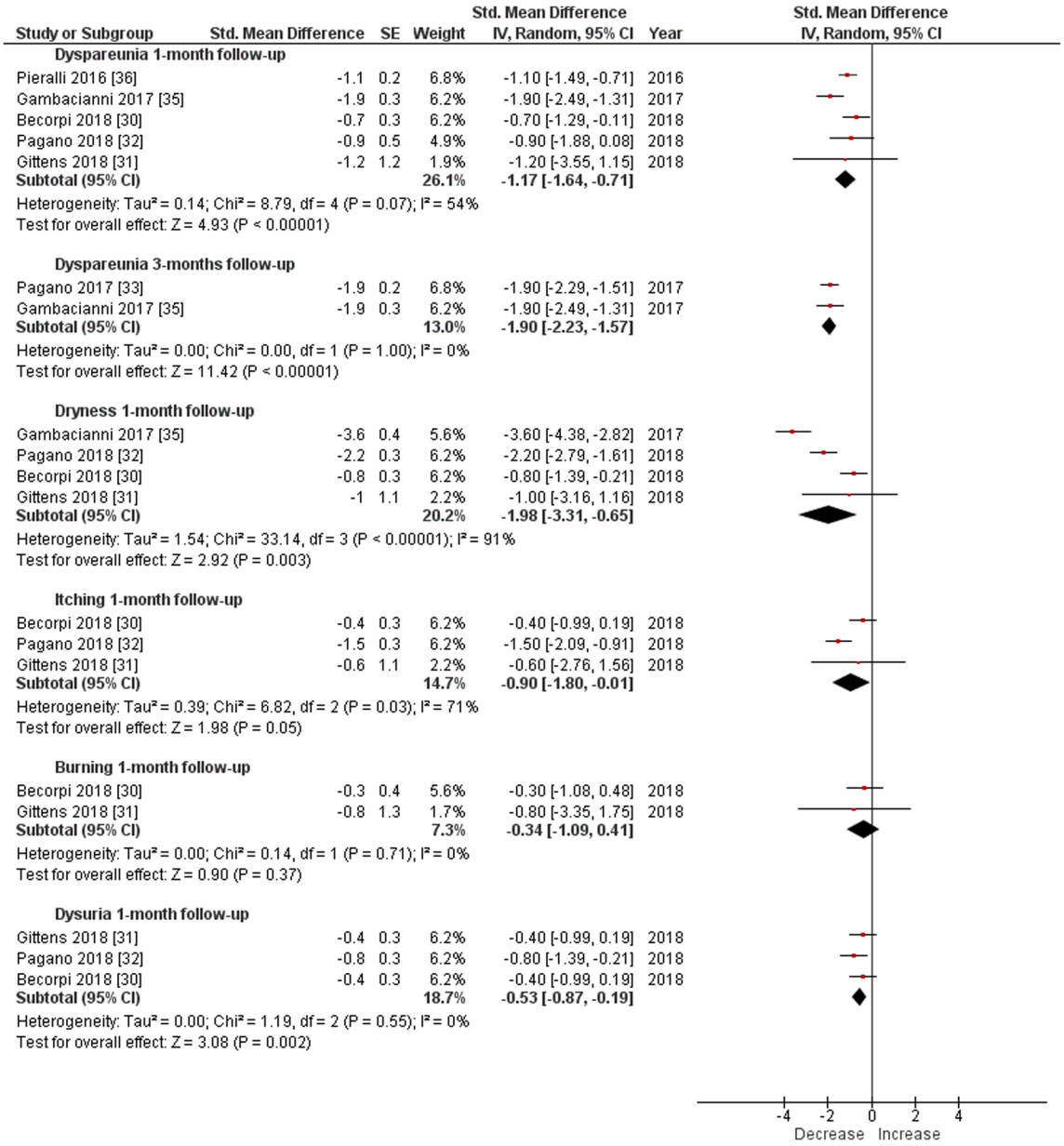


**Fig. 2** Forest plots of standardized mean differences between mean values of before the initiation of laser therapy and 1 month after the last laser therapy (1-month follow-up) or 3-month follow-up, including 2- and 3-therapy protocols and all energy-based devices for the outcomes: dyspareunia $n = 159$, vaginal dryness $n = 153$, Itching $n = 110$, burning $n = 28$, and dysuria n = 110 (assessed by Visual Analogue Scale (ranges 0–3 or 0–5 or 0–10) or Wong–Baker faces Scale (range 0–10))

and applied tissue laser energy varies [43]. In particular, $CO_2$ laser has a wavelength at 10.600 nm and produces a deep thermal and microablative effect, while Er:YAG laser has a wavelength at 2940 nm with photothermal effect [43]. Nevertheless, the mode of lasers' action seems to be independent to lasers beneficial effects on alleviating GSM symptoms and restoring vaginal mucosa to non-atrophic status, as suggested by the current literature on healthy postmenopausal women [15, 17–25, 44]. Moreover, the significant positive results can be maintained for more than 12 months for both lasers [15, 18–21, 44]. Thus, we performed this meta-analysis including both laser types and we used the "subgroup analysis" methodology depending on the type of laser.

BCS undergoing intravaginal laser therapies for dyspareunia and vaginal dryness may experience decrease in the intensity of their symptoms in a "dose-response" manner, as suggested by the present meta-analysis. In sensitivity analysis, using the 3-therapy protocol, a higher decrease in dyspareunia and vaginal dryness was found in comparison to the main analysis including 2- and 3-therapy protocols. A recent study found that in healthy postmenopausal women with GSM, extension of the therapeutic protocol to 4 or 5 laser

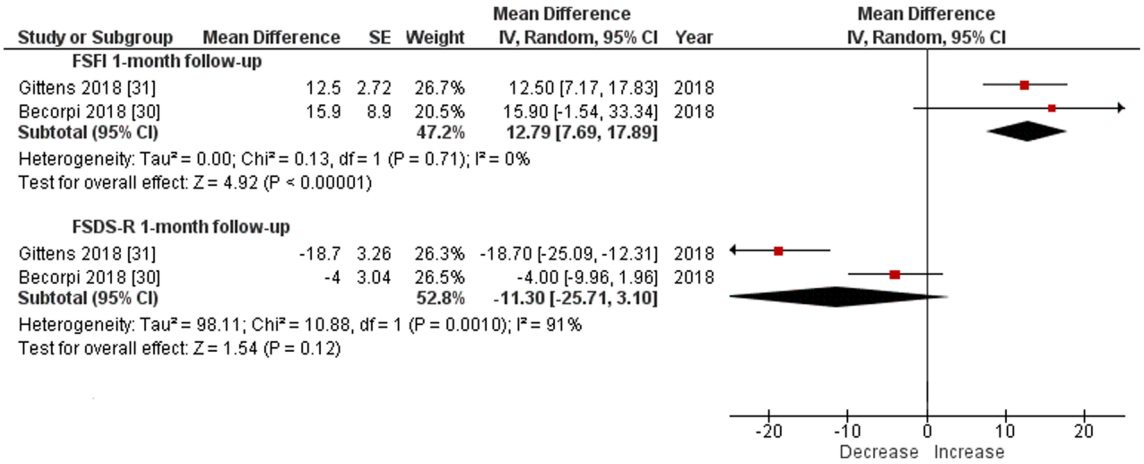


**Fig. 3** Forest plots of mean differences between mean values of before the initiation of laser therapy and 1 month after the last laser therapy (1-month follow-up) including 2- and 3-therapy protocols for sexual health ($n = 28$) assessed by Female Sexual Function Index (FSFI) and Female Sexual Distress Scale-Revised (FSDS-R)

sessions may have further improvement on symptom's severity and increase the proportion of symptom-free women up to 12-month follow-up [18, 45, 46]. It would be of interest if an additional fourth or fifth therapy might be beneficial for BCS, especially in those that seem unresponsive to therapies. Potential candidates could be women under tamoxifen as they are usually younger and often undergo combinations of therapies (i.e., tamoxifen plus GnRH agonists). Nevertheless, further research is required focusing on the type of antiestrogen/combination therapy used, as confounding factor to laser therapy response. In addition, it is of interest that the improvement of dyspareunia and dryness in this meta-analysis appeared to be heterogeneous among the included studies, while in a prior meta-analysis of laser's efficacy in healthy postmenopausal women with GSM, a consistent statistically significant decrease of these symptoms was apparent [16]. The latter further supports that research is required for safe conclusions to be obtained regarding response of laser therapy in CS.

Sexual dysfunction is a multifactorial condition including not only dyspareunia and vaginal dryness but also disorders of desire, arousal, orgasm, and satisfaction. FSFI assesses these aspects, but specific data for each domain are provided by just 1 study with 8 participants [31]. It is interesting that although total FSFI score increased significantly, FSDS-R remained unchanged. Perhaps, this discrepancy reflects either that there are only 2/8 (25%) studies ($n = 28$), assessing these aspects or that sexual distress is not only related to genital changes but also to body image perception or to psychological and intimacy changes [8]. Additionally, sexual distress may increase in cases where therapeutic efficacy does not meet patients' goals and expectations. It has been suggested

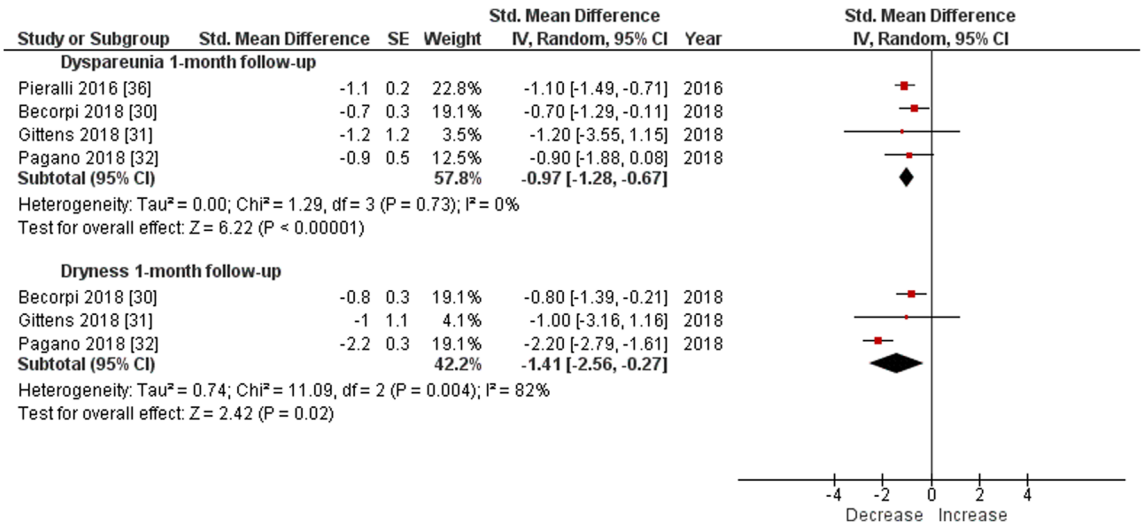


**Fig. 4** Forest plots of standardized mean differences between mean values of before the initiation of laser therapy and 1 month after the last laser therapy (1-month follow-up) using just $CO_2$ laser for dyspareunia ($n = 136$) and vaginal dryness ($n = 110$).

that a multidisciplinary approach is the best therapeutic approach in managing sexual health of CS [3]. However, such approach was not performed in the included studies.

Microbiological assessment of BCS did not find any significant differences following two laser therapies, but only a trend for increase of lactobacilli [30]. The effect might not be apparent due to the short follow-up and studies with longer follow-up might be needed to observe a potential long-term effect. The authors of this study stated that the stability of microbiological environment before and after laser application indicate the safety of these therapies [30]. Histopathological and cytological evaluation of healthy postmenopausal women have indicated that there are beneficial changes on vaginal mucosa (i.e., increased epithelial thickness, glycogen, vascularity) following three laser therapies [16]. These changes could have a positive impact on vaginal microenvironment as well. Indeed, a microbiological evaluation of vaginal fluid of healthy postmenopausal women with GSM observed a significant gradual increase in normal vaginal flora and lactobacilli accompanied by a decrease in uropathogens and pH values of the vaginal fluid following three laser therapies [22]. Discordance between the abovementioned studies including BCS or healthy postmenopausal women could be explained by the reduced number of therapies applied on BCS, or decreased level of applied energy at each session, or the use of antiestrogens or the relatively few studies in CS. In our opinion, a 2-therapy protocol and/or application of lower levels of energy are not adequate to restore the vaginal microenvironment to a healthier status in BCS.

A limitation of this study is the small sample size and the lack of controlled trials. Hence, possible placebo effect of the treatment could not be identified and comparisons with other available therapies could not be performed. Most of the studies assessed the use of $CO_2$ laser and studies are needed to assess other laser technologies such as the Er:YAG. In addition, a weakness of this analysis could be considered a short follow-up time of only 1 month, as different results may be observed at longer follow-ups. Another limitation of this study is inclusion of all relevant studies, regardless of study design or methodological quality in meta-analysis. Furthermore, some data were derived from subgroup analysis, regarding CS, of studies that were not focused in CS but in menopausal women with GSM in general. Nevertheless, the pre-specified study design of this review was to identify current evidence, regardless of the presence or not of controlled trials. Moreover, the included studies were published in peer-reviewed journals with impact factor and efforts were made to limit publication bias by including all available data and performing extensive search of databases and references, irrespective to the language of publication.

## Conclusions

CS with sexual problems could be considered ideal candidates for non-pharmacological therapies such as intravaginal energy-based devices, especially in the presence of hormone-dependent tumors. Available data suggests that dyspareunia, vaginal dryness, and FSFI may significantly improve following laser therapies. However, data are limited and of "very low" quality. Energy settings of the laser device and therapeutic protocols have not been standardized yet. Confounding factors have not yet been evaluated, while there is scarcity of data regarding the long-term efficacy of laser therapies and their impact on sexual function. High-quality RCTs comparing energy-based devices to other therapeutic modalities with large sample sizes, including assessment of sexual function and quality of life, are needed to clarify effectiveness and safety profile. In addition, long-term follow-up is of great importance as well as comparison of treatment results between healthy postmenopausal and CS.

### Compliance with ethical standards

**Conflict of interest** Stavros Athanasiou and Stefano Salvatore have had financial relations (expert testimonies and lectures) with DEKA Laser. The other authors report no potential conflicts of interest.

## References


1. Ferlay J, Colombet M, Soerjomataram I et al (2018) Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers 2018. EJC 103:356–387
2. Cancer Facts & Figures 2017. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf (Accessed on 13.02.2019)
3. Falk SJ, Dizon DS (2013) Sexual dysfunction in women with cancer. Fertil Steril 100:916–921
4. Dizon DS (2009) Quality of life after breast cancer: survivorship and sexuality. Breast J 15:500–504
5. Schover LR, van der Kaaij, van Dorst E, Creutzberg C, Huyghe E, Kiserud CE (2014) Sexual dysfunction and infertility as late effects of cancer treatment. EJC Suppl 12:41–53
6. Sadovsky R, Basson R, Krychman M et al (2010) Cancer and sexual problems. J Sex Med 7(349):373
7. Lester J, Pahouja G, Andersen B, Lustberg M (2015) Atrophic vaginitis in breast cancer survivors: a difficult survivorship issue. J Pers Med 5:50–66
8. Dizon DS, Suzin D, McIlvenna (2014) Sexual health as a survivorship issue for female cancer survivors. Oncologist 19:202–210
9. Pitsouni E, Grigoriadis T, Douskos A, Kyriakidou M, Falagas ME, Athanasiou S (2018) Efficacy of vaginal therapies on sexual function and orgasm of menopausal women: a systematic review and meta-analysis of randomized controlled trials. Eur J Obstet Gynecol Reprod Biol 229:45–56
10. Biglia N, Bounous VE, D'Alonzo M et al (2017) Vaginal atrophy in breast cancer survivors: attitude and approaches among oncologists. Clin Breast Cancer 17:611–617

11. Nappi RE, Palacios S, Panay N, Particco M, Krychman ML (2016) Vulvar and vaginal atrophy in four European countries: evidence from the European REVIVE Survey. Climacteric 19:188–197
12. ACOG Committee Opinion No 659 (2016) The use of vaginal estrogen in women with a history of estrogen-dependent breast cancer. Obstet Gynecol 127:e93–e96
13. Vanaman Wilson MJ, Bolton J, Jones IT, Wu DC, Calame A, Goldman MP (2018) Histologic and clinical changes in vulvovaginal tissue after treatment with a transcutaneous temperature-controlled radiofrequency device. Dermatol Surg 44: 705–713
14. Vicariotto F, DE Seta F, Faoro V, Raichi M (2017) Dynamic quadripolar radiofrequency treatment of vaginal laxity/ menopausal vulvo-vaginal atrophy: 12-month efficacy and safety. Minerva Ginecol 69:342–349
15. Gambacianni M, Levancini M, Russo E, Vacca L, Simoncini T, Cervigni M (2018) Long-term effects of vaginal erbium laser in the treatment of genitourinary syndrome of menopause. Climacteric 21:148–152
16. Pitsouni E, Grigoriadis T, Falagas ME, Salvatore S, Athanasiou S (2017) Laser therapy for the genitourinary syndrome of menopause. A systematic review and meta-analysis. Maturitas 103:78–88
17. Cruz VL, Steiner ML, Pompei LM et al (2018) 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 25:21–28
18. Athanasiou S, Pitsouni E, Grigoriadis T et al (2018) Microablative fractional CO2 laser for the genitourinary syndrome of menopause: up to 12-month results. Menopause. https://doi.org/10.1097/GME.0000000000001206
19. Gonzalez Isaza P, Jaguszewska K, Cardona JL, Lukaszuk M (2018) Long-term effect of thermoablative fractional CO2 laser treatment as a novel approach to urinary incontinence management in women with genitourinary syndrome of menopause. Int Urogynecol J 29: 211–215
20. Behnia-Willison F, Sarraf S, Miller J et al (2017) Safety and long-term efficacy of fractional CO2 laser treatment in women suffering from genitourinary syndrome of menopause. Eur J Obstet Reprod Biol 213:39–44
21. Sokol ER, Karram MM (2017) Use of a novel fractional CO2 laser for the treatment of genitourinary syndrome of menopause: 1-year outcomes. Menopause 24:810–814
22. Athanasiou S, Pitsouni E, Antonopoulou S et al (2016) The effect of microablative fractional CO2 laser on vaginal flora of postmenopausal women. Climacteric 19:512–518
23. Pitsouni E, Grigoriadis T, Tsiveleka A, Zacharakis D, Salvatore S, Athanasiou S (2016) Microablative fractional CO2-laser therapy and the genitourinary syndrome of menopause: an observational study. Maturitas 94:131–136
24. Zerbinati N, Serati M, Origoni M et al (2015) Microscopic and ultrastructural modifications of postmenopausal atrophic vaginal mucosa after fractional carbon dioxide laser treatment. Lasers Med Sci 30:429–436
25. Salvatore S, Pitsouni E, Del Deo F, Parma M, Athanasiou S, Candiani M (2017) Sexual function in women suffering from genitourinary syndrome of menopause treated with fractionated CO2 laser. Sex Med Rev 5:486–494
26. Vandenbroucke JP, von Elm E, Altman DG et al (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology 18:805–835
27. Slim K, Niki E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J (2003) Methodological index for non-randomized studies (MINORS): development and validation of a new instrument. ANZ J Surg 73:712–716
28. GRADE Handbook. http://gdt.guidelinedevelopment.org/app/handbook/handbook.html#h.wsfivfhuxv4r (Accessed on 12.02.2019)
29. Wan X, Wang W, Liu J, Tong T (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 14:135
30. Becorpi A, Campisciano G, Zanotta N et al (2018) Fractional CO2 laser for genitourinary syndrome of menopause in breast cancer survivors: clinical, immunological, and microbiological aspects. Lasers Med Sci 33:1047–1054
31. Gittens P, Mullen G (2018) The effects of fractional microablative CO2 laser therapy on sexual function in postmeopausal women and women with a history of breast cancer treated with endocrine therapy. J Cosmet Laser Ther. https://doi.org/10.1080/14764172.2018.1481510
32. Pagano T, De Rosa P, Vallone R et al (2018) Fractional microablative CO2 laser in breast cancer survivors affected by iatrogenic vulvovaginal atrophy after failure of nonestrogenic local treatments: a retrospective study. Menopause 25:657–662
33. Pagano I, Gieri S, Nocera F et al (2017) Evaluation of the CO2 laser therapy on vulvo-vaginal atrophy (VVA) in oncological patients: preliminary results. J Cancer Ther 8:452–463
34. Pieralli A, Bianchi C, Longinotti M et al (2017) Long-term reliability of fractionated CO2 laser as a treatment for vulvovaginal atrophy (VVA) symptoms. Arch Gynecol Obstet 296:973–978
35. Gambacianni M, Levancini M (2017) Vaginal erbium laser as second-generation thermotherapy for the genitourinary syndrome of menopause: a pilot study in breast cancer survivors. Menopause 24:316–319
36. Pieralli A, Fallani MG, Becorpi A et al (2016) Fractional CO2 laser for vulvovaginal atrophy (VVA) dyspareunia relief in breast cancer survivors. Arch Gynecol Obstet 294:841–846
37. Pagano T, De Rosa P, Vallone R et al (2016) Fractional microablative CO2 laser for vulvovaginal atrophy in women treated with chemotherapy and/or hormonal therapy for breast cancer: a retrospective study. Menopause 23:1108–1113
38. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr (2000) The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 26:191–208
39. Wiegel M, Meston C, Rose R (2005) The Female Sexual Function Index (FSFI): cross validation and development of clinical cutoff scores. J Sex Marital Ther 31:1–20
40. Derogatis L, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y (2008) Validation of the female sexual distress scale-revised for assessing distress in women with hypoactive sexual desire disorder. J Sex Med 5:357–364
41. Hajebrahimi S, Nourizadeh D, Hamedani R, Pezeshki MZ (2012) Validity and reliability of the international consultation on incontinence questionnaire-urinary incontinence short form and its correlation with urodynamic findings. Urol J 9:685–690
42. Weber MA, Limpens J, Roovers JPWR (2015) Assessment of vaginal atrophy: a review. Int Urogynecol J 26:15–28
43. Tadir Y, Gaspar A, Lev-Sagie A et al (2017) Light and energy based therapeutics for genitourinary syndrome of menopause: consensus and controversies. Lasers Surg Med 49:137–159

44. Gaspar A, Brandi H, Gomez V, Luque D (2017) Efficacy of erbium: YAG laser treatment compared to topical estriol treatment for symptoms of genitourinary syndrome of menopause. Lasers Surg Med 49:160–168
45. Mc Cabe MP, Sharlip ID, Atalla E et al (2016) Definitions of sexual dysfunctions in women and men: a consensus statement from the fourth international consultation on sexual medicine 2015. J Sex Med 13:135–143
46. Athanasiou S, Pitsouni E, Falagas ME, Salvatore S, Grigoriadis T (2017) CO2-laser for the genitourinary syndrome of menopause. How many laser sessions. Maturitas 104:24–28