Received: 9 November 2020 | Revised: 14 February 2021 | Accepted: 17 February 2021

DOI: 10.1111/tbj.14211

ORIGINAL ARTICLE

The Breast Journal WILEY

Fractional CO_2 vaginal laser for the genitourinary syndrome of menopause in breast cancer survivors

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Funding information
No specific funding was obtained for this study.

Abstract

Adjuvant chemotherapy and endocrine therapy can induce early iatrogenic menopause or worsen pre-existing menopausal symptoms in breast cancer survivors (BCS). The second most frequent menopausal symptom after hot flushes is the genitourinary syndrome (GSM). Since hormone replacement therapy is contraindicated in BCS, vaginal laser might represent a new nonhormonal option for GSM. This study aims at evaluating the effectiveness of the fractional CO_2 vaginal laser for GSM in BCS compared with healthy women. This is a retrospective study on 135 postmenopausal women (45 BCS and 90 healthy women) who underwent fractional CO_2 laser for GSM. Objective (VHI and VVHI) and subjective outcomes (VAS for dyspareunia and vaginal dryness and a pain questionnaire) were evaluated at baseline visit and at every follow-up visit. Subjective and objective parameters improved significantly in both groups after laser therapy. The improvement was progressive and long-lasting up to 12 months after the end of the treatment. No severe adverse events were observed during the treatment. Fractional CO_2 vaginal laser induces a significant and long-lasting improvement on GSM symptoms in BCS. However, this improvement is slower than in healthy women undergoing the same treatment. Laser therapy turns out to be safe and well-tolerated.

KEYWORDS
breast cancer survivors, vaginal atrophy, vaginal laser

1 | INTRODUCTION

The genitourinary syndrome of menopause (GSM)is a set of sexual, genital and urinary signs and symptoms associated with serum estrogen decline.[1] It represents an under diagnosed and poorly treated condition which occurs in about 50% of postmenopausal women.[2]

Hypoestrogenism leads to a thinning of the vaginal epithelium, an increase in pH, a lower vascularization of the subepithelium, a reduction of the elasticity of the vaginal walls and urethral atrophy, in addition to other anatomical changes. All these modifications lead to the typical symptoms of GSM, including genital dryness, dyspareunia, irritation or burning of vulva or vagina, decreased arousal, dysuria, and recurrent urinary tract infections. Contrarily to vasomotor symptoms, GSM is chronic and progressive if untreated.[3]

GSM is greater in breast cancer survivors (BCS)as a result of adjuvant therapy.[4] About 70% of BCS suffer from GSM[5,6] and about 28% of women undergoing adjuvant endocrine therapy report the intention to discontinue it due to side effects.[7] Breast cancer is the most frequently diagnosed cancer in women worldwide. Due to diagnostic anticipation and therapeutic progress, a significant drop in mortality was observed in the last decades, leading several women to face these problems long life, with a negative impact on the quality of life.[8]

As hormone replacement therapy is contraindicated in BCS,[9] current guidelines recommend nonhormonal moisturizers and lubricants

as first-line therapy for GSM in these patients,[10] even if these treatments provide a transient benefit only. Low-dose vaginal estrogens can be taken into consideration for BCS not responding to nonhormonal therapies, only after a careful evaluation of risks and benefits, especially in women undergoing aromatase inhibitors (AI) treatment.[10,11]

In this setting, nonpharmacological treatments such as vaginal laser, management of psychosocial distress, regular sexual activity, vaginal dilatators, and pelvic floor physical therapy play an important role in BCS.[12]

In 2010, the FDA approved CO_2 laser for incision, excision, ablation, vaporization, and coagulation in many medical specialities,[13] even if in 2018, the same agency stated that the safety and effectiveness of energy-based medical devices to treat vaginal symptoms related to menopause had not been established.[14]

Nevertheless, in 2011, Gaspar et al. first showed that the treatment with the fractional CO_2 vaginal laser led to a significant improvement in the clinical and histology of vaginal atrophy.[15] Recently, some articles have been published on the fractional CO_2 vaginal laser, and erbium laser both for healthy women[15-18] and BCS[19-23] with promising results and laser therapy has become one of the standard "non-hormonal" treatments for women with GSM.

The present study aims to confirm the safety and effectiveness of the fractional CO_2 vaginal laser for GSM in BCS compared with healthy women.

2 | MATERIALS AND METHODS

A retrospective analysis was carried out between January 2014 and April 2019 at the "SedesSapientiae Institute" and at the "Umberto I Hospital," in Turin, Italy.

During this time, frame 531 postmenopausal women received fractional CO2 laser therapy for GSM.

Eligibility criteria required for patients to receive fractional CO2 laser therapy were as follows: menopausal status (assessed as amenorrhea for at least 12 months or for six months with serum levels of estradiol ≤20 pg/ml and follicle-stimulating hormone ≥50 IU/l); negative cervical smear in the 12 months before the study; symptoms of GSM.

Exclusion criteria from laser treatment were as follows: active genital infection, BMI >40 kg/m2, use of photosensitizing drugs, inability to sign the informed written consent, use of drugs that may interfere with the efficacy and tolerability of the laser therapy, cervical smear with dysplasia or cancer, cerebrovascular and thromboembolic events in the last six months.

In the present study, 135 postmenopausal women with GSM symptoms were included: 45 BCS matched 1:2 for BMI and age to 90 patients in the comparison group without a history of breast cancer.

Figure 1 (consort diagram) explains the type of analysis performed. Seven relevant time points were considered for the evaluation of treatment results: baseline (T0), before the first laser application (T1), before the second laser application (T2), before the third laser application (T3), three months after the last laser application (T4), six months after the last laser application (T5), and 12 months after the last laser application (T6). Relevant demographic characteristics, pretreatment clinical data, and inclusion/exclusion criteria were recorded at T0.

Women were evaluated using objective and subjective parameters. Objective parameters included the Vaginal Health Index (VHI), and the Vulvo-Vaginal Health Index (VVHI) completed by the provider at each time point of the study. The VHI consists of five measures: elasticity, fluid secretion, pH, epithelial mucosa, and moisture.

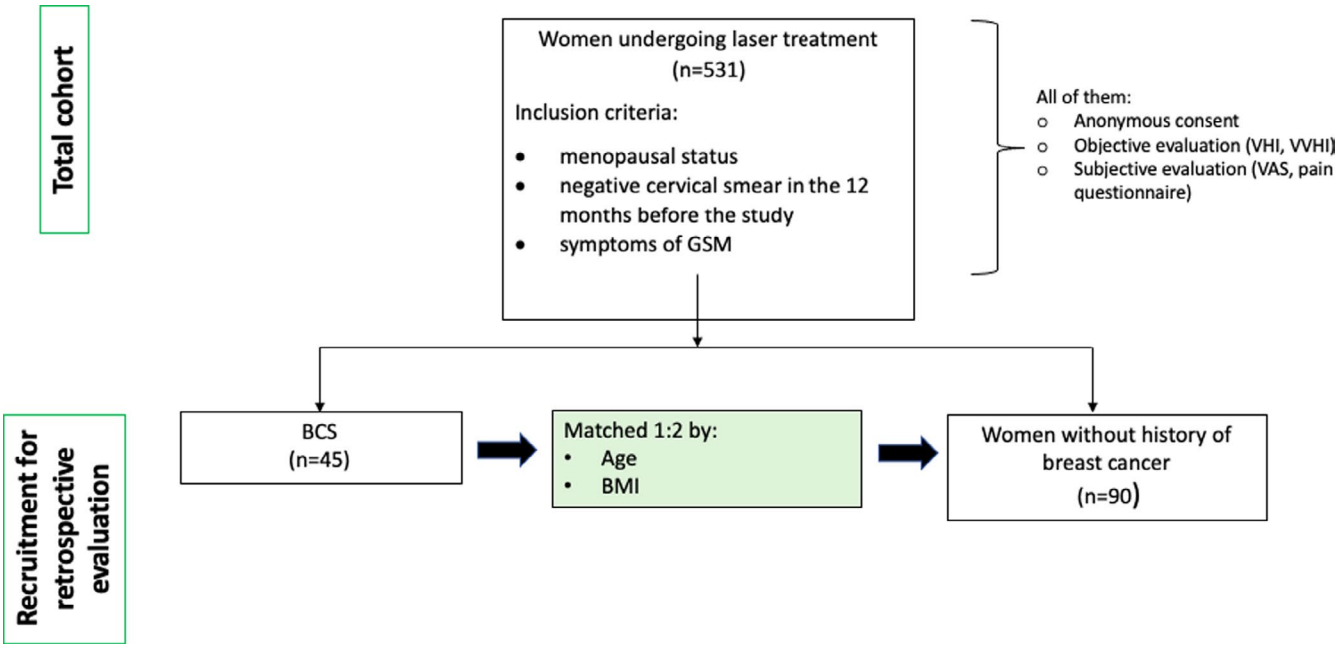

FIGURE 1 Consort diagram explaining the type of analysis performed

TABLE 1 (a) Characteristics of BCS and nonbreast cancer population. (b) GSM symptoms present at entry. (c)Type of treatment for BCS

	BCS *N* = 45	Control group *N* = 90	*p*-value
Age			
Average ± *SD*	60.62 ± 8.18	58.37 ± 8.40	
BMI			
Average ± *SD*	22.14 ± 2.51 (range 18–29.97)	20.41 ± 1.17 (range 19.47–28.34)	
Median (IQR)	21.97 (25–75:20.7–23.34)	20.20 (25–75:19.84–20.6)	
Underweight	8.89%	0%	
Normal weight	80%	97.78%	
Overweight	11.11%	2.22%	

(b) GSM symptoms present at entry

	BCS *N* = 45	%	Control group *N* = 90	%	*p*-value
First indication to treatment					
Apareunia	18	40	22	24.44	0.332
Dyspareunia	19	42.22	48	53.33	
Vaginal dryness	5	11.11	11	12.22	
Others	3	6.67	9	10	
Second indication to treatment					
Apareunia	5	11.90	5	6.33	**0.011**
Dyspareunia	1	2.38	6	7.59	
Vaginaldryness	36	85.71	56	70.89	
Others	0	0.00	12	15.19	

(c)Type of treatment for BCS	*N* (%)
SURGERY	
Breast-conserving surgery	35 (77.8)
Mastectomy	10 (22.2)
CHEMOTHERAPY	8 (17.7)
ENDOCRINE THERAPY	
Previous *n* = 18 (51.4%)	
AI	2 (11.1)
AI + GnRhanalogues	0 (0)
Tamoxifen	10 (5.5)
Tamoxifen + GnRhanalogues	6 (33.3)
Current *n* = 17 (48.6%)	
AI	11 (64.7)
AI + GnRhanalogues	1 (5.8)
Tamoxifen	5 (29.4)
Tamoxifen + GnRhanalogues	0 (0)

Each parameter is graded from 1 to 5. If the total score is <15, the vagina is considered atrophic.[24] The VVHI consists of eight measures: labia majora, labia minora, clitoris, urethra, vaginal introitus and elasticity, color, bother and pain, other elements (eg, ulcerations, petechiae). Each parameter is graded from 0 to 3. If the total score is >8 or if the total is 3 for any of the categories, the vulva is considered atrophic.[25] Subjective parameters included Visual Analogic Scale (VAS) for pain both for dyspareunia and vaginal dryness, completed by the patient at each time point of the study; a questionnaire about the degree of pain encountered in the procedure (insertion of

the probe, vaginal treatment, and vulvar treatment), filled after each laser treatment. The VAS is a 10-cm scale, where the left extreme indicates "absence of symptom" and the right indicates "symptom as bad as it could be."

Patients were treated with the fractional micro ablative CO_2 laser system (SmartXide2 V2LR, Monalisa Touch, DEKA, Florence, Italy) using the following setting: for endovaginal treatment dot power 40 watt and smart stack parameter from 1 to 3. A vaginal probe was inserted up to the top of the vaginal channel, withdrawn and rotated 45° in order to provide a complete treatment of the vaginal walls. Then, the vaginal introitus and the vulvar zone (labia majora, labia minora, clitoris, and interlabial sulci) were treated with a lower power: for the treatment of introitus dot power ranging from 15 to 35 watt and smart stack parameter 1 or 2; for the vulvar treatment dot power from 15 to 35 and smart stack parameter 1 or 2. The treatment of the introitus and the vulvar zone was performed with a special probe, similar to the one used for skin. The outer limits of the treated vulvar area were as follows: anterior labial commissure (superior), labia majora (lateral), and posterior labial commissure (inferior). The protocol included three laser treatments of about 20 min, one every 30 days. Pain and adverse events questionnaires were administered to both groups after every laser session.

No specific ethical approval was required, since in the two institutions, in the case of observational studies in which no supplementary examinations or treatments beyond the standard procedures are prescribed, the only requirement is that the patients signed a statement consenting to the procedure and to the use of their anonymized clinical and laboratory data for research purposes. The intervention and questionnaires were administered as a component of standard of care for all patients undergoing laser treatment. The consent to use anonymized data was obtained prospectively in advance of the procedures.

2.1 | Statistical analysis

Statistical analysis was performed using the software Stata 13 (Stata Corp., College2013). A descriptive analysis of the sample was carried out, stratified by the variable "presence of breast cancer," reporting frequencies and percentages for categorical variables, mean and standard deviation for continuous variables. The same procedure was conducted for the description of the individual items and overall of the scales taken into consideration in the study. The difference between the means of the two groups for the continuous variables was evaluated by Student's t test, while the statistical significance of the potential differences found for dichotomous and categorical variables was evaluated by Fisher's exact test.

The potential predictors of dyspareunia, dryness, and vaginal atrophy were examined by conducting multilevel multivariate analysis through linear regression models (VAS scale for dyspareunia and dryness, continuous VHI and VVHI scales) and logistics (dichotomized VHI and VVHI variables). The follow-up period was considered as the first level and the patients themselves as a second level.

The data were reported as coefficients and p-values in the case of linear regression models and in the form of correct odds ratio and p-value in the case of logistic regression models. A difference between was considered as statistically significant when it was associated with a two-tailed $p < 0.05$.

3 | RESULTS

3.1 | Study population

Characteristics of breast cancer and nonbreast cancer populations are described in Table 1A.

Table 1B describes GSM symptoms present at entry for both groups.

Dyspareunia was the main indication for laser therapy for both BCS and the comparison group. Apareunia is defined as lack of intercourse for four months due to severe GSM and is reported as a first indication for laser treatment by 40% of BCS and by one fourth of the controls.

Table 1C describes the treatments performed for cancer in BCS.

3.2 | Laser therapy parameters

The median number of laser session was 3 (range 3–4) for both groups ($p = 0.999$).

The mean laser power for vaginal treatment was 40 W, with SmartStack 3, in all three sessions, with no differences among the two groups. This might be explained by the poor innervation of the upper third of the vagina, which leads to good tolerance to vaginal dosage in all patients.

At introital level, laser power ranged between 25 and 35 W with SmartStack 1 as the most commonly used degree, without significant differences among the two groups.

At vulvar level, laser power ranged between 20 and 30 W with SmartStack1 as the most commonly used degree, without significant differences among the two groups.

3.3 | Questionnaires

The pain questionnaires results, which were administered to both groups after every laser session, considering pain at probe insertion and vulvar/vaginal periprocedural pain, are resumed in Figure 2.

At the first session, probe insertion was not reported as uncomfortable in most of the patients of both groups ($p = 0.332$).

At the third session, the reported vulvar and introital periprocedural pain were reported by a minor percentage of patients in both groups compared with the previous sessions.

No adverse events were reported among the two groups.

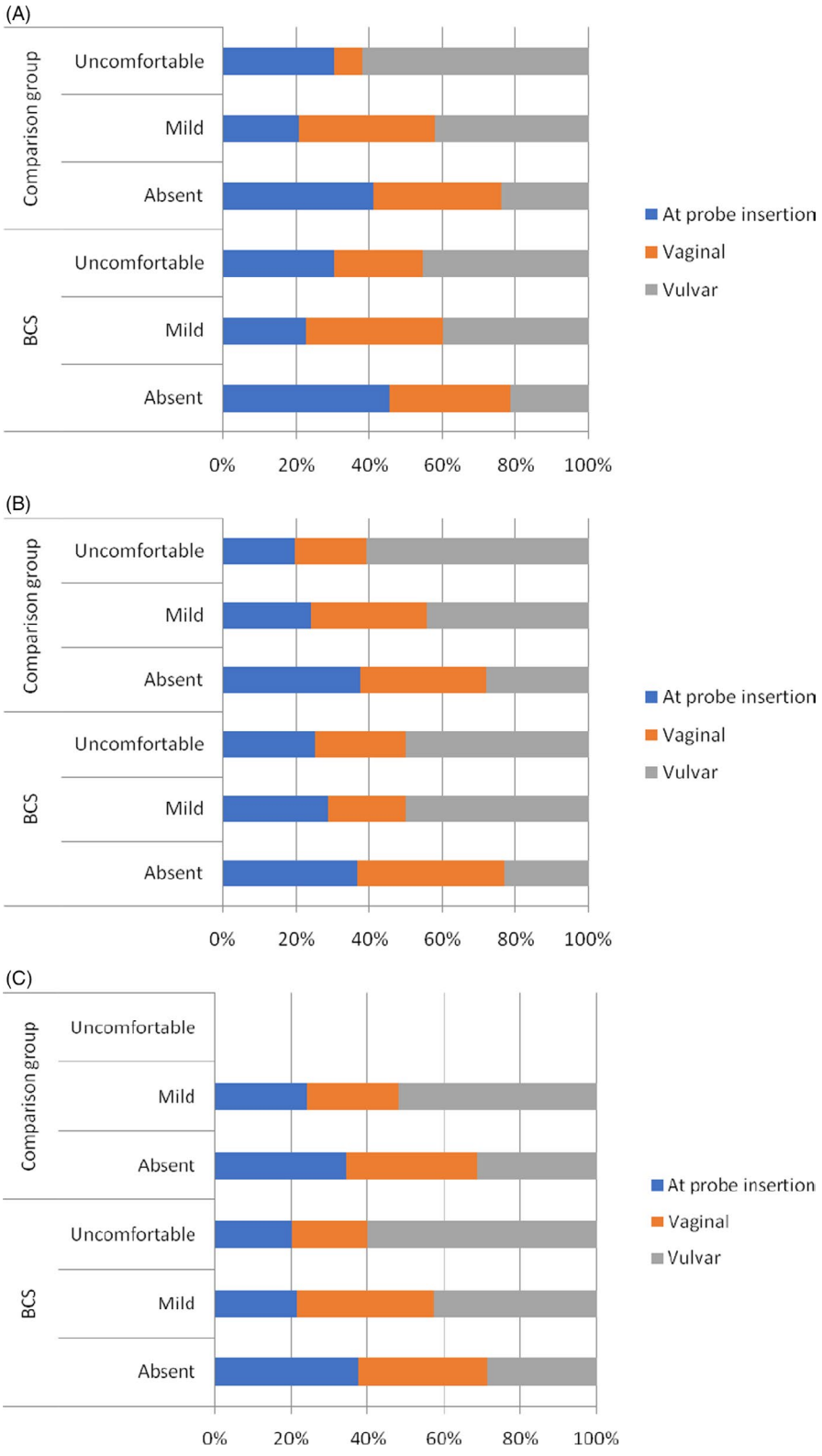

FIGURE 2 Reported periprocedural pain. (a) At first session. (b) At second session. (c) At third session

3.4 | Dyspareunia assessment by VAS scale

Dyspareunia results, expressed as VAS average score, were, respectively, 8.19 and 8.44 in the two groups at baseline. A significant improvement was observed in both groups after three months from the last laser session (5 in BCS and 2.88 among the comparison group). This improvement was obtained more slowly among BCS, showing significantly higher levels of dyspareunia since third laser session until six months follow-up visit.

The improvement was long-lasting in both groups, persisting after 12 months from the last laser session (3.33 and 2.44 among BCS and comparison group, respectively).

At the multivariate analysis, VAS for dyspareunia resulted progressively significantly lower at every visit (Table 2).

3.5 | Vaginal dryness assessment by VAS scale

Vaginal dryness results, expressed as VAS score, were, respectively, 8.55 and 7.34 in the two groups at baseline. After three months from the last laser session, the improvement was significant for both groups (3.57 in BCS and 1.88 among patients in the comparison group). This improvement was obtained more slowly among BCS, which showed significantly higher levels of vaginal dryness since the third laser session until the six months follow-up visit.

The improvement was long-lasting, being VAS 1.8 for both groups at the 12 months since the last laser session evaluation.

At the multivariate analysis, VAS for vaginal dryness at every follow-up visit resulted significantly lower as compared to previous assessments (Table 2) and more frequent among BCS ($p = 0.006$).

3.6 | VHI and VVHI evaluation

The VHI outcomes were, respectively,10.69 and 13.80 in the two groups at baseline. Among BCS, VHI was not anymore in a level of vaginal atrophy after two laser sessions, while in the comparison group it was within normal limits after one laser session. Six months after the last laser application, good VHI values were seen in both groups (20.75 among comparison group and 17.38 in BCS). The result was long-lasting, being persistent also at the 12-month control for both groups.

VHI scores presented a significant, constant improvement after every follow-up visit, as indicated by the multivariate analysis for VHI (Table 2). BCS presented more frequently a worse pretreatment VHI ($p < 0.001$).

The VVHI outcomes were, respectively, 13.45 in BCS and 11.17 in the comparison group at baseline. For both groups, VVHI did not indicate vulvar atrophy after two laser sessions. The improvement was significantly constant at every laser session (Table 2) and continued to improve after the end of treatments (after 3, 6, and 12 months). At this last evaluation, vulvar atrophy completely recovered (3.25 and 3.23, respectively, among BCS and the patients in the comparison group). BCS presented more frequently a worse pretreatment VVHI ($p = 0.003$).

4 | DISCUSSION

Breast cancer is the most common tumor in women.[26] Adjuvant chemotherapy and endocrine therapy may induce menopause or worsen symptoms in postmenopausal women.

GSM occurs in approximately 50% of postmenopausal women, with greater severity among BCS as a result of adjuvant therapies.[4]

TABLE 2 Multivariate analysis

	VAS Dyspareunia		VAS Vaginaldryness		*VHI*		VVHI	
	Coefficient	***p***	**Coefficient**	***p***	**Coefficient**	***p***	**Coefficient**	***p***
Observation time								
Before 1° session	Ref	–	Ref		Ref	–	Ref	–
Before 2° session	−2.18	<0.001	−1.87	<0.001	3.40	<0.001	−3.41	<0.001
Before 3° session	−3.84	<0.001	−3.32	<0.001	5.62	<0.001	−6.45	<0.001
At 3 months	−5.58	<0.001	−4.69	<0.001	6.88	<0.001	−8.17	<0.001
At 6 months	−5.76	<0.001	−4.77	<0.001	8.22	<0.001	−9.22	<0.001
At 12 months	−6.08	<0.001	−5.36	<0.001	8.03	<0.001	−9.62	<0.001
Previous breast cancer								
No	Ref	-	Ref	-	Ref	–	Ref	–
Yes	1.01	0.006	0.74	0.128	2.42	<0.001	1.59	0.003
Indication to treatment								
Apareunia	Ref	-	Ref	–	Ref	–	Ref	–
Dyspareunia	−0.79	0.035	−1.37	0.008	1.11	0.059	−1.15	0.034
Vaginaldryness	−0.15	0.789	−2.14	0.013	0.64	0.459	−0.51	0.526
Others	−4.24	<0.001	−4.93	<0.001	5.38	<0.001	−3.57	<0.001
Average(±SD) improvement among the two groups before third session								
BCS	4.65 ± 2.03	<0.05	5.85 ± 2.11	<0.05	16.30 ± 2.62	<0.001	7.16 ± 2.91	<0.001
Control group	3.42 ± 2.18		2.88 ± 2.14		18.94 ± 2.97		5.20 ± 2.50	
Average(±SD) improvement among the two groups after 12 months								
BCS	1.88 ± 1.46	n.s.	3.33 ± 1.63	n.s.	17.43 ± 3.95	n.s.	3.25 ± 2.76	n.s.
Control group	1.81 ± 1.63		2.44 ± 2.17		20.21 ± 3.31		3.53 ± 2.41	

This study confirmed that BCS are most likely to present severe GSM symptoms compared with the comparison group. At the pretreatment evaluation in our series, BCS presented significantly higher levels of dyspareunia assessed by VAS scale and a significantly worse degree of vaginal and vulvar dryness, assessed subjectively by VAS scale and objectively by VHI and VVHI.

As hormone replacement therapy is contraindicated for BCS,[9] the main options for GSM in these patients are nonhormonal moisturizers and lubricants, ospemifene at the end of adjuvant treatments or nonpharmacological therapies (such as the management of psychosocial distress, a regular sexual activity, the use vaginal dilators, and the pelvic floor exercises). In this setting, CO_2 laser might be an effective alternative for GSM in BCS.

In 2011, Gaspar et al. first showed that the treatment with the fractional CO_2 vaginal laser significantly improved vaginal atrophy.[15] A study on healthy postmenopausal women in 2014 by Salvatore et al. showed a significant improvement after 12 weeks in GSM symptoms and VHI, by applying the same vaginal laser protocol which was adopted in our study, consisting in 30 W, 1000 μs, 1000 μm, SmartStack 1 to 3.[27] Another study by Salvatore et al. in 2015 showed that laser therapy leads to an improvement in terms of sexual life in healthy postmenopausal women.[17]

In the present study, a group of patients with a history of breast cancer and a comparison group were evaluated through subjective and objective evaluations, after receiving fractional CO_2 laser treatment for GSM symptoms. A significant improvement in GSM outcomes was observed in both groups, confirming that vaginal laser could be useful in the treatment of vaginal atrophy, even in BCS. These results are consistent with the few existing studies on the impact of laser therapy for GSM in BCS.[19-23,28,29]

As regards the subjective evaluations, dyspareunia evaluated by VAS scale, changed from severe to moderate after the first session of treatment, with constant improvement after every session and it was referred as mild at 12 months follow-up visit in both groups.

Significant improvements in VAS scale among BCS treated for GSM with CO_2 laser therapy were also found in the study by Pieralli et.al.,[28] 11 months after the end of the treatment, in the study by Pagano et.al in which BCS were evaluated 30 days after the last session of laser therapy[29] and in a study by Gambacciani et.al. in which significant improvement in VAS scale was found in BCS at 18 months since last erbium laser session.[21]

Both VAS values, for dyspareunia and vaginal dryness in the entire study population significantly decreased at every follow-up visit. A more gradual improvement in BCS group was observed, probably because of the deeper estrogen deprivation caused by the adjuvant chemotherapy and endocrine therapy.

Furthermore, the present study evaluated the pain at vaginal probe insertion and the vaginal, vulvar, and introital pain during treatment, showing that the discomfort progressively decreased and the tolerance to the treatment improved, allowing to increase laser power, at every session. Our results on vulvar periprocedural pain are consistent with two studies by Pagano et al.[23,29]

As to objective evaluations, we found a significant improvement in the VHI score after two sessions of CO_2 laser treatment in BCS and after one session in the control group. In the study by Pieralli et al.,[28] the average VHI was modified from 8 to 21 after three laser sessions. A further study by Becorpi et al. confirmed the effectiveness of vaginal laser in improving VHI levels in BCS and the safety of the treatment, showing the absence of changes in the vaginal microbiome at swabs after laser therapy.[22] In the present study, a constant significant improvement in VHI was observed until the last 12 months follow-up visit. The study performed by Gambacciani et.al. showed a persisting improvement in VHI in BCS after 12 months since last treatment with erbium laser.[21] In the study by Mothes et.al.[19] On 16 BCS, a significant improvement in VHI after one session of treatment with erbium laser was observed.

Since most of the patients reported pain at the vulvar ostium during intercourses, the field of the laser was widened to include this area and power levels were modulated according to patients' tolerance levels. In another study performed by our group on 87 patients (of whom 13 were BCS), in which laser administration was extended to the vulvar area, a significant improvement in vulvar atrophy, assessed by VVHI scale, was found after two sessions of laser treatment.[18] In the present study, among the 45 BCS, the mean pretreatment VVHI index was suggestive for vulvar atrophy while after two sessions of treatment it was decreased under the cut-off of atrophy (<8) in both groups.

Consistent with the safety data on vaginal laser reported in the literature,[22,23,28,29] also in this study no severe adverse events were observed in both groups.

5 | CONCLUSION

This study, despite several limitations (such as the small sample size and the need for a follow-up time longer than 12 months) showed that fractional CO_2 vaginal laser leads to a long-term improvement in GSM symptoms, even in BCS, representing an effective, nonhormonal option in these patients.

These findings should be confirmed in larger randomized controlled trials with a longer follow-up.

CONFLICT OF INTEREST

Nicoletta Biglia received occasional grants from Shionogi and Gedeon Richter (member of advisory boards and/or consultant). The other authors declare that they have no conflict of interest.

CONSENT TO PARTICIPATE AND TO PUBLISH

Informed consent was obtained from all individual participants included in the study. All patients gave their written consent to the anonymous use and publication of their data for scientific purposes.

DATA AVAILABILITY STATEMENT

Due to the sensitive nature of the questions asked in this study, patients were as- sured raw data would remain confidential.

Nevertheless, data will be available under request if a signed confidentiality agreement is pro-vided.

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How to cite this article: Siliquini GP, Bounous VE, Novara L, Giorgi M, Bert F, Biglia N. Fractional CO_2 vaginal laser for the genitourinary syndrome of menopause in breast cancer survivors. *Breast J*. 2021;00:1–8. https://doi.org/10.1111/tbj.14211