Supportive Care in Cancer
https://doi.org/10.1007/s00520-019-05211-3

ORIGINAL ARTICLE

Fractional CO2 laser therapy for genitourinary syndrome of menopause for breast cancer survivors

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Received: 8 July 2019 / Accepted: 24 November 2019

Abstract

Purpose Fractional CO2 laser therapy is an emerging treatment for genitourinary syndrome of menopause (GSM). The objective of this study was to determine the feasibility and preliminary efficacy of fractional CO2 laser therapy in breast cancer survivors.

Methods This was a single arm feasibility study of breast cancer survivors with dyspareunia and/or vaginal dryness. Participants received three treatments of fractional CO2 laser therapy at 30-day intervals and returned for a 1-month follow-up. Feasibility was defined as treatment completion without serious adverse events (SAE) in 80% of patients. We collected data on the Vaginal Assessment Scale (VAS), the Female Sexual Function Index (FSFI), the Urinary Distress Index (UDI), and SAE.

Results A total of 64 patients participated in the study. The majority of women had Estrogen receptor/Progesterone receptor (ER/PR) positive/Her2neu negative ($n = 37$; 63%), stage I ($n = 32$, 54%) or II ($n = 19$, 32%) breast cancer. Most were receiving endocrine therapy ($n = 54$, 92%), most commonly aromatase inhibitors (AI; $n = 40$, 68%). Fifty-nine (88.1%) of those enrolled completed all treatments according to protocol with no reported SAE. No patient withdrew due to SAE. The scores of the VAS (mean $\Delta -0.99$; 95% CI [−1.19, −0.79], $p < 0.001$)), FSFI (mean Δ 9.67; 95% CI [7.27, 12.1], $p < 0.001$), and UDI (mean $\Delta -8.85$; 95% CI [−12.75, −4.75], $p < 0.001$)) improved from baseline to follow-up.

Conclusion Fractional CO2 laser treatment for breast cancer survivors is feasible and appears to reduce GSM symptoms across treatment and follow-up.

Keywords Vaginal atrophy · Genitourinary syndrome of menopause · Breast cancer · Fractional CO2 laser therapy

Introduction

Genitourinary changes develop as a result of natural, surgical, or oncologic treatment-induced menopause. Decreased lubrication and elasticity of the vagina lead to symptoms including vaginal dryness, burning, pain, bleeding, dyspareunia, and dysuria [1–3]. Together, these symptoms are referred to as genitourinary syndrome of menopause (GSM) [4]. Between 50 and 75% of breast cancer survivors have symptoms of GSM as a result of physiologic changes of menopause, discontinuing hormone therapy after a cancer diagnosis, and/or treatment [3]. Chemotherapy can induce an abrupt temporary or permanent menopause in 80% of premenopausal women from premature ovarian failure and can also further decrease estrogen levels after a natural menopause [3]. Women with breast cancer on endocrine therapy, including tamoxifen

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00520-019-05211-3) contains supplementary material, which is available to authorized users.

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Published online: 06 December 2019

and aromatase inhibitors (AIs), have higher rates of vaginal dryness and dyspareunia than do postmenopausal controls, with the highest rates in those on AI therapy. These symptoms can decrease sexual function, quality of life, and compliance with endocrine therapy [3, 5]. In one study, 93% of women with breast cancer on AI therapy had sexual dysfunction and 79% developed a new sexual problem that was not present prior to therapy [6].

Vaginal symptoms of GSM may worsen with time and do not typically resolve without treatment [7]. A number of local hormonal and non-hormonal strategies have been studied for relief of GSM in breast cancer survivors [5, 8–10]. Fractional CO2 laser therapy is an emerging potentially effective treatment for GSM that remodels vaginal tissue by activation of fibroblasts, collagen production, and neovascularization [11]. Prospective non-randomized observational trials have provided support that this treatment is effective for relief of symptoms of GSM in postmenopausal women [12–17]. A recently published randomized controlled trial showed that fractional CO2 laser therapy and vaginal estrogen treatment both improved GSM symptoms in postmenopausal women and that there was no significant difference between the two treatments [18].

Retrospective studies and nonrandomized prospective observational trials of the use of fractional CO2 laser treatments in breast cancer survivors have also demonstrated improvement of symptoms of GSM [1, 2, 19, 20], which makes laser therapy an appealing treatment option over topical estrogen for women with breast cancer to eliminate the concern for systemic absorption. Because of the number of women with breast cancer who suffer from GSM, additional safe and effective treatments are needed. Of the two prospective studies of fractional CO2 laser therapy in women with breast cancer, very few women on AI therapy were included [1, 20]. Therefore, due to the limited data on the use of this treatment in breast cancer patients, particularly women on AI therapy who are the most symptomatic from profound estrogen deprivation [3, 21], the current pilot study was conducted to better determine the feasibility and preliminary efficacy of fractional CO2 laser treatment in breast cancer survivors.

Methods

Sample and eligibility

Participants were recruited from breast medical oncology clinics during routine follow-up for their breast cancer. Women reporting vaginal dryness and/or dyspareunia were given information about the study. If interested in participating, they were referred to the Female Pelvic Medicine and Reconstructive Surgery clinic where they were screened for eligibility and consented for treatment.

Women with stage 0-III breast cancer with symptoms of GSM were recruited for this study. Inclusion criteria were self-reported dyspareunia and/or vaginal dryness of any severity. Patients had to have completed any planned cancer treatment with surgery, chemotherapy, and radiation. Patients who were on endocrine therapy and/or trastuzumab were eligible. There was no restriction on enrollment based on the time since their initial treatment or breast cancer diagnosis.

Patients were excluded from participation if they had metastatic breast cancer; vaginal stenosis preventing vaginal probe placement; active genital infection; pelvic organ prolapse greater than stage II; prior reconstructive pelvic surgery involving mesh for prolapse; and systemic hormone therapy, local vaginal estrogen, or dehydroepiandrosterone within 6 weeks prior to enrollment.

The study was approved by the Ohio State University Medical Center Cancer Institutional Review Board.

Procedures

Demographics, clinical data, and inclusion/exclusion criteria were obtained and recorded for all patients at their initial consultation. Subjective and objective symptoms of GSM were assessed at baseline (T0) or prior to the first treatment (T1), prior to the second and third treatment (T2, T3), and at follow-up (T4). Additional questionnaires assessing sexual function, urinary function, and global impression of improvement were assessed at the same time.

The treatment consisted of fractional microablative CO2 laser (MonaLisa Touch ™, DEKA Florence, Italy) at three time points 30–45 days apart, according to standard protocol [1]. Treatments were compliant with laser safety protocol according to institutional policy and were executed by one of three trained physicians following a consistent protocol. Prior to treatment, vaginal exam and pH testing were performed. EMLA cream was applied to the introitus and removed after 15 min. The laser was set to 30-W power with a dwell time of 1000 μs, a dermal optical thermolysis spacing of 1000 μm, and a smart stack parameter of one for the first treatment and three for remaining treatments. The standard internal probe was inserted to the vaginal apex or cervix, and a burst of laser pulses were delivered to treat the entire circumference and length of the vagina from the apex to the introitus [22]. The vestibule and posterior fourchette from 3 o'clock to 9 o'clock were then treated separately using the external vulvar probe. For this external treatment, the laser was set to 26-W power with a dwell time of 800 μs, a dermal optical thermolysis spacing of 800 μm, and a smart stack parameter of one for every treatment.

Participants were asked to abstain from intercourse and use of vaginal creams/lubricants for 48 h prior to and following the procedure. Participants were asked to return for follow-up

at T4 at which time a gynecologic exam was done and the questionnaires were completed by the patients.

Measures

Self-reported measures

Subjective vaginal symptoms The Female Sexual Medicine and Women's Health Program form developed at Memorial Sloan Kettering Cancer Center was used to assess the subjective findings related to GSM [23]. This form consists of the Vaginal and Vulvar Assessment Scales (VAS and VuAS), which are validated clinical measurement tools that assess vulvovaginal symptoms including vaginal dryness, soreness, irritation, and dyspareunia over the preceding 4 weeks. Symptoms are rated as mild, moderate, or severe, and each item is scored from 0 (none) to 3 (severe) with a composite score calculated by taking the average of the items answered. A lower score indicates better function [23, 24].

Sexual function Sexual function was measured using the Female Sexual Function Index (FSFI), a 19-item self-reported instrument that has been previously validated to measure sexual functioning in women in clinical trials. It measures 6 domains of sexual functioning. Overall test-retest reliability coefficients are high for each domain, and the internal consistency is high with a Cronbach's alpha of 0.82 and higher. A score of < 26.55 indicates risk for sexual dysfunction, with higher scores indicating better sexual function [25]. It has been validated in patients with breast cancer [26].

Urinary function Urinary symptoms were assessed using the Urogenital Distress Inventory-6 (UDI-6), a validated 6-item questionnaire with three subscales: irritative symptoms, obstructive/discomfort, and stress symptoms. The subscale scores are added for a total score, with a higher score indicating higher disability [27]. The UDI-6 questions were asked in two parts: 1. Do you experience the symptom? and 2. How much does it bother you? Each question was scored using the five-point scale with no = 0, not at all = 1, somewhat = 2, moderately = 3, and quite a bit = 4. The average score was calculated for the answered items only. No subject was missing more than two responses. The average UDI was multiplied by 25 to scale the total to a score of 100. If a subject answered no for the first question and not at all for the second question they were given a score of 0.

Global satisfaction Overall patient assessment of symptoms was obtained prior to T2 and T3 and at T4 using the Patient Global Impression of Improvement scale (PGI-I), a single item questionnaire with a seven-point Likert scale that is validated to measure change of symptoms [28, 29].

Adverse events Adverse events (AE) were self-reported prior to T1, T2, and T3 and at T4. They were graded according to the NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Clinician assessment

Objective vaginal symptoms All participants had a gynecologic evaluation for objective symptoms related to GSM at T0 using the Vaginal Health Assessment (VHA), a physical exam tool that accompanies the VAS and VuAS (Appendix 1) [24]. Exam findings included vaginal pH, moisture, elasticity, rugosity, length, epithelial thickness, vascularity, and integrity and was repeated prior to each treatment at T2, T3, and at T4.

Statistical analysis

The primary objective of this study was to estimate the feasibility of fractional CO2 laser therapy in a sample of breast cancer patients with GSM. Participants with only baseline measures were considered as drop-outs and were not included in the feasibility analysis. The study was to be deemed feasible if 80% or more of the patients were able to complete all planned treatments without serious adverse events (SAE), which was compatible with other studies that have shown the treatment to be well tolerated [13, 15]. The primary measure for preliminary efficacy was the change in the VAS score from T0 to T4. Secondary endpoints included change in VuAS, FSFI, UDI-6, and PGI for global improvement in symptoms. Changes in the VHA were also analyzed. Descriptive statistics using means and 95% confidence intervals for continuous variables and proportions for categorical variables were used to summarize demographics, clinical characteristics, and endpoints. The change in continuous outcomes from T0–T4 was compared using a paired *t* test or a Sign Rank test (UDI).

Results

A total of 67 patients were enrolled in the study. Three patients withdrew from the study at screening prior to any treatment, resulting in a total of 64 treated participants. An additional 5 patients withdrew after starting treatment. Two patients withdrew after the second laser treatment (one moved out of town, and one was lost to follow-up), and two patients withdrew after the third laser treatment and refused follow-up. One patient did not receive a third treatment or follow-up due to study suspension.

Participant and breast cancer treatment characteristics are summarized in Table 1.

Table 1 Patient demographic and clinical characteristics

		Total (n=64)
Age	Mean (SD)	57.4 (9.5)
Stage	0	3 (4.7%)
	I	32 (50.0%)
	II	21 (32.8%)
	III	7 (10.9%)
	IV *	1 (1.6%)
Histology	Adenocarcinoma	51 (76.7%)
	Other	13 (20.3%)
ER status	Negative	5 (7.8%)
	Positive	58 (90.6%)
	Unknown	1 (1.6%)
PR status	Negative	15 (23.4%)
	Positive	47 (73.4%)
	Unknown	2 (3.1%)
Her2 Neu status	Negative	50 (78.1%)
	Positive	11 (17.2%)
	Unknown	3 (4.7%)
	ER-/PR-	5 (7.8%)
	ER+/PR+	47 (73.4%)
	ER+/PR-	10 (15.6%)
	Unknown	2 (3.1%)
Chemotherapy	No	27 (42.2%)
	Unknown	1 (1.6%)
	Yes	36 (56.3%)
Endocrine therapy use	No	4 (6.3%)
	Unknown	1 (1.6%)
	Yes	59 (92.2%)
Type of endocrine therapy	Tamoxifen	13 (20.3%)
	AI	44 (68.8%)
	Tamoxifen ovarian suppression	2 (3.1%)
	Not applicable	5 (7.8%)

*Patient had incidental finding of an ovarian metastasis at the time of oophorectomy and was disease free for 5 years prior to enrolling

Feasibility

In total, 59 (88.1%) (95% CI 77.9%, 94.1%) of those enrolled on the study were able to complete all laser treatments according to protocol. Of those participants who received one laser treatment ($n = 64$), 92.2% (95% CI 82.7.0%, 97.4%) were able to complete all three laser treatments. Only 5 (7.8%; 95% CI 2.6%, 17.3%) participants who started treatment did not complete all three treatments. No patient withdrew due to AE. There were no AE attributable to the laser treatment other than grade 1–2 vaginal discharge ($n = 69$, 54.3%) and vaginal dryness ($n = 30$, 23.6%). No grade 3 or higher AE were identified.

Preliminary efficacy

At the time of screening, 81.2% reported moderate ($n = 16$, 27%) to severe ($n = 32$, 54.2%) dyspareunia compared with 30.5% ($n = 18$) at the time of follow-up (13.5% moderate; 17% severe). Similarly, 88.1% reported moderate ($n = 28$, 47.5%) to severe ($n = 24$, 40.7%) vaginal dryness at screening compared with 30.5% ($n = 18$) at follow-up (18.6% moderate; 11.9% severe). The total VAS score, comprised from the score of vaginal dryness, vaginal soreness, vaginal irritation, and dyspareunia, decreased from baseline to follow up, indicating an improvement in symptoms (mean $\Delta -0.99$; 95% CI [$-1.19, -0.79$], $p < 0.001$)). Figure 1 shows the mean VAS score at baseline, prior to the second and third treatments, and at follow-up.

Secondary endpoints (VuAS, FSFI, UDI, PGI)

There was a statistically significant improvement in the VuAS score from baseline to follow up (mean $\Delta -0.72$; 95% CI [$-0.95, -0.48$] $p < 0.001$). The FSFI and UDI scores also improved from baseline to follow-up (mean Δ 9.67; 95% CI [7.27, 12.08], $p < 0.001$ and mean $\Delta -8.85$; 95% CI [$-12.45, -4.75$], $p < 0.001$, respectively). Figures 2 and 3 show FSFI and UDI scores at baseline, prior to the second and third treatments and at follow-up.

Patient reported improvement in symptoms based on the PGI-I showed that as early as cycle 2, 45.8% of participants reported that their symptoms were a little better, 11.9% reported that they were much better, and 3.4% reported they were very much better. At the time of follow-up, 33.9% of participants reported that their symptoms were a little better, 28.8% reported they were much better, and 22.0% reported they were very much better. Overall, 8.5% reported no change in symptoms and 1.7% reported that their symptoms were a little worse.

Objective physical exam findings

At T0, 46% of the participants had a vaginal pH > 6.5, and 37% had a pH between 5 and 6.5. At T4, only 24% had a vaginal pH > 6.5, and 69% had a pH between 5 and 6.5, indicating a trend toward normalization. Additional physical exam findings, including vaginal moisture, elasticity, rugosity, wall thickness, epithelial integrity, and vascularity, also improved from T0–T4 as shown in Fig. 4.

Discussion

This study demonstrated that fractional CO2 laser therapy is feasible in breast cancer survivors, with 88% of women completing all three laser treatments without SAE. In addition,

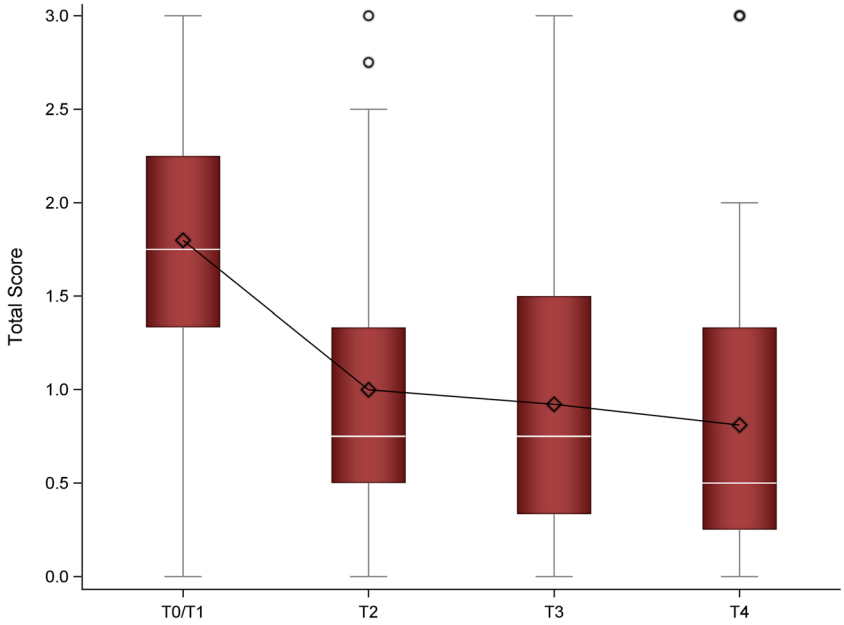

Fig. 1 Distribution of VAS scores at baseline (T0/1), prior to the second (T2) and third (T3) treatments, and at follow-up (T4). Mean (diamond), median (white line), and the 1st and 3rd quartiles are displayed. The whiskers are the distance equal to 1.5 times the interquartile range (IQR). The diagram also shows outliers (circles) which are values that above or below the whisker ends

subjective and objective vaginal symptoms improved from baseline to follow-up, preliminarily suggesting efficacy of treatment. The study also supports an improvement in sexual and urinary function after completion of study.

Vaginal symptoms from lack of estrogen can have a significant impact on the sexual health and quality of life of women with breast cancer [6–8]. The use of vaginal estrogens to treat GSM is the gold standard treatment for GSM in postmenopausal women without a history of breast cancer [30] but is controversial in breast cancer survivors, due to concern for increase cancer recurrence risk [7]. Although no study has shown an association with adverse cancer outcomes, several studies have demonstrated a transient increase in serum estradiol levels in women using vaginal estrogens [3, 5, 31] and many providers prefer non-hormonal therapy over estrogen therapy due to concerns of systemic absorption which could counteract the effects of endocrine therapy [32].

Women on AI therapy have worse GSM symptoms compared with women on tamoxifen and postmenopausal women [3, 33]. The majority of women on AI will have sexual dysfunction within the first 2 years of starting AI therapy and, as a result, many women will choose to become sexually inactive, to switch to tamoxifen for endocrine therapy, or even discontinue endocrine therapy altogether [6]. Improving vaginal symptoms in this population is crucial, not only for quality of life but also to reduce non-adherence or discontinuation of

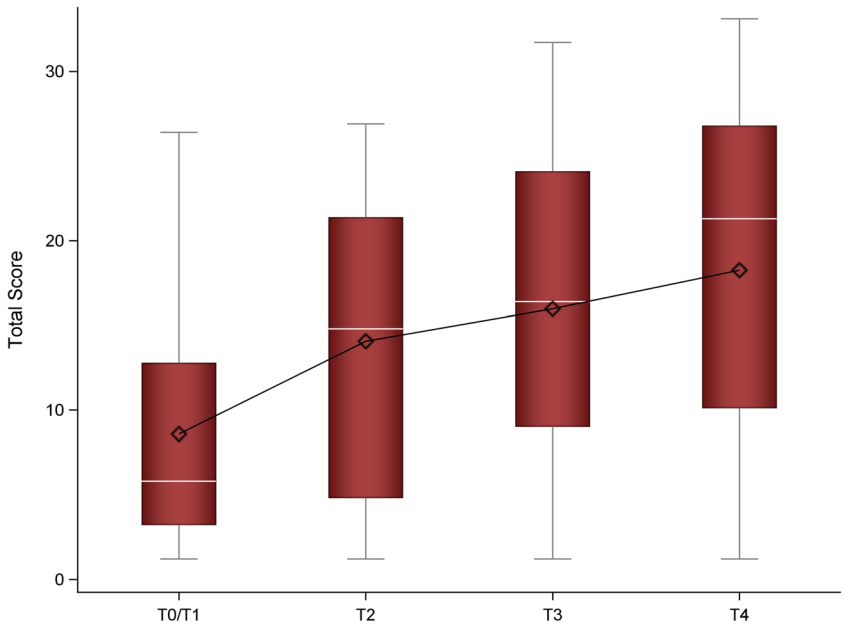

Fig. 2 Distribution of FSFI score at baseline (T0/1), prior to the second (T2) and third (T3) treatments, and at follow-up (T4). Black diamonds indicate sample means at each time point. Mean (diamond), median (white line), and the 1st and 3rd quartiles are displayed. The whiskers are the distance equal to 1.5 times the interquartile range (IQR). The diagram also shows outliers (circles) which are values that above or below the whisker ends

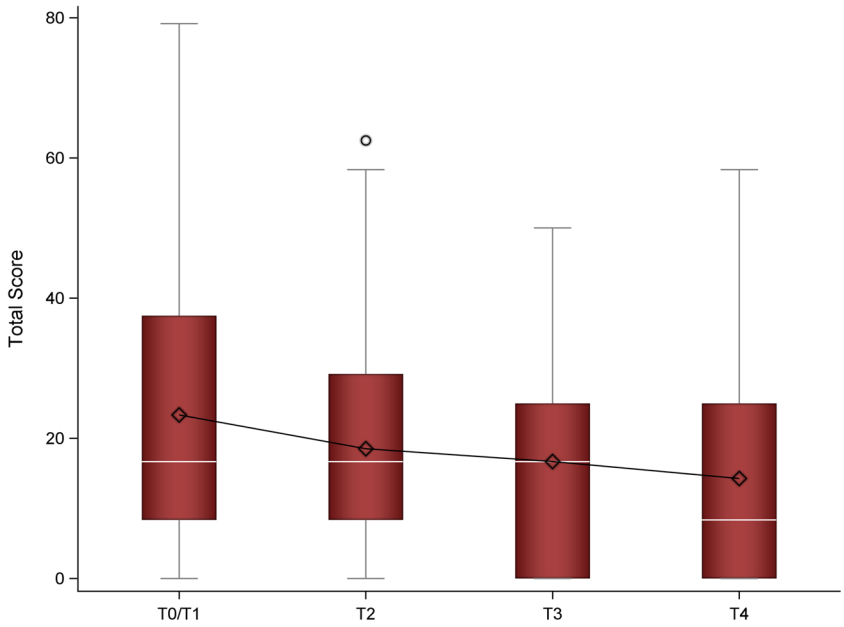

Fig. 3 Distribution of UDI score at baseline (T0/1), prior to the second (T2) and third (T3) treatments, and at follow-up (T4). Black diamonds indicate sample means at each time point. Mean (diamond), median (white line), and the 1st and 3rd quartiles are displayed. The whiskers are the distance equal to 1.5 times the interquartile range (IQR). The diagram also shows outliers (circles) which are values that above or below the whisker ends

endocrine therapy, which can increase breast cancer mortality [34, 35]. AI therapy in conjunction with ovarian suppression is now also being used more common in premenopausal women on endocrine therapy, thus potentially increasing the number of breast cancer survivors affected by this treatment [34, 36].

To date predominately non-estrogen–based topical agents have been studied for women with breast cancer as a means to treat vaginal symptoms [5, 9, 10]. The recently reported VeLVET study randomized 69 postmenopausal women participants with GSM to fractional CO2 laser therapy or to vaginal estrogen. The study found no difference in improvement in vaginal symptoms with laser therapy compared with estrogen therapy [18]. Fractional CO2 laser therapy may provide an alternative treatment option over topical agents, including vaginal estrogens, which are only effective if the patient remains complaint with regular use [37]. Although these data have been promising, it is unclear that breast cancer survivors receiving ongoing endocrine therapy, who experience a greater degree of GSM symptoms than postmenopausal women [3], would benefit from laser therapy or if laser therapy is even safe to use in severely atrophic vaginal tissue from endocrine therapy [38].

The data from the current study are consistent with other prospective nonrandomized studies of postmenopausal women with vaginal atrophy who were treated with fractional CO2 laser therapy, further supporting that the treatment was feasible and well tolerated [12, 13, 15] . Similarly, this study is consistent with others that have demonstrated improvement in vaginal dryness, dyspareunia, sexual function, and urinary symptoms [12, 14–17, 22, 39]. Data on the use of fractional CO2 laser therapy are limited in breast cancer, and, to date, there are only four published studies [1, 2, 19, 20] . The first is a prospective nonrandomized study of 50 women with a history of breast cancer treated with fractional CO2 laser therapy. Less than half the women were on endocrine therapy, which

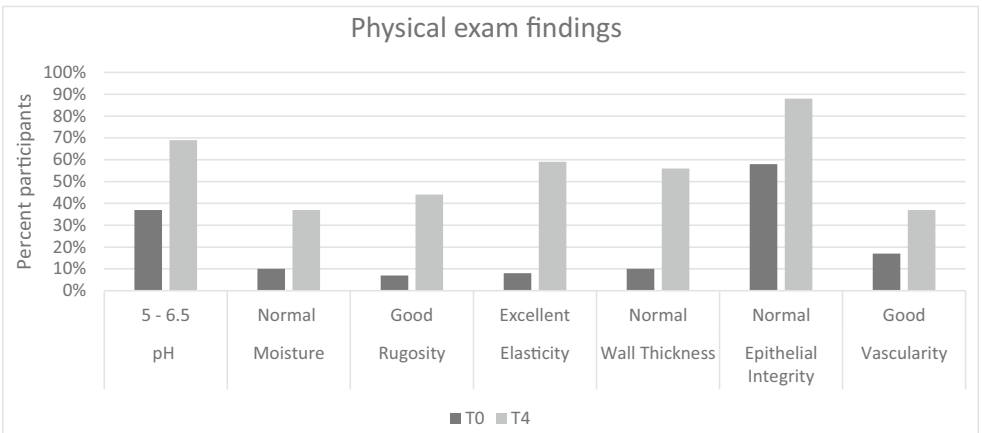

Fig. 4 Changes in physical exam findings based on the Vaginal Health Assessment from T0–T4

differs from the current study that had 54 participants (92%) on endocrine therapy. At 11-month follow-up, women had improvement in objective and subjective symptoms of GSM, consistent with the present study results. Two retrospective studies by Pagano et al. showed improvement in GSM symptoms in breast cancer survivors with three fractional CO2 laser treatments. Based on their study results, the authors concluded that fractional CO2 laser therapy was safe and may be effective for treatment of GSM in women with breast cancer [19]. More recently, Becorpi et al. published a case series of 20 postmenopausal breast cancer survivors treated with vaginal CO2 laser therapy [20]. They observed improvements in subjective symptoms, including vaginal dryness, dyspareunia, itching, and burning. In addition, sexual function and physical exam findings on the vaginal health index improved.

Although long-term safety and efficacy data are lacking, anecdotal cases of substantial toxicity with fractional CO2 laser therapy have been reported [40]. The US Food and Drug Administration has issued a warning against the use of vaginal lasers for vaginal "rejuvenation" or vaginal cosmetic procedures (https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-use-energy-based-devices-perform-vaginal-rejuvenation-or-vaginal-cosmetic), but no study to date has reported significant toxicity as a result of treatment, similar to our findings of no grade 3 or higher adverse events. The recently published VeLVET study reported only mild AE including vaginal pain, bleeding, and discharge with the laser treatments [41].

The strength of the current study is that it is larger than any other prospective study of breast cancer survivors published to date and includes the largest number women on AI therapy studied to date [1]. Thus, this study is the first to support a benefit in a larger population of women on AI therapy, who are known to have more symptoms of GSM than postmenopausal women in the general population or than women with breast cancer on tamoxifen [3].

The limitations of the study include the follow-up at only 4 weeks from the last treatment. Further investigations with longer-term follow-up are needed to assess safety as well as the duration of symptom improvement and the potential need for additional treatments. Additional important limitations of our study include the lack of a placebo comparison arm, lack of blinding, and no treatment randomization. Therefore, the next step in answering these questions in breast cancer survivors is a double-blind, randomized controlled trial, comparing fractional CO2 laser therapy versus sham laser treatment.

Conclusion

In conclusion, this trial supports that fractional CO2 laser therapy is feasible and preliminarily appears effective for symptoms of GSM in women with breast cancer, including those on endocrine therapy. A double-blind, randomized clinical trial with a placebo/sham laser and longer follow-up to determine safety and efficacy of treatment is currently under development.

Funding information Funding was provided by OSU FAME PRO (AQ) and by the OSU Spielman Development Funds (MBL).

Compliance with ethical standards

Conflict of interest No financial support was provided by Hologic inc. The laser devise was provided by loan to OSU from Hologic/Cynosure. None of the investigators received financial support from Hologic/Cynosure. The company was not involved in study data analysis or manuscript preparation. The corresponding author has full control of the primary data and can be reviewed by the journal if requested.

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