INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

Effectiveness of CO_2 laser on urogenital syndrome in women with a previous gynecological neoplasia: a multicentric study

Roberto Angioli,[1] Salvatore Stefano,[2] Maurizio Filippini,[3] Annalisa Pieralli,[4] Roberto Montera,[1] Francesco Plotti,[1] Alessandra Gatti,[1] Martina Bartolone,[1] Daniela Luvero[1]

[1]Department of Gynecology, University Campus Biomedico, Rome, Italy
[2]Department of Obstetrics and Ginecology, IRCCS San Raffaele Hospital, Milan, Lombardia, Italy
[3]Department of Ostetrics and Gynecology, Hospital State of Republic of San Marino, San Marino, Republic of San Marino
[4]Department of Women and Child Health, Careggi University Hospital, Florence, Toscana, Italy

Correspondence to
Dr Daniela Luvero, Department of Gynecology, University Campus Bio-Medico, Rome 00128, Italy; d.luvero@unicampus.it

Received 4 November 2019
Revised 6 December 2019
Accepted 10 December 2019

Check for updates

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To cite: Angioli R, Stefano S, Filippini M, *et al. Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2019-001028

Highlights

- Urogenital syndrome is characterized by vaginal dryness, dyspareunia, pain at vaginal introitus, burning, and/or itching.
- Microablative CO_2 laser is an effective treatment of urogenital syndrome, with greatest success in vulvovaginal atrophy.
- Dryness, dyspareunia, burning, pain at introitus, and itching were all improved with microablative CO_2 laser treatment.

ABSTRACT

Background Many women diagnosed with gynecological cancers undergo adjuvant therapy, which may lead to transient or permanent menopause that ultimately leads to urogenital syndrome and vulvovaginal atrophy. Studies advise against the use of estrogen in women with a history of hormone-dependent cancer. One alternative is vaginal microablative fractional CO_2 laser, which promotes tissue regeneration through the production of collagen and elastic fibers.

Objective To evaluate the effectiveness of CO_2 laser in the treatment of urogenital syndrome—in particular, symptomatic vulvovaginal atrophy in women who have survived gynecological cancers.

Methods A retrospective study was carried out, including all patients with a history of gynecological cancers and vulvovaginal atrophy who underwent CO_2 laser treatment between November 2012 and February 2018 in four Italian centers. The study was approved by the local ethics committee of each participating institution. The inclusion criteria were women aged between 18 and 75; Eastern Cooperative Oncology Group performance status <2; and history of breast, ovarian, cervical, or uterus cancer. Patients had to have vulvovaginal atrophy and at least one of the following symptoms of urogenital syndrome: vaginal dryness, dyspareunia, vaginal introitus pain, burning, or itching. Three applications were administered at baseline, 30 days, and 60 days. All patients were evaluated before the first laser session, at each session, and 4 weeks after the last session. In particular, patients were asked to indicate the intensity of symptoms before the first session and 4 weeks after the last session, using Visual Analog Scale (VAS) scoring from 0 ('no discomfort') to 10 ('maximum discomfort').

Results A total of 1213 patients underwent CO_2 laser treatment and of these, 1048 were excluded because they did not meet the inclusion criteria in the analysis. Finally, a total of 165 patients were included in the study. The mean age at the time of treatment was 53 years (range 31–73). Dryness improved by 66%, dyspareunia improved by 59%, burning improved by 66%, pain at introitus improved by 54%, and itching improved by 54%. The side effects were evaluated as pain greater than VAS score 6 during and after the treatment period. No side effects were seen in any sessions.

Conclusions Fractional microablative CO_2 laser therapy offers an effective strategy in the management of the symptoms of genitourinary syndrome in post-menopausal women and in survivors of gynecological cancer.

INTRODUCTION

Breast cancer is the most common cancer in women.[1] Early diagnosis through mammography screening and improvements in options for treatment have increased 5-year survival rates to 90%.[2] Adjuvant therapies may lead to a transient or permanent menopause in young women diagnosed with cancer.[3–6] This is particularly relevant, since a high percentage of women are diagnosed with cancer before the age of 50,[2] and 11% of new breast cancer diagnoses occur in women under the age of 44.[7] Endometrial cancer is the fourth cancer by incidence overall among women,[1] with 20% of diagnoses occurring in the pre-menopausal years.[8] Ovarian cancer, despite its lower incidence, is the fifth cancer by mortality in women,[1] with 10% of diagnoses occurring before the age of 50.[9] Lastly, comes cervical cancer with 50% of diagnoses occurring before the age of 50.[10]

One of the most common complaints reported by women with spontaneous or iatrogenic menopause is known as the urogenital syndrome, a group of symptoms that affect the bladder and vagina. In particular, vulvovaginal atrophy, a direct consequence of estrogen deficiency, is a commonly reported symptom, with greater intensity among women with iatrogenic menopause than among those with spontaneous menopause.[11] The decrease in estrogen levels causes structural and functional changes to vulvar and vaginal tissues, and as a result, urogenital syndrome leads to vaginal dryness, itching, burning, bleeding, dyspareunia, and/or dysuria.[12] A number of treatments are available for urogenital syndrome

and, in particular, for vulvovaginal atrophy: vaginal estrogen (the 'gold standard' for the treatment of atrophy), selective estrogen receptor modulators with action on the vaginal wall, vaginal lubricants, and hyaluronic acid-based creams are the most commonly used.[13] Although no unequivocal data are available on the safety of local treatment with estrogen, some studies advise against its use in women with a history of hormone-dependent cancer.[14–16] More natural therapies, such as hyaluronic acid, despite their proven efficacy, have been shown to have a temporally limited effect.[17–19]

One recent alternative for the management of urogenital syndrome is microablative fractional CO_2 laser, applied vaginally, in order to promote tissue regeneration through the production of collagen and elastic fibers. This technique has been previously shown to provide effective resolution of symptoms related to vulvovaginal atrophy for up to 18–24 months[20–23]. Several studies have demonstrated the effectiveness of laser in the treatment of vaginal atrophy, but only a few studies have tested the effectiveness of CO_2 laser in cancer survivors.[7 21] The aim of our study was to evaluate the effectiveness of CO_2 laser treatment of urogenital syndrome, in survivors of gynecological cancer (breast, ovarian, uterine, cervical), particularly breast cancer.

METHODS

This is a retrospective study, which included all patients with a history of gynecological cancers and vulvovaginal atrophy who underwent CO_2 laser treatment between November 2012 and February 2018. The study was approved by the local ethics committee. Women were recruited from four centers in Italy: the gynecology departments of Università Campus Biomedico, Rome; Ospedale di Stato della Repubblica di San Marino, San Marino; Azienda Ospedaliera Careggi, Florence; and Ospedale San Raffele, Milan.

All patients who met the following criteria were included: women aged between 18 and 75; Eastern Cooperative Oncology Group performance status <2; history of breast, ovarian, cervical, or uterus cancer. Patients had to have had vulvovaginal atrophy with at least one of the following symptoms of urogenital syndrome: vaginal dryness, dyspareunia, vaginal introitus pain, burning, and/or itching. Patients were required to have undergone three or four sessions of fractional CO_2 laser treatment; had to have a negative Pap smear performed before undergoing treatment; had to have pre-treatment and post-treatment Visual Analog Scale (VAS) scores for the reported symptoms. Patients were excluded if they had any of the following: pregnant at the time of the study; decompensated psychiatric disorders or history of alcoholism or illegal drug abuse in the year before the study; urinary infections or asymptomatic bacteriuria at the time of enrollment; history of recurrent urinary tract infections (≥2 in the year before the study); macroscopic hematuria and/or urinary blood clots; abscesses, fistulas or other anatomical abnormalities that could interfere with treatment; pre-existing vaginal infections; use of hormone replacement therapy in patients with a hormone-sensitive cancer; use of vaginal preparations or lubricants in the 15 days before therapy.

All patients were evaluated before the first laser session, at each session, and 4 weeks after the last session. We evaluated pH; dryness; dyspareunia; burning; itching; and vaginal introitus pain. In particular, patients were asked to indicate the intensity of symptoms before the first session and 4 weeks after the last CO_2 laser session using VAS scoring from 0 ('no discomfort') to 10 ('maximum discomfort') in order to determine the change in the intensity of symptoms before and after treatment. All centers used the VAS scale for all patients. VAS scores were collected by the physician during the medical interview. In a subgroup of patients, it was possible to study the change in pH measured before the first session and 4 weeks after the last treatment session.

A fractional CO_2 laser system (SmartXide2V2LR, Deka m.e.l.a., Florence, Italy) was used with a vulvovaginal laser reshaping scanning system and appropriate probes for the vaginal area. This treatment method is based on the interaction between a specific CO_2 pulsed laser and the vaginal mucosa. Briefly, a laser beam is emitted fractionally, and the CO_2 laser is focused in small spots (called dots) that are separated by healthy tissue. Every pulse consists of constant high-energy peak power to produce rapid ablation of the epithelial component of the atrophic mucosa, followed by longer emission times that allow the CO_2 laser to penetrate further into the mucosa. The pulses are distributed over the vaginal wall and are spaced (dot spacing) to cover the entire treatment area. A specific probe is used to deliver the pulses, which allows for energy emission at 360 degrees. To completely treat the vaginal area, it is necessary to emit many laser spots while progressively extracting the probe from the vaginal fundus. Each treatment spot consists of two steps. After the first energy release, the probe is rotated approximately 2 cm (using the regulatory tool) clockwise while remaining at the same vaginal distance. The laser energy was set at 40 W power and transmitted through an intra-vaginal probe with a dwell time of 1000 µs and dot spacing of 1000 µm in order to treat the entire circular surface of the vagina covered by the probe. A similar protocol has been used by previous authors.[21]

During all treatment sessions, the following two-phase protocol was followed: first, positioning of the speculum and observation of the vagina, then careful introduction of the probe deep into the vaginal canal before starting the procedure. Each session lasts 6 min. No vaginal lubricants or creams were recommended during or after the laser sessions. The protocol included at least three applications: at baseline, 30 days, and 60 days. No patient needed local anesthesia or any kind of preparation. Patients were asked to inform the operator about any complications during or after the treatment, such as bleeding, leucorrhea or post-procedure pain. Periodic evaluations were performed during the laser session and at the end of the laser treatment. No patient required a second cycle of treatment. Data from the aforementioned centers were compared and standardized in order to combine them into a single sample. For each variable, the arithmetic average of pre-treatment and post-treatment VAS scores was calculated to evaluate whether the difference between the two averages was statistically significant ($p<0.05$) using the Wilcoxon test. Improvement rates were also evaluated with the following formula: ((post-treatment VAS – pre-treatment VAS) × 100)/pre-treatment VAS. The authors attest to the fact that there are no conflict of interests with the laser manufacturer to declare.

Table 1 Results for the total number of patients

	No of patients	Pre-treatment	Post-treatment	P value	Improvement (%)
Dryness	146	8.34	2.86	<0.00001	66%
Dyspareunia	124	8.89	3.66	<0.00001	59%
Burning	56	6.26	1.92	<0.00001	66%
Introitus pain	48	8.5	3.9	<0.00001	54%
Itching	31	5.29	1.49	<0.00001	54%
pH	48	7.08	6.19	<0.00001	11%

RESULTS

A total of 1213 patients underwent CO_2 laser treatment during the time period of the study. The distribution among the participating centers was as follows: 590 from San Marino; 323 from Florence; 201 from Milan; 99 from Rome. Of these, 1048 patients were excluded because they did not meet the inclusion criteria (994 patients had no history of gynecological cancer, 31 patients had no data for pre- and/or post-treatment VAS scores, 22 patients received fewer than three laser sessions, one patient received five laser sessions). No woman was pregnant, had a synchronous gynecological cancer, or had undergone previous pelvic radiation. After applying the above-listed criteria, 165 patients were included in the study: 49 from San Marino (29.7%); 71 from Florence (43%); 29 from Rome (17.6%); 16 from Milan (9.7%).

The mean age at the time of treatment was 53 years (range 31–73), with mean age of menopause at 45 years (range 31–54) and mean age of cancer diagnosis at 47 years (range 31–56). Patients were divided into groups based on reported symptoms. There was a statistically significant difference between the pre- and post-treatment values for each of the variables considered in both the patients with gynecological cancer and those with breast cancer (Table 1, Figures 1-2). Dryness (146 women) improved by 66% (pre-treatment VAS mean value 8.34, post-treatment VAS mean value 2.86). Dyspareunia (124 women) improved by 59% (pre-treatment VAS 8.89, post-treatment VAS 3.66), burning (56 women) improved by 66% (pre-treatment VAS 6.26, post-treatment VAS 1.92), pain at introitus (four women) improved by 54% (pre-treatment VAS 8.5, post-treatment VAS 3.9), and itching (31 women) improved by 54% (pre-treatment VAS 5.29, post-treatment VAS 1.49). Level of pH (48 women) improved by 11% (pre-treatment PH 7.08, post-treatment PH 6.19). The side effects were evaluated as pain greater than VAS score 6 after and during the treatment period, and no side effects were observed in any sessions, such as problems in sexual function after and during the treatment period, the presence of abrasions, or ulcerations after the laser treatment.

Based on the type of cancer, patients were subsequently divided into two subgroups: a group with breast cancer (135 women) and a group with gynecological cancer (10 ovarian, 15 uterine, 5 cervical cancers). No patient was receiving radiotherapy and/or chemotherapy at the time of the laser sessions. Statistically significant differences between pre- and post-treatment values were seen in women with breast cancer (Table 2,Figure 1and Figure 2 . Dryness improved by 64% (pre-treatment VAS 8.3, post-treatment VAS 2.98), dyspareunia improved by 59% (pre-treatment VAS 8.99,

Table 2 Results for patients with breast cancer and gynecological cancers

	Patients with breast cancer (n)	Pre-treatment breast cancer	Post-treatment breast cancer	P value breast cancer	Percentage of improvement breast cancer
Dryness	128	8.3	2.98	<0.00001	64%
Dyspareunia	115	8.99	3.66	<0.00001	59%
Burning	47	6.08	1.97	<0.00001	68%
Introitus pain	37	8.59	4.14	<0.00001	52%
Itching	28	5.14	1.47	<0.00001	71%
pH	39	6.97	6.23	0.00164	11%
	No of patients gynecological cancers	**Pre-treatment gynecological cancers**	**Post-treatment gynecological cancers**	**P value gynecological cancers**	**Percentage of improvement gynecological cancers**
Dryness	18	8.56	2.08	<0.00001	76%
Dyspareunia	9	7.56	3.67	0.02444	51%
Burning	9	7.22	1.67	0.00058	77%
Introitus pain	11	8.18	3.09	0.00228	62%
pH	9	7.56	6	0.00614	21%

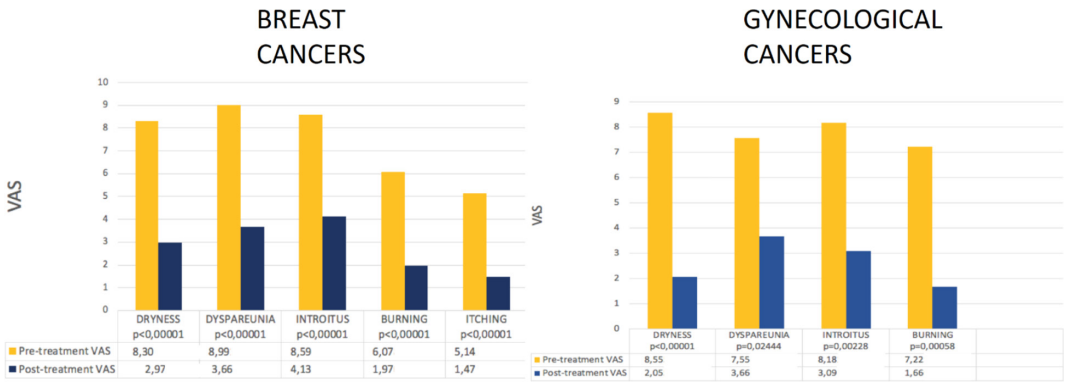

Figure 1 Pre-treatment and post-treatment Visual Analog Scale (VAS) mean values in the group of patients with breast cancer and gynecological cancers

post-treatment VAS 3.66), burning improved by 68% (pre-treatment VAS 6.08, post-treatment VAS 1.97), pain at introitus improved by 52% (pre-treatment VAS 8.59, post-treatment VAS 4.13), and itching improved by 71% (pre-treatment VAS 5.14, post-treatment VAS 1.47). The level of pH improved by 11% (pre-treatment PH 6.97, post-treatment PH 6.23).

In survivors of gynecological cancer, statistically significant differences were also seen between pre- and post-treatment values (Table 2, Figure 1Figure 2). Dryness improved by 76% (pre-treatment VAS 8.56, post-treatment VAS 2.08), dyspareunia improved by 51% (pre-treatment VAS 7.56, post-treatment VAS 3.67), burning improved by 77% (pre-treatment VAS 7.22, post-treatment VAS 1.67), and pain at introitus improved by 62% (pre-treatment VAS 8.18, post-treatment VAS 3.09). Level of pH improved by 21% (pre-treatment PH 7.56, post-treatment PH 6.).

DISCUSSION

This study shows that dryness, dyspareunia, burning, pain at introitus, and itching were all improved by microablative CO_2 laser treatment. This is an important finding, since an increasing number of women have disorders related to the menopause induced by cancer therapies, given the high survival rates of women with gynecological cancers and the increased incidence of cancer in pre-menopausal women. The European Menopause and Andropause Society and International Gynecologic Cancer Society joint statement on managing the menopause after gynecological cancer, which has recently been published, reminds us that the approach should be individualized, and should consider age, tumor type and stage, concomitant morbidities, and therapies. This is best handled by a multidisciplinary team.[37]For survivors of breast cancer, the use of systemic estrogen therapy is considered a contraindication by some, although data in the literature lack consensus.[22] The largest studies of the clinical risk related to hormone replacement therapy in this subset of patients are the Hormonal Replacement After Breast Cancer—Is It Safe (HABIT) trial and the Stockholm trial. In the HABIT prospective trial, Holmberg and colleagues compared the differences in the risk of cancer recurrence in a group of 442 women with breast cancer treated with or without hormone replacement therapy. An increased relapse rate of 17.6% was seen among women with hormone replacement therapy versus 3.2% of women without hormone replacement therapy.[24] In the Stockholm prospective and randomized trial, 378 patients with a history of breast cancer were studied. Fahlen and colleagues assessed the difference in risk of cancer recurrence among a group of patients treated with hormone replacement therapy (188 women) and a control group (190 women) after a follow-up of 10.8 years[25] . No statistically significant difference between the two groups was seen in cancer recurrence (60 among women taking hormone replacement therapy vs 48 in controls), or in mortality.

For survivors of ovarian cancer, data on the safety of hormone replacement therapy are inconclusive.[22] Pre-clinical studies, and in vitro and in vivo studies show that estrogen promotes the growth of ovarian cancer cells.[26 27] These data are confirmed by a large meta-analysis on 21 488 menopausal women with ovarian cancer receiving hormone replacement therapy. The data show an increased risk in women treated with hormone replacement therapy for 5 years and this risk does not seem to decrease after

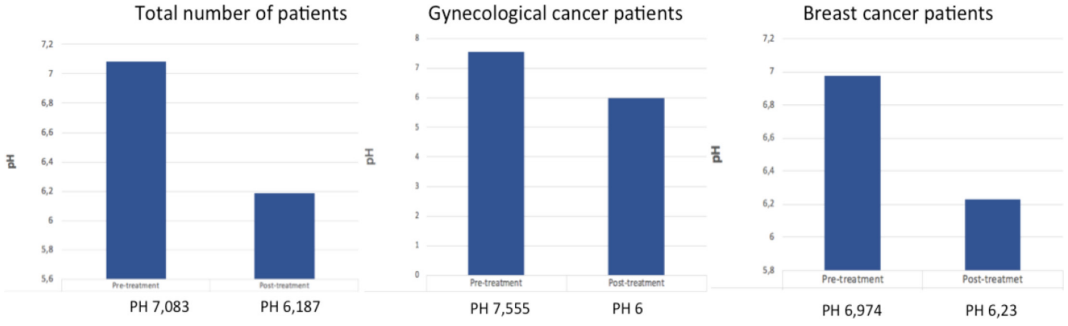

Figure 2 Pre-treatment and post-treatment pH mean values in the total number of patients treated, in the group of patients with gynecological cancers, and in patients with breast cancer

the discontinuation of therapy.[28] However, other studies observed a favorable outcome in survivors of ovarian cancer who use hormone replacement therapy compared with those who do not use it.[29 30]

In survivors of endometrial cancer, estrogen therapy does not appear to be associated with an increased risk of relapse.[22] Barakat et al, in their randomized double blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer, showed that the incidence and absolute recurrence rate of malignancy were low in the group treated with estrogen.[31] Specifically, a 2014 meta-analysis compared the risk of recurrence between 896 women receiving hormone replacement therapy and 1079 controls, demonstrating the lack of an increased risk of recurrence in patients treated with hormone replacement therapy. Furthermore, a possible protective effect of combined hormone replacement therapy on cancer relapse was seen, but these results require further confirmatory studies.[32] For cervical cancer, hormone replacement therapy has not been associated with the development of squamous malignant cells.[22] However, one study observed a significant risk of cervical adenocarcinoma in women treated with hormone replacement therapy (OR=2.7).[33]

The clinical safety of local estrogen therapy has long been debated and conflicting data have been reported. Indeed, some studies have shown an increase in serum estradiol levels in women who were receiving topical aromatase inhibitors and estrogen.[14 15] In addition, a 2015 review of 33 studies evaluated the dose-dependent effects of vaginal estrogen therapy on plasma estradiol levels, observing an increase in serum estradiol levels even for medium-to-low local estrogen doses.[16] In this scenario, and particularly in this subset of patients, CO_2 laser seems to be a valid alternative for the local treatment of vulvovaginal atrophy, as it reduces the intensity of the reported symptoms, and also has a regenerative effect on vaginal tissues. Several studies report the effectiveness of laser in vulvovaginal atrophy treatment, but few studies have tested the efficacy of CO_2 laser on women who survived a gynecological cancer.[7 21]

For the effectiveness of CO_2 laser, Zerbinati and colleagues demonstrated the stimulation of collagen synthesis, the increase of acid mucopolysaccharides, and the increase of glycogen content in the epithelial cells in biopsy samples of vaginal tissue treated with CO_2 laser.[34] In 2014, Salvatore and colleagues showed that CO_2 laser treatment in post-menopausal women leads to significant improvements in vulvovaginal symptoms with follow-up of up to 12 weeks.[35] In another study, the investigators showed that CO_2 laser is associated with a significant improvement in sexual satisfaction and quality of life in postmenopausal women.[36] In addition to our study, other studies have been performed on patients diagnosed with gynecological cancers, demonstrating a statistically significant difference between pre- and post-CO_2 laser treatment.[7 21] However, these studies had smaller sample sizes than our study.

In our study, we observed significant improvements in post-treatment symptoms, confirming the effectiveness of CO_2 laser therapy in survivors of gynecological cancer. In addition, no side effects were seen in any laser CO_2 sessions. The strength of our study, compared with previous similar studies,[7 21] is that it is a multi-center study, with a large sample size, including women with breast, ovarian, uterine, or cervical cancers. The retrospective nature and the limited follow-up limit the validity of our study from a statistical point of view. This possible bias is balanced by the high number of women included. We are planning a prospective study with a longer follow-up to better assess the long-term outcome of these patients. Furthermore, patient satisfaction could not be evaluated because not all centers planned to value this parameter. Fractional microablative CO_2 laser therapy is an effective method for treating the symptoms of genitourinary syndrome in post-menopausal women and in survivors of gynecological cancer.

Contributors RA, DL, SS, MF, and AP contributed to the planning of the study, AG, MB, and RM contributed to conducting the study, and FP and DL to reporting of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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