Histological study on the effects of fractional CO2 laser on genito-urinary atrophy in symptomatic oncological and non oncological patients: pilot study

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ABSTRACT

AIM: To evaluate the efficacy of fractionated CO2 laser therapy on the improvement of vaginal atrophy and mild/moderate SUI symptoms in women in physiological menopause or surgical menopause due to a history of cancer.

MATERIALS AND METHODS: Between February and December 2015, we enrolled 63 post-menopause patients for physiological reasons or due to medical and/or surgical cancer treatments, with local symptoms evaluated using VHIS (Vaginal Health Index Score) and VAS (Visual Analogue Score). The impact of urinary incontinence on the patients' everyday life was evaluated by administering an ICIQ (International Consultation on Incontinence Questionnaire). The patients' objective and subjective symptoms were evaluated both before treatment (T1) and progressively at each treatment performed at 30-day intervals (T2 and T3).

RESULTS: It was observed that even after the first treatment there was a significant improvement in both the VHI and the VAS scores, with a significant reduction in both subjective symptoms (dryness, burning, dyspareunia) and objective symptoms ($P < 0.01$) and, also, a reduction in the frequency and quantity of stress urinary incontinence (SUI) ($P<0.01$), improvements that persist even after the subsequent treatments. In addition, the improvements in VHI scores were significantly greater in oncological patients than non-oncological patients. 90% of all patients were satisfied with the procedure - which is free of side effects - and said that there had been a significant improvement in their quality of life.

CONCLUSIONS: Fractionated CO2 laser therapy can be considered a safe, efficacious and easy to perform treatment for resolving the subjective and objective symptoms typical of the post-menopausal period, especially vaginal atrophy and SUI.

INTRODUCTION

Genitourinary Syndrome of Menopause (GSM) affects 50% of women, in some cases, even before menstruation stops completely. It is a chronic, progressive condition that tends to modify the style and quality of life of post-menopausal women, causing significant alterations in the sexual sphere. [1-3]

GSM is characterised by an involution of the genitourinary mucosae and vulvovaginal tissues, and it is directly related to the reduction in ovarian function with a drop in circulating hormone levels (oestrogens, androgens, etc.) whose receptors are abundantly expressed in the various tissues of the female body and especially in the genitourinary tract. [4]

GSM is caused by histological, morphological and clinical changes resulting from collagen modifications; there is a change in the relationship between type I and type III collagen fibrils, which lose their typical three-dimensional trabecular arrangement; there is also a reduction in the quantity of elastic fibres and vascularisation and the vaginal epithelium starts to thin and loses its characteristic stratified appearance. [5] Consequently, the diameter of the vagina is reduced and it loses its elasticity and the vaginal epithelium becomes pale and tends to develop petechiae. Clinically, these changes present as dryness, burning sensation, irritation, severe dyspareunia, dysuria and stress urinary incontinence (SUI). This has a considerable influence on the quality of the subject's sex life, with symptoms that can be invalidating and that, if untreated, tend to worsen over time. [7-8] Considering the progressive rise in the age of the general population, women have to face this problem, and the related disorders, for more than one third of their lives. [9]

A variety of therapeutic options have been proposed to provide relief from the symptoms of the menopause, including topical and systemic hormonal therapies and non-hormonal therapies. [10] Non-hormonal treatments and lubricants improve symptoms in the short term, however, the effect does not persist over time. Topical hormonal therapy is the gold standard for the symptoms of genitourinary syndrome; however, patient compliance remains poor, especially long-term treatment and it excludes patients who have had breast cancer and who, due to their young age and adjuvant therapy, present the most severe forms [11-12]

In recent years, a novel therapeutic option has been introduced with a regenerating anti-age treatment for the vaginal mucosa, using a fractionated CO2 laser, which has positive effects on tissue remodelling, collagenogenesis and angiogenesis. [13] This system induces a remodelling of the collagen and the elastic fibres of the vaginal wall in a completely asymptomatic and side-effect free manner. The action of the fractionated CO2 laser on vaginal trophy is obtained by means of a microablative action involving the interaction of heat shock proteins (43,47,70) activating the local increase in specific cytokines, which, in

turn, activate the fibroblasts to produce the other components of the extracellular matrix (proteoglycans, glycosaminoglycans).

Amongst the activated cytokines, a fundamental role is played by transforming growth factor-beta, which stimulates the proteic matrix in the production of collagen by fibroblast growth factor and epidermal growth factor that stimulate angiogenic activity and the migration and proliferation of the endothelial cells by platelet-derived growth factor that stimulates the fibroblasts to produce the components of extracellular matrix and by vascular endothelial growth factor that governs vasculogenesis and neoangiogenesis. [14-16]

The action process has three phases: the first characterised by early thermal damage (within 48-72h of treatment), followed by the proliferation phase" with fibroblast recall and new production of collagen and extracellular matrix (in the following 30 days) and, lastly, the remodelling phase (after 40 days) with the apposition of mature collagen fibres and new elastic fibres. [17]

This therapy constitutes a true tissue-regeneration treatment, also known as light-induced eutrophication, which improves the condition of the vaginal mucosa by means of a novel procedure, exploiting fractionated CO2 laser technology with pixel technology and using a probe developed specifically for the vaginal anatomy. [Fig.1]

The laser's energy is therefore diffused into the various layers of the vaginal wall, reactivating the synthesis of extracellular matrix and collagen, with the recovery of tissue trophism and a consequent improvement in related symptoms.

The purpose of this study is to evaluate the efficacy and effects of CO2 laser therapy (Femilift Alma Lasers) on vaginal atrophy and mild-to-moderate stress urinary incontinence (SUI) [Fig. 2] in women in the post-physiological or surgical menopause period

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Figure 1. Endovaginal laser probe

Type of SUI	***Description***
Type 0 SUI	The patient has a typical history of stress urinary incontinence, but no urine leak is observed during the physical and urodynamic exam.
Type 1 SUI	Under stress, the neck of the bladder and proximal urethra open and drop less than 2 cm; incontinence is apparent when there is an increase in intra-abdominal pressure. It is thought to be a symptom of intrinsic sphincteric deficiency (ISD).
Type 2 SUI	Under stress the neck of the bladder and the proximal urethra open and drop by more than 2 cm, with rotational bladder and urethra descent; there may be concomitant ISD and a low leak point pressure.
Type 2B SUI	Under stress there may be further descent and the proximal urethra opens with signs of incontinence; there may be concomitant ISD and a low leak point pressure.
Type 3 SUI	The proximal urethra no longer has a sphincteric function, the neck of the bladder and proximal pressure can open at rest in the absence of dextrusor contractions.

Figure 2. Stress-Incontinence classification

MATERIALS AND METHODS

This pilot study was conducted between February and December 2015 on 63 patients with vaginal atrophy and type 0, 1 or 2 SUI symptoms, who were evaluated clinically and with instrumental investigations in order to quantify the entity of symptoms and gauge the improvement after treatment. The patients were treated in the outpatient clinics of the Azienda Ospedaliera Cannizzaro di Catania Obstetrics and Gynaecology Unit.

The pre-treatment assessment required: a general and a local physical exam, a smear test performed within the previous 12 months, a thorough assessment of the inclusion and exclusion criteria [Annex 1] and the completion of quality of life questionnaires, in order to gauge the symptoms experienced by patients; those who complained of isolated urinary incontinence or urinary incontinence associated with a genital disorder underwent a urological - gynaecological visit, urine analysis and urine culture and answered questionnaires used to evaluate the SIU (type 0-1-2).

Once the need for treatment had been confirmed, all patients were administered an informed consent form.

A CO2 laser (AlmaLaser) was used, in combination with a special "Femilift" protocol, involving the application, through holographic lenses, of microablative CO2 laser energy, with an 81-pixel beam in a 9x9 template. [Annex 2]

Treatment consists of 3 applications, at time points 0, 1 and 2 months (T1, T2, T3), 30 days apart, and a follow-up visit 3 months after the end of treatment.

Symptoms were evaluated using validated international quality of life questionnaires devised for the reported condition and SUI. More specifically, the intensity of dyspareunia was evaluated using a pain visual analogue scale (VAS), with a range of 0-10 (0: complete absence of symptoms, 10: worst symptoms). The impact of urinary incontinence on the everyday life of the patients was evaluated by administering the ICIQ [Annex 3] and assessing the change in the final score. Both the subjective evaluations were performed at each outpatient appointment, in order to observe their evolutions.

The objective evaluations were performed using the Vaginal Health Index Score (VHI-S), which was recorded before each laser treatment and at the follow-up visit 3 months after the end of treatment [Annex 4].

In September 2015, we assessed the first 33 patients (51.5%), who were distributed as follows per condition: 16 patients (48.5%) treated for vaginal atrophy only and 17 patients (51.5%) for vaginal atrophy and SUI. 15 of the 33 patients (45.4%) had a history of cancer treatments.

The 33 evaluable patients underwent a pre-treatment biopsy and, at the current time, 20 post-treatment biopsy samples have been collected in compliance with the protocol 3 months from the end of treatment.

The characteristics of the sample examined are shown in Tab. 1.

Statistical analysis was performed also considering mean and standard deviation; an ANOVA model was used for repeated measurements and an ad hoc T-test was used to evaluate the efficacy of the single treatments on symptoms.

	Mean	**SD**	**Min-Max**
Age	52,3	9,9	33-71
Age at Menopause	47.0	6.5	38-61
Years since menopause	7.0	5.8	1-20
Equality	2	0.86	0-5
Menarche	11.72	1.1	10-14
Surgical meno.	46.06	6.6	38-54
Physiological meno.	47.42	5.3	39-59

Tab. 1

The characteristics of patients with a history of cancer are indicated in Fig. 3.

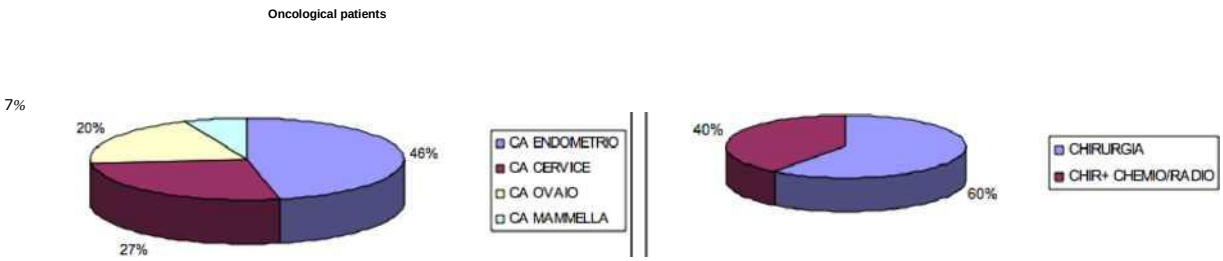


Fig 3

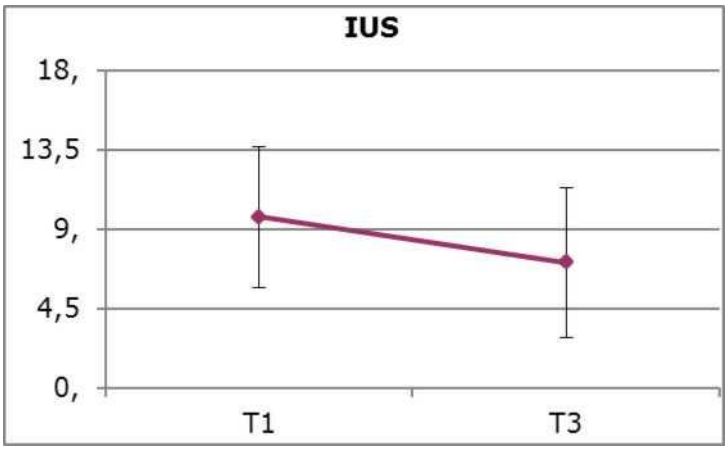
The pre- and post-treatment vaginal biopsy was performed using a punch needle with a diameter of 2mm, in order to obtain and cylinder of tissue to be embedded in paraffin and examined. This procedure was performed under local anaesthetic with an evaluation of the right or left lateral vaginal wall.

The efficacy of the laser was evaluated by means of the histological modifications in the vaginal wall in terms of both overall thickness and the relationship between the various components of the dermis, especially by typing the collagen, for which, in addition to the conventional morphological assessment, a qualitative evaluation of the concentration of type III and IV collagen was performed on sections of formalin-fixed tissue with anti-collagen IV and anti-collagen IV antibodies produced by Biogenex.

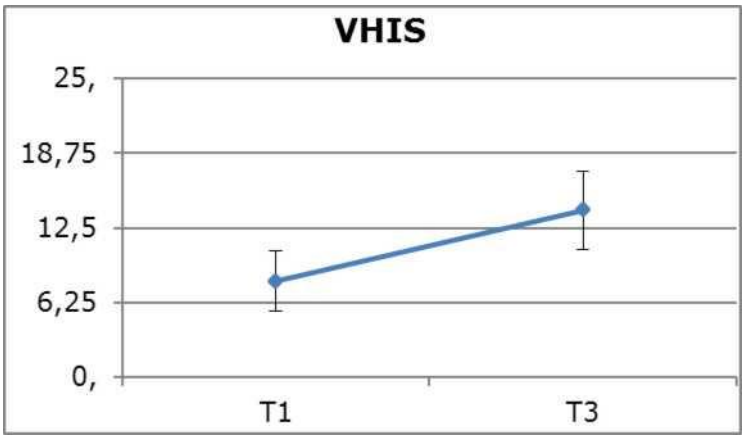
RESULTS

Graph 1 shows the significant progressive reduction in the scores during treatment T1 (before), and T3 (after 3rd) confirming the improvement in SUI symptoms, p-value<0.05. In the opposite direction, graph 2 clearly shows the progressive increase in the vaginal atrophy scores, showing a significant improvement in the objective evaluation assessed using the VHI-S, p-value <0.05; lastly, also the VAS scores for dyspareunia underwent a significant reduction, p-value <0.05, as shown in graph 3.

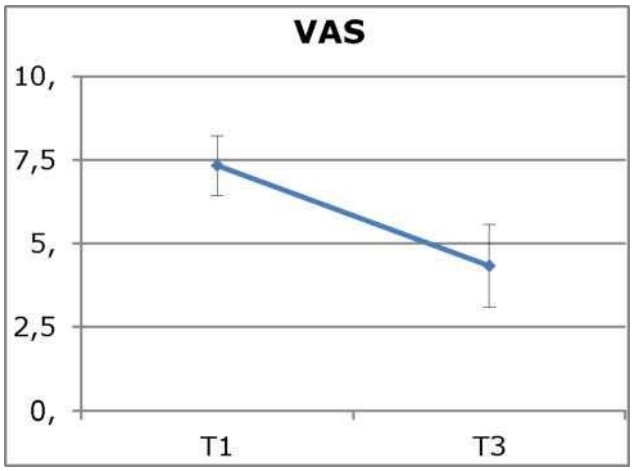
No adverse event occurred during the study period.



Graph 1 Effect on SUI- ICIQ (0 best -18 worst)



Graph 2 Effect on atrophy - VHI score (5 worst - 25 best)



Graph 3 Effect on dyspareunia - VAS (0 best- 10 worst)

The change in scores measured at time points T1 and T3 for the whole population is shown in table 2.

	T1	T3
SUI*	9.7 ± 4.0	7.1 ± 4.2
VHI score	8.0 ± 2.5	14.0 ± 4.5
Dyspareunia**	7.3 ± 0.8	4.3 ± 1.2

Note: Data are presented as mean ± sd *Measured on ICIQ
**Measured on VAS scale (range 0-10)

Tab. 2

Within our caseload, the two populations oncological patients and non-oncological patients were examined (tab. 3), comparing the following menopause-related characteristics (tab. 4)

	no. onc. pat. (%)	no. non-onc. pat. (%)
Atrophy	7 (21.2)	9 (27.2)
SUI	0	4 (12.1)
Atrophy+SUI	8 (24.2)	5 (15.1)

Tab. 3

	oncological patients			non oncological patients		
	Mean	SD	Min-Max	Mean	SD	Min-Max
Age	50.4	10.6	33-70	55.1	9.4	39-71
Age at Menopause	45.8	6.5	38-58	48.5	6.2	39-61
Years since menopause	5.4	5.1	1-20	9.1	5.9	1-20

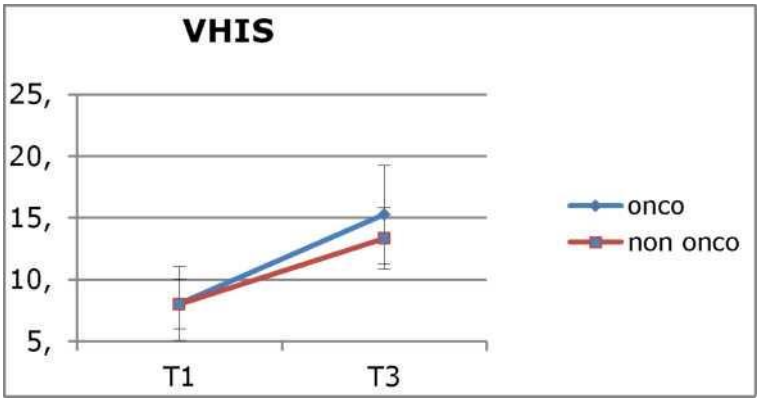
Tab. 4)

We obtained the following results in the two populations.

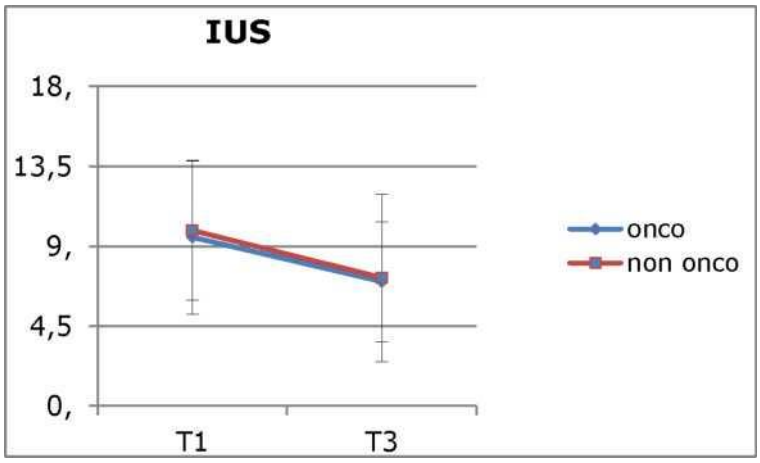
Gradual increase in vaginal atrophy scores in the two populations, p-value<0.05, showing the significant improvement in the objective evaluation using the VHI-S [Graph 4].

Significant progressive reduction in the scores, confirming the improvement in SUI symptoms, p-value<0.05 for the oncological population and for the non-oncological population, p-value<0.05 [Graph 5].

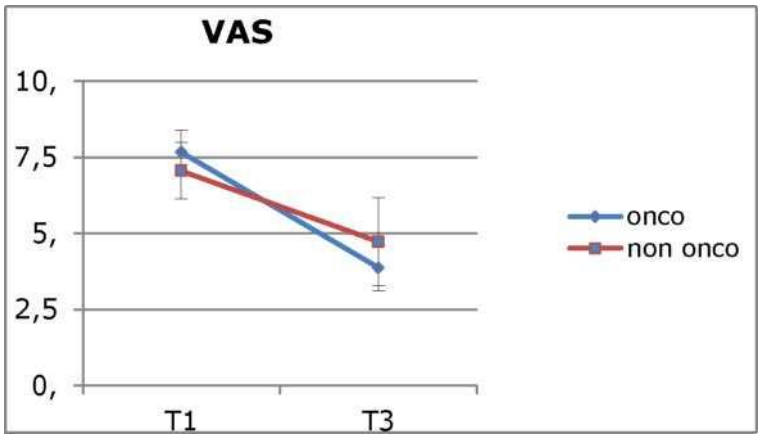
The VAS scores for dyspareunia also showed a significant reduction, p-value<0.05, in the oncological population and in the non-oncological population, p-value <0.05 [Graph 6]



Graph 4. VHI score variation in the two populations



Graph 5. ICIQ score variation in the two populations



Graph 6. VAS score variation in the two populations

The change in scores measured at time points T1 and T3 for both populations is shown in table 3.

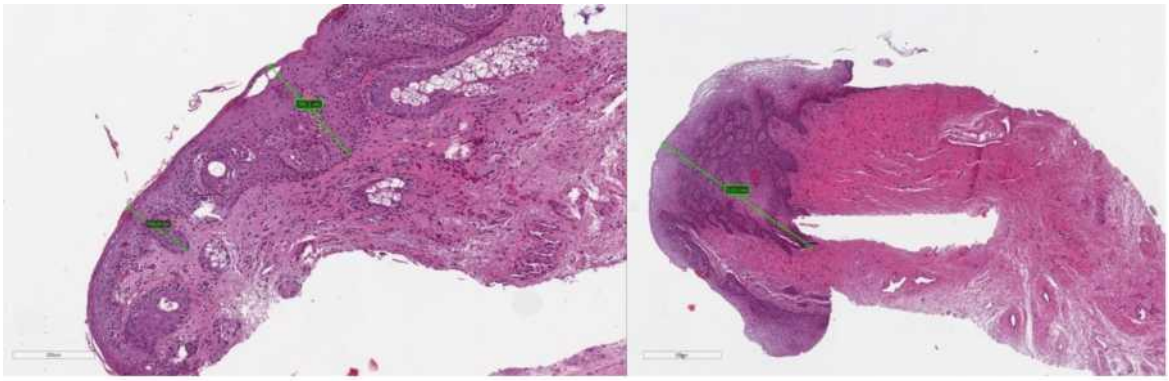
	oncological		non -oncological	
	T1	**T3**	**T1**	**T3**
SUI*	9.5 ± 4.3	7 ± 3.3	15.2 ± 4.4	10 ± 4
VHI score	8 ± 3	3.8 ± 0.7	2 7 ± 1	4.5 4.7 ± 1.4
Dyspareunia**	7.6 ± 0.7			

8 ±7.2 ± 5.1 13.3 ±

Note: Data are presented as mean ± sd *Measured on ICIQ **Measured on VAS scale (range 0-10) **Tab.3**

A comparison between the two populations immediately reveals that, surprisingly, the oncological population obtained a greater improvement than the population that had not been previously treated for cancer, especially in terms of improvement in the subjective symptoms and condition of the vagina as observed during the clinical exam.

The variations in histological characteristics in terms of the thickness of the vaginal mucosa observed with this protocol are shown in figure 4. Before treatment, the stratified squamous epithelium appears atrophic and thin, with the disappearance of the crests of the Malpighian layer and dermal papillae, with a flat dermo-epidermal junction. After the treatment, the various layers were seen to have been restored, especially the Malpighian layer, with the re-appearance of the dermal papillae.



A B

Fig. 4 Histological preparation of a section of H&E-stained vaginal mucosa

(A) Vaginal mucosa before treatment.

(B) Vaginal mucosa after treatment. Significant increase in the thickness of the epithelium (301.1 μm versus 1133 μm)

Figure 5 clearly shows the immunohistochemical evaluation of type III and type IV collagen, indicating the greater production of type III collagen responsible for the improvement in function and for re-establishing the equilibrium of the vaginal mucosa.

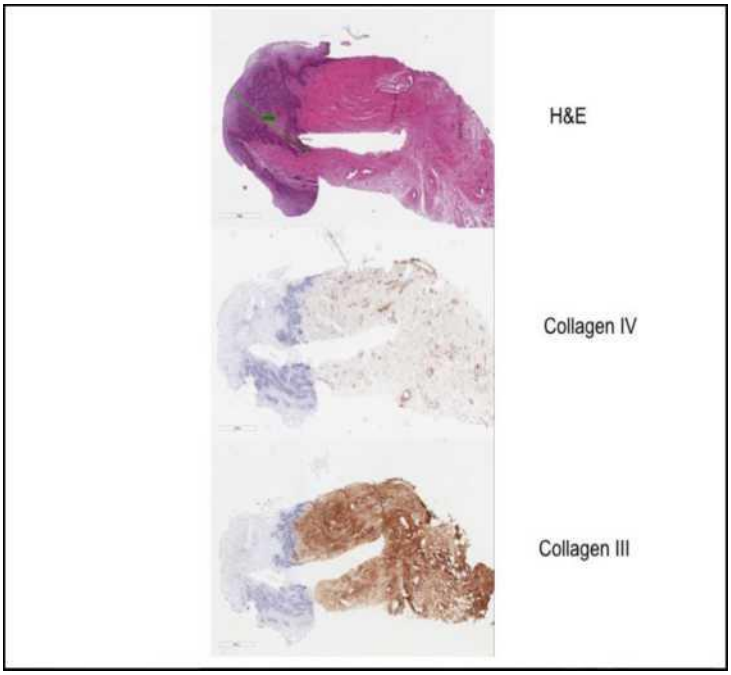


Fig. 6-7 Evaluation of type III collagen using monoclonal antibody

(A) Vaginal mucosa before treatment.

(B) Vaginal mucosa after treatment. Significant increase in the thickness of the epithelium

Fig.5 Post-treatment immunohistochemical evaluation of type III and IV collagen.

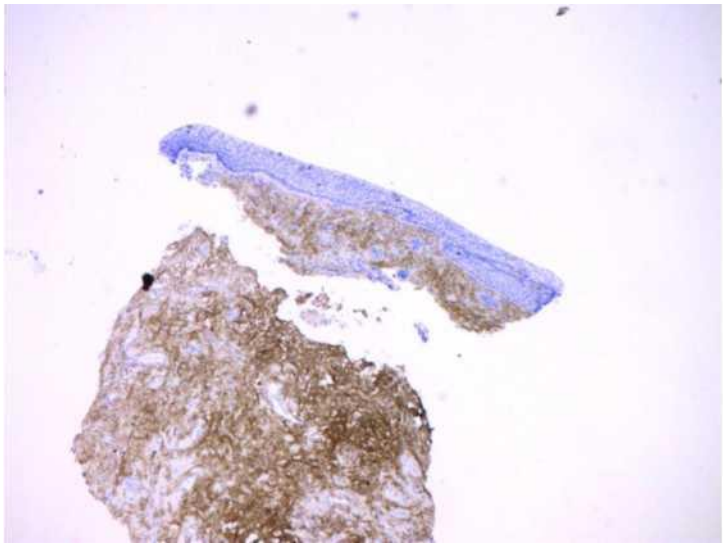


Fig.6 Pre-treatment immunohistochemical evaluation of type III and IV collagen.

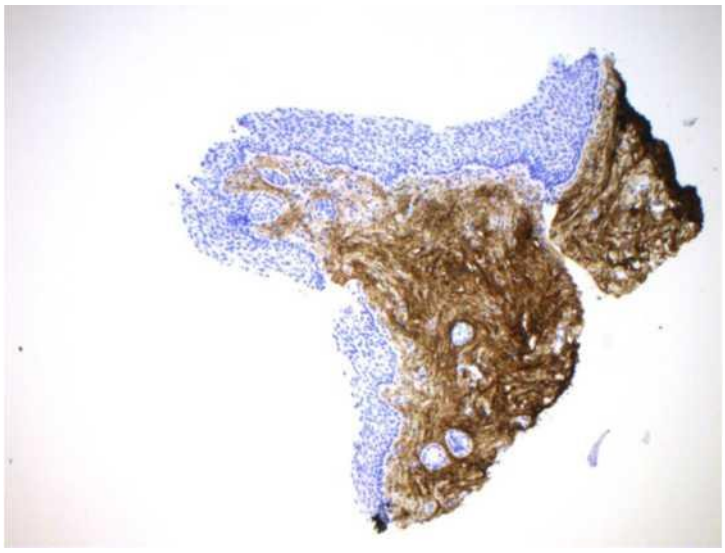


Fig.7 Post-treatment immunohistochemical evaluation of type III and IV collagen.

DISCUSSION

Over the past decade, the use of CO2 laser has been extensively adopted in dermatology and cosmetic and plastic surgery. This treatment consists in transforming light energy into heat by exploiting a mixture of gases activated by electric energy. The heat causes the water contained in the target cells to evaporate. The mechanism is based on the activation of a small family of proteins, known as heat shock proteins, whose sub-types 43, 47 and 70, act as chaperones to collagen, and are over expressed after CO2 laser treatment, playing a predominant role in the induction of other growth factors. Of these, TGF-beta is recognised as being the key cytokine in the inflammation phenomena and fibrogenetic processes that produce collagen and extracellular matrix. [18-19]

The effect of the laser is based on the rapid and temporary activation of the heat shock proteins, causing a repeated change in cell metabolism and inducing the expression of certain receptor patterns only on the surface of the cells of the tissue treated. [20-21] Thermal stress causes the denaturation of the tissue proteins and the activated HSP protect the denatured protein cells, therefore avoiding erroneous aggregations. [22-23] Its power is expressed in Watts, and density depends on the spot size. The lens used to focus the beam can be of the refraction or reflection type and the focal length determines the effective spot size. A system of zinc selenide lenses is required for the refraction of the optical beam and a system of mirrors is used to reflect it.

The fractionated CO2 laser treatment consists of two phases: a first thermoablative phase and a second proliferative phase. The rapid and efficacious administration of microablative energy split into tissue micropixels able to provide a thermal effect deep in the structures of the vagina stimulates collagen remodelling and epithelium thickening, therefore guaranteeing a restoration of metabolic trophism and the dynamicity of the epithelium, which improves the elasticity and moisture of the vaginal walls and provides relief from discomfort in menopausal women.

The laser treatment applied to the vagina allows a "regeneration of the tissues", using a minimally-invasive treatment that improves the elasticity and moisture of the vaginal wall, providing relief from the discomfort of menopausal symptoms.

The preliminary results of our study revealed how the vaginal wall radiated with fractionated CO2 laser immediately caused histological changes in qualitative and quantitative terms with

an objective remodelling of the tissue. The most obvious effect was neocollagenogenesis and the reconstruction of the trabecular architecture typical of collagen, with a consequent reduction in elastosis and therefore in the tissue laxity typical of the post-menopausal period. In addition, the neovascularisation and

the increase in thickness of the dermal papillae, contributed to improving the moisture and objective characteristics of the vaginal mucosa (pH, secretions, epithelial characteristics, moisture and elasticity).

The analysis of this preliminary study shows that Femilift/Pixel CO2 provides effective relief from the predominant symptom (dyspareunia) calculated using the VAS, therefore improving the VHI scores (8.0 ± 2.5 T1 versus 14 ± 4.5 T3) and SIU scores (9.7 ± 4.0 T1 versus 7.1 ± 4.2 T3).

No side effects were observed and the procedure was well tolerated and did not require any local or systemic pharmacological or behavioural treatments. This favourable condition can most likely be attributed to the stringent application of the study's inclusion and exclusion criteria.

I The preliminary results obtained in this small group of patients call for further assessments with a larger caseload and completion of the planned 2-year follow-up period, in order to confirm the already very encouraging results obtained, which must be validated in subsequent randomised studies.

A number of issues remain open, such as the duration over time of the subjective and objective improvements achieved and the possibility of repeating the laser treatment.

CONCLUSIONS

The Pixel CO_2 laser is a high power and precision tool and represents a novel approach for outpatient medical treatments, with excellent treatment results, paving the way for new, safe and efficacious, outpatient surgical treatment options that are free from side effects and completely asymptomatic. As far as the treatment of grade 1 stress urinary incontinence is concerned, the treatment is extremely promising when used as an intermediate step between perineal rehabilitation and minimally-invasive suburethral sling surgery.

Patients treated for cancer, especially gynaecological cancers (breast, uterine and ovarian cancers), who developed treatment-induced menopause at a young age or who are already in the menopause, but with a contraindication for hormone therapy, constitute a real challenge in the treatment of genitourinary atrophy and SUI, considering the consequent severe change in quality of life. These survivors, who have already had to face the ordeal of cancer, have an extremely delicate mental balance; the limits deriving from the condition described and the contraindication for efficacious medical treatment have a significant effect on their quality of life with further difficulties in getting over the trauma they have experienced and returning to a normal life.

As the medical management of these patients must taken into account both physical and psychological needs, it is extremely complex and requires experience and appropriate treatment individualisation. In our study, it was this population that yielded the best results and expressed a higher level of satisfaction as regards both sexual and general quality of life.

The albeit preliminary data have shown that the CO2 laser with Femilift treatment protocol, constitutes for the female population treated for cancer a new and efficacious non-surgical treatment option, sometimes the only one available, when therapeutic limits and the contraindications for permanent or temporary hormonal treatments do not allow satisfactory results without posing risk for patients.

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Annex 1

Inclusion Criteria Check list

Age from 30 to 70 years old Menopause
Vaginal atrophy or Type I or II SUI or both Dispareunia
Signed informed consent Questionnaire completed

Exclusion Criteria Check list

Degenerative neurological disease
Urge or Mixed urinary incontinence (for pure SUI)
Genito-urinary cancer during treatment
Patients with pelvic organ prolapse staged > Stage II according ICS (for pure SUI)
Active vaginal infections
HPV/HSV local infections
Positive pregnancy test
Autoimmune disorders
Anamnestic allergic reactions to laser energy
Patient under treatment with photo sensitivity side effects medication Severe obesity
Patient unable to follow post treatment instructions Patients with over expectations

Energy and modality tretment

110 mj/ppxl with high laser mode and 0,5 Hz

- 3 sessions: interval period of one month between the sessions

Annex 1

- 3 passes during every session, with energy of 30 Watts and power between 60-100 mj/ppxl.

Energy for first application (between 60 and 100 mJ in relation of patient's menopausal age and comfort) will be given in the 2nd and 3rd sessions at 20% lower power (eg: 100 mJ in first session would be 80 mJ in second and third session).

If only SUI

3 positions: 11-12-1 clock position

- 1 cm beyond of the mid urethra level, directly under the mid urethra,

- -1 cm before the mid urethral level.

Annex 1

International Consultation on Incontinence modular Questionnaire short form (ICIQ-UI)
Monaco 1998

1. How often do you leak urine?

(0) Never

(1) About once a week or less often (2) Two or three times a week (3) About once a day (4) Several times a day (5) All the time

2. We would like to know how much urine you think leaks.
How much urine do you usually leak (whether you wear protection or not)?

(0) None (1) A small amount (2) A moderate amount (3) A large amount

3. Overall, how much does leaking urine interfere with your everyday life?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10

4. When does urine leak?

(Please tick all that apply to you)

□ Never - urine does not leak

□ Leaks before you can get to the toilet Leaks when you cough or sneeze Leaks when you are asleep

□ Leaks when you are physically active/exercising

□ Leaks when you have finished urinating and are dressed Leaks for no obvious reason

□ Leaks all the time

ICIQ score: sum scores 1+2+3:

Annex 1

Vaginal Health Index Score

Score	1	2	3	4	5
Elasticity	none	poor	fair	good	excellent
Fluid Volume (Pooling of Secretion)	none	Scant amount, vault not entirely covered	superficial amount, vault entirely covered	moderate amount of dryness (small areas of dryness on cotton tip applicator)	normal amount (fully saturates on cotton tip applicator)
pH	≥ 6.1	5.6 - 6.0	5.1 - 5.5	4.7 - 5.0	≤ 4.6
Epithelial Integrity	petechiae noted before contact	bleeds with light contact	bleeds with scraping	not friable – thin epithelium	normal
Moisture (Coating)	none, surface inflamed	none, surface not inflamed	minimal	moderate	normal