PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	Effectiveness of Ablative Fractional 2940 nm Laser Treatment for Vulvar Lichen Sclerosus
Principal Investigator	Roger Lefevre, MD

B1. PURPOSE OF PROTOCOL

The object of this non-randomized, prospective study is to assess the effectiveness of ablative fractional 2940 nm laser treatment of vulvar lichen sclerosus.

Aim 1: To assess physical and histological changes related to vulvar lichen sclerosus before and after laser treatment.

Aim 2: To evaluate participant satisfaction for laser treatment of vulvar lichen sclerosus.

The results of this study will determine whether fractional 2940 nm laser is an effective treatment option for lichen sclerosus, particularly for those participants not eligible for high-dose topical steroids or who have failed prior treatment with topical steroids.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Vulvar lichen sclerosus is an autoimmune condition affecting the epithelial lining and dermis of the anogenital region. On gross visual exam, vulvar lichen sclerosus is often described as ivory-white plaques or patches extending from the clitoris to the labia majora, perineum, and perianal region.[7] This inflammatory dermatologic condition causes thinning of overlying tissue, resulting in pruritus, pain, dyspareunia, and dysuria. Affected tissue is often compromised by symptoms of pruritus that cause scratching, leading to trauma to the skin such as excoriations, ecchymoses, fissures, and edema. The chronic inflammatory state often induces loss of vulvar architecture, including instances of flattening of the labia majora and minora, fusion between the prepuce and clitoris, and narrowing of the vaginal introitus.[5] These physical changes to the anogenital regional further exacerbate symptoms. Additionally, physical symptoms are compounded by dyspareunia and inability to comfortably have intercourse, which can influence sexual behavior and mental well-being. This chronic condition can often result in feelings of "isolation, hopelessness, depression, anxiety, anger, and low-self-esteem."[7] Vulvar lichen sclerosus most commonly affects prepubertal and perimenopausal or postmenopausal women, with an incidence of 14.6 per 100,000 women.[2] The etiology remains unknown, with many possible multi-factorial components such as hormones, genetics, presence of other autoimmune conditions, and local and environmental factors acting as potential causes.

Vulvar lichen sclerosus is often diagnosed by gross physical exam and participant report of symptoms, but is definitively diagnosed by biopsy of affected tissue. Histologically, vulvar lichen sclerosus commonly exemplifies hyperkeratosis, epidermal atrophy, basal cell degeneration, dermal hyalinization, and lymphocyte infiltration.[5] Women with untreated or poorly controlled lichen sclerosus are at a higher risk for squamous cell carcinoma of the vulva, further supporting the need for definitive treatment, even in asymptomatic participants.[4] First-line treatment has traditionally involved super potent topical corticosteroids, such as clobetasol or halobetasol. Treatment generally involves daily application initially for 2-4 weeks and then 2-3 times weekly for maintenance. Side effects from these topicals include skin atrophy, telangiectasia, and striae.[7] Super potent steroids have been compared to other topical agents such as testosterone and progestin, and found to be superior and result in statistically significant improvement in comparison.[5] However, not all patients are eligible for treatment with high-dose topical steroids.

Although super potent steroids are the mainstay of therapy, they are not without risk or adverse effects. Such steroids can cause atrophy, telangiectasia, and striae, particularly in non-hair bearing areas.[7] In those participants with particularly resistant disease or skin changes not penetrable by topical steroids, intralesional corticosteroids, topical calcineurin inhibitors, or retinoids are other potential alternatives.

One proposed alternative treatment involves laser therapy with CO_2. In 1982, Rosemberg and Jacobs first brought to light the use of CO_2 laser as a successful treatment of penile lichen sclerosus.[9] Since that time there have been numerous small case studies regarding CO2 laser treatment and its application to vulvar lichen sclerosus and other dermatological conditions, such as vulvovaginal atrophy and genitourinary syndrome.[1,3,6,8,9,10] Laser therapy functions by using heat to ablate the epidermis and dermis.[3] As a result, hyperkeratotic skin is ablated with microthermal injury inducing a rapid process of repair,[6] revealing new normal functioning epidermal-dermal junction without previously dysregulated signaling.[3]

In a study involving 21 perimenopausal women with vulvovaginal atrophy, Arroyo et al. treated women with fractional CO_2 laser over a series of 3 treatments and then reevaluated symptoms and tissue 12 and 24 weeks later via vaginal health index (VHI) scores.[1] At 12 weeks, 82% of patients had significant improvement in VHI. Additionally, 97% of patients reported no to mild discomfort with treatment. Itching was the most commonly reported side effect (20%).

Lee et al. used ablative CO_2 laser and fractional CO_2 laser therapy on five patients with hyperkeratotic vulvar lichen sclerosus that was previously unresponsive to topical steroids. This study included five women with vulvar lichen sclerosus recalcitrant to topical treatment with clobetasol propionate 0.5% ointment as evidence by ongoing symptoms and gross physical exam. Of the 4 women who reported symptoms before treatment, 100% experienced improvement after CO_2 laser treatment. Coyle also used laser therapy via the ProFractional Er:YAG Fractional Ablative Laser (Sciton, Inc.). This study is unique in that pretreatment biopsies were used to determine depth of vulvar lichen sclerosus. Using this histologically determined depth, the investigator individualized depth of laser treatment to match over 3 laser treatment sessions. A total of 15 patients were enrolled, and at 3 months, a repeat biopsy showed 7 participants (58.3%) had no vulvar lichen sclerosus with 41.6% of participants reporting improvement in symptoms compared to baseline. Peterson et al. also had successful results in two patients using CO_2 laser therapy with a treatment protocol that involved two passes of the CO_2 laser or until there was no evidence of disease present.[8]

Another consideration related to laser therapy is long-term results. Windahl et al. evaluated 62 male patients who had histologically proven lichen sclerosus and treated with CO_2 laser therapy.[10] Of the 62 men evaluated, 50 were available to interview and 80% reported no recurrence of symptoms; median follow-up was 14 years.

The laser to be used in this study is the ProFractional Er: YAG 2940nm laser from Sciton, Inc. This device has been approved by the FDA for use in ":surgical applications requiring the excision, incision, ablation, vaporization, and coagulation of soft tissue, and for skin resurfacing. Soft tissue includes skin, subcutaneous tissue, striated and smooth tissue, muscle, cartilage,… mucous membrane, …organs and glands. Surgical specialties and applications include general surgery, plastic surgery, aesthetic surgery, dermatology, urology, gynecology, genitourinary,…" For genitourinary surgery of soft tissue, one of the specific indications is "lesions of the external genitalia," which includes vulvar lichen sclerosus.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Overview

This will be a non-randomized, open-label, prospective study. Participants will be recruited in general and subspecialty obstetric and gynecology clinics. Participants who meet all eligibility criteria, including providing written informed consent, will have three treatment visits and two follow-up visits in an outpatient setting. Participants will not be charged for any treatments.

At each treatment visit, participants will be asked to complete questionnaires to assess their symptoms. We also will take photographs of the affected area at the first and third treatment visits. Photographs will include only the area of lichen sclerosus, such that individuals cannot be identified in the photographs. Participant photographs will be taken using the BIDMC PhotoConsult iOS application that allows providers to upload photographs to a patient's online medical record through a secure application.

Women with biopsy-proven lichen sclerosus will be treated with the ProFractional hand piece using the sapphire plate stand-off (Sciton, Inc. Palo, Alto, CA). The laser energy is delivered in a scanning fractional pattern to ablate microchannels in tissue to allow faster healing. Treatment will be delivered in 3 sessions scheduled 4 weeks (+/- 1 week) apart.

Prior to receiving treatment, topical anesthetic will be applied to the affected area for 20-30 minutes and then wiped away. The treatment area will be cleaned and dried of any moisture prior to treatment. The disinfected standoff with sapphire plate will then be applied to the ProFractional hand piece. Based on the biopsy results, the appropriate ablation depth will be inputted with 11% treatment density selected. Each treatment will include two passes of the laser over the affected area.

- Visit 1, month 0: On the first pass, the depth of the laser will be from 300 to 500 microns, or the thickness of 3 to 5 sheets of paper; the depth will be based on the biopsy that was used to diagnosis the lichen sclerosus. On the second pass, the depth will be 50 microns deeper than the first pass and the hand piece rotated 45˚.
- Visit 2, month 1: The first pass of the laser will be the same depth as the second pass from the last visit. The second pass will be 50 microns deeper and the hand piece rotated 45˚.
- Visit 3, month 2: The first pass of the laser will be the same depth as the second pass from the last visit. The second pass will be 50 microns deeper and the hand piece rotated 45˚.

Participants will return for follow-up visits at 1 and 3 months (months 3 and 5 of the study) following the third treatment.

- Visit 4, month 3
  - Participants will be asked to complete questionnaires to assess outcomes.
- Visit 5, month 5
  - Participants will be asked to complete questionnaires to assess outcomes.
  - We will take photographs of the affected area.
  - Biopsy of area with lichen sclerosus; the biopsy will be done the same way as the one that was done to diagnosis your lichen sclerosus

If participants prefer not to come in person for Visit 4 due to concerns over COVID-19, they may have a telehealth visit instead to check in with their provider. In that case, the participant would complete the Visit 4 survey remotely, either over the phone with the study coordinator or online via REDCap.

Outcome Assessment

The primary outcomes will be change in histology and depth of disease from baseline to three months

after the last laser treatment. The baseline depth of lichen sclerosus will be based on the results of the clinical biopsy performed before study participation. We will use the study biopsy collected at the follow-up visit three months after the last treatment to determine resolution of disease or, if disease persists, to what depth. The biopsies will therefore serve as an objective means to determine effective treatment of disease.

The secondary outcomes will include the following:

- Change in symptoms and quality of life using the Vulvovaginal Symptom Questionnaire
- Change in symptom severity using the Patient Global Impression scales for severity and improvement
- Vulvar lichen sclerosus improvement as assessed using photographs. Photographs will be rated by observers blinded to whether a photo is before or after treatment.
- Satisfaction with treatment using a participant satisfaction questionnaire

B. Statistical Considerations

Sample size

Based on the limited prior data, we anticipate that 60% of participants will achieve the primary outcome, which is resolution of lichen sclerosus on biopsy at three months after completion of treatment. Using a one-sample binomial proportion test and assuming a two-sided alpha=0.05 and power=85%, we would need to 27 evaluable participants to show that 60% is statistically different from a reference proportion of 30%. To account for 10% potential loss to follow-up, we aim to enroll 30 participants.

Statistical Analysis

We will present data as mean (± standard deviation), median (interquartile range), or proportion, based on data type and distribution. Continuous data will be compared with the appropriate parametric or non-parametric test, accounting for paired data as needed. Categorical data will be compared with the chi-square, Fisher's exact, or McNemar's test. P values <0.05 will be considered statistically significant. Analyses will be conducted with SAS 9.4 (SAS Institute, Cary, North Carolina).

C. Participant Selection

Inclusion criteria

- Female
- Aged 18 years old or older
- Biopsy-proven active vulvar lichen sclerosus
- Characteristic changes of vulvar lichen sclerosus on gynecological exam
- Self-reported indication of one or more of the following symptoms of lichen sclerosus
    - Dryness
    - Itching
    - Burning
    - Bleeding
    - Blistering
    - Soreness
    - Easily bruises
    - Easily tears
    - Ulcerated lesions
    - Painful intercourse
- Ability to complete questionnaires in English
- Written, informed consent
- Willing and able to logistically follow schedule of treatments and follow-up visits

Exclusion criteria

- Receiving systemic immunosuppressant's (e.g. corticosteroids) within 4 weeks of enrollment
- Use of topical vulvar steroid-containing creams at the affected area within 4 weeks of enrollment
- Immunocompromised (e.g. lymphoma, AIDS, Wiskott-Aldrich syndrome)
- History of uncontrolled malignant disease
- Additional genital skin disease
- Known allergy or intolerance to topical anesthesia
- Known history of connective tissue disease
- Known propensity for keloid formations

B4. POSSIBLE BENEFITS

It is possible that participants may benefit from an improvement in their vulvar lichen sclerosus symptoms and quality of life. Patients with vulvar lichen sclerosus and their providers will benefit from the increased clarity on the effectiveness of laser treatments, potentially expanding the now limited treatment options available to those who are ineligible for high potent topical steroids or have failed topical treatment.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

This study poses minimal risks to participants. As shown in a peer-reviewed study where the fractional Er:YAG laser was used to improve postsurgical facial scars from skin cancer surgery, adverse effects were limited to transient hyperpigmentation and erythema.[12] The treatments will be carried out by skilled and trained providers. Any discomfort caused by the laser treatments themselves will be attempted to be mitigated by the application of topical anesthetic prior to treatments.

Other than potential discomfort from the laser, other risks include vulvar spotting (light bleeding), allergic reaction to topical anesthetic, and infection from the biopsy or the laser treatment

The only other foreseeable risk is that associated with participant confidentiality. To protect participant privacy, all data will be handled in a confidential manner. All electronic data will be kept in a password-protected folder on the BIDMC secure server behind the firewall or in REDCap. Any paper associated with the study will be kept in a locked office.

Risks associated with this study are minimal. Given the possible benefits both for participants themselves and scientific knowledge gained, the benefits are believed to outweigh the risks.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

We will attempt to identify and recruit study participants at a clinical visit with gynecology, gynecologic oncology, radiation oncology, or surgical oncology. We will also post flyers at these clinics in order to inform potential participants about this study.

Consent

Written, informed consent will be obtained by members of the study team from participants prior to the collection of any data. Informed consent will occur in a private area; study staff will be able to answer any questions from potential participants. Potential study participants will be clearly informed that it is unclear whether fractional 29240 nm laser therapy is beneficial for symptoms of lichen sclerosus.

Participant Protection

All potential participants will be informed that participation in the study will in no way affect their clinical care. Written, informed consent will be obtained from all participants, and participants will be informed that they can withdraw from the study at any point.

B7. STUDY LOCATION

Privacy

All consent and data collection will be conducted in a private setting. The information being collected is limited to only the minimum amount of data necessary to accomplish our objectives.

Physical Setting

We have a dedicated procedure room where all laser treatments will be performed.

B8. DATA SECURITY

All electronic data will be kept in a restricted-access folder on the BIDMC secure server, behind the firewall or in REDCap. Any paper resulting from this study will be kept in a locked office belonging to a member of the study staff.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No ☒ N/A (This is not a multi-site study.)

Is the BIDMC PI the lead investigator of the multi-site study? ☒ Yes ☐ No

B10 Dissemination of Research Results

We plan to present the data at national and international meetings and publish the results in a peer-reviewed journal. Data will be reported only in aggregate.

References

1. Arroyo C. Fractional CO(2) laser treatment for vulvovaginal atrophy symptoms and vaginal rejuvenation in perimenopausal women. Int J Womens Health. 2017 Aug 28;9:591-595. doi: 10.2147/IJWH.S136857. eCollection 2017.
2. Bleeker MC, Visser PJ, Overbeek LI, et al. Lichen Sclerosus: Incidence and Risk of Vulvar Squamous Cell Carcinoma. Cancer Epidemiol Biomarkers Prev 2016; 25:1224.
3. Brightman LA, Brauer JA, Anolik R *et al*. Ablative and fractional ablative lasers. *Dermatol. Clin.* 2009; 27: 479–89.
4. Carli P, Cattaneo A, De Magnis A, Biggeri A, Taddei G, Giannotti B. Squamous cell carcinoma arising in vulvar lichen sclerosus: a longitudinal cohort study. Eur J Cancer Prev. 1995 Dec;4(6):491-5. PubMed PMID: 8580785.
5. Chi CC, Kirtschig G, Baldo M, Lewis F, Wang SH, Wojnarowska F. Systematic review and meta-analysis of randomized controlled trials on topical interventions for genital lichen sclerosus. J Am Acad Dermatol. 2012;67:305–12.
6. Gold, M. H. (Ed.). (2010). Update on Fractional Laser Technology. *The Journal of Clinical and Aesthetic Dermatology*, *3*(1), 42–50.
7. Nair, P. A. (2017). Vulvar Lichen Sclerosus et Atrophicus. *Journal of Mid-Life Health*, *8*(2), 55–62. http://doi.org/10.4103/jmh.JMH_13_17

8. Peterson CM, Lane JE, Ratz JL. Successful carbon dioxide laser therapy for refractory anogenital lichen sclerosus. Dermatol Surg. 2004 Aug;30(8):1148-51. Review. PubMed PMID: 15274708.

9. Rosemberg SK, Jacobs H. Continuous wave carbon dioxide treatment of balanitis xerotica obliterans. *Urology* 1982; 19: 539–41.

10. Windahl T. Is carbon dioxide laser treatment of lichen sclerosus effective in the long run? Scand J Urol Nephrol. 2006;40(3):208-11.

11. Erekson EA, Yip SO, Wedderburn TS, Martin DK, Li FY, Choi JN, Kenton KS, Fried TR. The Vulvovaginal Symptoms Questionnaire: a questionnaire for measuring vulvovaginal symptoms in postmenopausal women. Menopause. 2013 Sep;20(9):973-9. doi: 10.1097/GME.0b013e318282600b.

12. Cohen JL. Minimizing skin cancer surgical scars using ablative fractional Er:YAG laser treatment. J Drugs Dermatol. 2013;12(10):1171-1173.