The efficacy and safety of secondary focused ultrasound therapy for recurrence of non-neoplastic epithelial disorders of the vulva

Ruizhen Li and Jianfa Jiang

Department of Obstetrics and Gynecology, The Third Xiangya Hospital of Central South University, Changsha, China

ABSTRACT
Objective: To investigate the efficacy, safety, and influencing factors of secondary focused ultrasound (FU) therapy for recurrence of non-neoplastic epithelial disorders of the vulva (NNEDV).

Methods: Patients with NNEDV who have relapsed after initial FU treatment were included in this study. They were treated with secondary FU therapy between July 2015 and July 2021. Outcome measures included the degree of symptom severity and operative complications. We further analyzed the relationships between age, course, time between relapse and initial treatment, menopause status, lesion size, pathological types, severity of symptoms, and curative rate.

Results: There were 98 patients enrolled in this study, with a mean age of 47.4 ± 11.4 years. All patients successfully underwent secondary FU therapy. Blister developed among 16 (16.3%) patients, of whom 6 (6.1%) developed superficial skin ulcers. A curative response was observed among 46 (46.9%) patients, while an effective response was observed among 44 (44.9%) patients. Only 8 (8.2%) patients showed no improvement. The total response rate was 91.8%. A total of 12 (12.2%) cases recurred among all effective cases. Patients with a recurrence of NNEDV after more than 1.5 years following their first FU therapy demonstrated a higher response rate than those with a recurrence after less than 1.5 years.

Conclusions: A second FU therapy remains effective for patients with recurrent NNEDV with no obvious side effects. The response rate, however, is higher for patients who experience recurrence of NNEDV after more than 1.5 years.

Introduction

Non-neoplastic epithelial disorders of the vulva (NNEDV) comprise a heterogeneous group of vulval lesions, including lichen sclerosus, lichen planus, and lichen simplex chronicus [1], and are one of the most common chronic vulvar skin disease problems. The true incidence and prevalence of this group of conditions are unknown and difficult to estimate because affected patients, if they choose to see a physician for their potentially embarrassing symptoms, present to various specialists [2]. Symptoms include chronic or recurrent vulvar itching, irritation, burning, and pain, which lead to significant physical discomfort and emotional distress that can affect mood and sexual relationships [3]. Moreover, lichen sclerosus not only affects quality of life, but is also associated with an increased risk of squamous cell carcinoma of the vulva [4]. Therefore, treatment of these vulvar conditions is not only helpful for symptomatic relief and prevention of progressive vulvar scarring, but it is also supportive of surveillance for associated vulvar cancers.

The pathogenesis of NNEDV is still unclear, and treatment methods are diverse. Local drugs, such as corticosteroids, have been widely accepted and provide prompt symptomatic relief [5]. Corticosteroids have been a mainstay in the treatment of inflammatory skin conditions for decades, and there is ample evidence to support their long-term efficacy and safety. The British Association of Dermatologists guidelines for the management of lichen sclerosus advocate for an individualized treatment regimen of topical steroids to maintain disease control and prevent scarring [6]. However, advice given to patients with NNEDV by other healthcare professionals regarding corticosteroid-related risks—including dermal thinning, adrenal suppression, systemic immunosuppression, and tachyphylaxis—may represent a barrier to compliance with long-term corticosteroid usage among female patients [7,8].

Focused ultrasound (FU) therapy has received increasing interest in the treatment of gynecological and other diseases in recent years. From 1999 to 2002, a randomized study showed that FU therapy was feasible and effective in treating patients with vulvar dystrophy. Recently, several studies have demonstrated FU therapy to be an effective treatment for NNEDV [9–11]. However, with the extension of follow-up time, the effective rate gradually decreased, and the recurrence rate reached 22.79%–36% after 4–5 years of treatment [10,12]. To date, few studies have addressed specific issues...
such as whether secondary FU therapy can achieve the same therapeutic effect after recurrence, whether secondary FU therapy increases the rate of complications, and which factors correlate with the effectiveness of secondary focused ultrasound therapy. The purpose of this study was to investigate the efficacy, safety, and influential factors of secondary FU therapy for recurrent NNEDV.

Materials and methods

Ethical considerations

All procedures performed in this retrospective study involving human participants were approved and were in accordance with the ethical standards of the institutional review board of the Third Xiangya Hospital of Central South University (No.21002). The requirement for informed consent to conduct the research was waived by the institutional review board of the Third Xiangya Hospital of Central South University.

Patient selection

This study included patients with recurrent NNEDV who received secondary FU therapy at the Third Xiangya Hospital of Central South University, Changsha, China, between July 2015 and July 2021. Patients were identified by conducting a search of available electronic medical records. The inclusion criteria were as follows: (1) patients who were >18 years of age; (2) patients with a diagnosis of recurrent NNEDV based on medical history and gynecological examination according to diagnostic standards; (3) patients treated with their first FU therapy at least six months prior to enrollment; (4) patients had not received other physical therapy for nearly three months before enrollment. Exclusion criteria were as follows: (1) patients without complete follow-up data; (2) patients with serious heart, liver, or kidney disease or uncontrolled diabetes; (3) patients with vulvar intraepithelial neoplasia. Data on age, course, time between relapse and initial FU therapy, menstruation, symptoms, vulvar skin signs examination, pathologic type, treatment parameters, therapeutic effect, and complications were collected from a review of electronic medical records and telephone interviews.

FU therapy

A CZF focused ultrasound therapeutic device (developed by Chongqing Haifu Medical Technology) was used to perform the FU therapy in this study. The device comprised a power generator, therapeutic transducer, central console and circulating degassed water system. The treatment procedure was performed avoiding menstruation to prevent menstrual cramps from affecting vulvar wound healing. Detailed treatment procedures have been described in our previous study [9]. In brief, patients were placed in a bladder lithotomy position during the treatment, and the skin of the vulva was prepared preoperatively. After local infiltration anesthesia using 10–20 ml 0.5% lidocaine, FU therapy was applied. The treatment area included the lesion area and 5 mm of normal skin beyond the margin of the lesion. During FU treatment, the probe was in close contact with the skin above the lesion via the ultrasound couplant. (The probe should be moved continuously during treatment to avoid irreversible tissue damage caused by prolonged local irradiation.) The therapy was deemed complete when the treatment area showed mild congestion, swelling, and local temperature rises to 39–40 °C. An intermittent ice compress was applied (12–24 h after treatment) to the treatment area to relieve the congestion and swelling and moist burn ointment was applied intermittently to the treated area to reduce burn reaction.

Follow-up

During the first month post-treatment, patients attended a follow-up visit every week so that the effectiveness and any side effects of the treatment could be observed. Further follow-ups were conducted after 6 months and then once per year after the treatment. The treatment responses were classified as curative (no symptoms remained), effective (the symptoms were relieved), or ineffective (the symptoms remained the same) based on the patients’ responses to the therapy [13]. The cure rate was the primary study outcome. Effective, ineffective, and recurrent rates and postoperative complications were the secondary study outcomes. Recurrence is defined the reappearance of symptoms, such as vulva pruritus and pain, vulva skin depigmentation and a decrease in elasticity six months after FU therapy. Intra- and postoperative complications were recorded. Potential complications included blisters, scleroma, and infection either during or after the procedure.

Statistical analysis

The Statistical Program for the Social Sciences 22.0 (SPSS Inc., Chicago, IL) was applied to conduct the statistical analysis. Qualitative data were described with frequencies and percentages. Normally distributed continuous data were presented as mean ± standard deviation, and non-normally distributed continuous data were presented as the median and range. A chi-square test was used to compare the difference between groups and p < 0.05 was considered to be significantly different.

Results

Baseline characteristics of participants

There were 98 patients enrolled in this study; the demographic and baseline characteristics of the study population can be found in Table 1. The patients were aged 21–83 years, with a mean age of 47.4 ± 11.4 years. The median time between the recurrence of the disease and the first FU therapy was 1.5 (0.5, 10.0) years. The median course of their disease recurrence was 1.0 (0.1, 8.0) years. Of the total sample, 67 had lichen simplex chronicus and 31 had lichen sclerosus.
Table 1. The demographic characteristics of patients with recurrence of non-neoplastic epithelial disorders of the vulva.

| Demographic characteristics | Values |
|-----------------------------|--------|
| Age, years                  | 47.4 ± 11.4 |
| Time between relapse and initial treatment, years | 1.5 (0.5, 10.0) |
| Course of diseases recurrence, years | 1.0 (0.1, 8.0) |
| Menopause                   |        |
| Pre-menopause               | 52 (53.1) |
| Post-menopause              | 46 (46.9) |
| Symptoms                    |        |
| Mild                        | 4 (4.1) |
| Moderate                    | 31 (31.6) |
| Severe                      | 63 (64.3) |
| Lesion size/vulva size       |        |
| <30%                        | 22 (22.5) |
| 30–50%                      | 46 (46.9) |
| >50%                        | 30 (30.6) |
| Pathological type            |        |
| Lichen sclerosus            | 31 (31.6) |
| Lichen simplex chronicus    | 67 (68.4) |

Values are given as n (%) unless otherwise stated.

Table 2. The results pertaining to the focused ultrasound therapy for non-neoplastic epithelial disorders of the vulva recurrence.

| Variables                              | Values |
|----------------------------------------|--------|
| Sessions of focused ultrasound therapy | 1      |
| Sonication time, min                   | 22.4 ± 8.1 |
| Power                                  |        |
| Level 2                                | 40 (40.8) |
| Level 3                                | 58 (59.2) |
| Treatment energy, J                    | 4179.0 (1527, 10388.0) |
| Adverse effects                        |        |
| Blister                                | 16 (16.3) |
| Ulcer                                  | 6 (6.1) |
| Efficacy                               |        |
| Curative                               | 46 (46.9) |
| Effective                              | 44 (44.9) |
| Ineffective                            | 8 (8.2) |

Values are given as n (%) unless otherwise stated.

These diagnoses were confirmed by pathology before the first FU therapy. Moreover, 52 patients were pre-menopausal and 46 were post-menopausal. Most patients (95.9%) had moderate or severe symptoms.

**Effectiveness of secondary FU treatment for NNEVD recurrence**

All patients successfully underwent FU therapy. The results pertaining to the treatment are shown in Table 2. The sonication time was 22.4 ± 8.1 min, and the median treatment energy was 4179.0 (1527, 10388.0) J. The skin and mucosa in all patients developed transient hyperemia and edema, which usually faded away within a week using moisture exposed burn ointment. Blisters developed in 16 (16.3%) patients, of whom 6 (6.1%) developed superficial skin ulcers. Of these 16 patients, 10 had lichen simplex chronicus and 6 had lichen sclerosus. The sonication time was 23.65 ± 6.2 min. Of the 6 patients who developed superficial skin ulcers, 4 had lichen simplex chronicus and 2 had lichen sclerosus. The sonication time was 24.6 ± 8.1 min. The wound healed within one month of treatment without scar formation. No damage occurred in adjacent organs such as the bowel and urinary tract.

On average, the patients received follow-up for 51.5 months after the procedure (a range of 6–83 months). Out of 98 patients, a curative response was observed among 46 (46.9%) patients while an effective response was observed in 44 (44.9%) patients. Only 8 patients (8.2%) showed no improvement and were thus categorized as having an ineffective response. The total response rate was 91.8%.

Among all the effective cases, 12 (12.2%) recurred, with two patients developing recurrent symptoms within the first year after treatment. Four developed recurrence in the second year, three in the third year, and three in the fourth year (post-treatment).

**Comparison of the therapeutic effect on different influential factors**

To examine prognostic factors, the 98 patients were divided into different groups according to age, the course of the disease, the interval between recurrence of the disease and the first FU therapy, menopause status, lesion size, pathological types, severity of symptoms, and power.

Comparison of the therapeutic effect on different influential factors is shown in Table 3. The cure rates of patients with different age, disease courses, menopause status, lesion size, pathological types, severity of symptoms, and power showed no significant differences (p > 0.05). The cure rates of patients in varying intervals between the recurrence of the disease and the first FU therapy were significantly different (p < 0.05). There was a higher response rate among patients who experienced a recurrence of NNEVD more than 1.5 years after the first FU therapy compared to those with a recurrence in less than 1.5 years.

**Discussion**

Non-neoplastic epithelial disorders of the vulva are a group of intractable gynecological diseases with a long disease course. Although the etiology and pathogenesis of NNEVD are not well defined, pathological studies have shown a possible link to immunity, infection, hormonal, or genetic factors. Occurrence is primarily due to secondary degeneration in the epidermis caused by microvascular lesions in the dermis, or growth disorders and epidermal cell degeneration caused by insufficient nutrient supply after nerves and blood vessels degenerate locally. The ideal treatment should aim to induce symptomatic relief, reverse signs, and prevent further anatomic changes. Different methods have been attempted to treat NNEVD, including corticosteroids [14], topical calcineurin inhibitors [15], mixed methylene blue compound injection [16], photodynamic therapy [17], and fractional carbon dioxide laser treatment [18,19]. However, none of these treatments presently works well. The disease often recurs and severely affects quality of life. Corticosteroids, which can relieve pruritus, are the first line therapy for NNEVD [20]. Long-term maintenance therapy with corticosteroids is important for suppression of ongoing inflammation, and long-term maintenance strategies aimed at preventing recurrences are required [21]. However, application of
Focused ultrasound is a mechanical wave that has demonstrated good performance in tissue penetration, locating, and energy deposition. Previous studies have shown that the count of microvessels increased and their lumens recovered after FU therapy among women with NNEDV. Melanin cells underwent normal pigmentation after FU therapy [22].

Thus, FU therapy as a local therapy has demonstrated encouraging results among patients with NNEDV. However, the recurrence rate is still high. Li et al. used FU therapy to treat 76 patients with NNEDV, and the total recurrence rate at 4 years was 36% [12]. Wu et al. found that the total recurrence rate of focused ultrasound treatment for NNEDV was 22.79% within a 5-year period. Ye et al. investigated 950 patients with pathologically confirmed NNEDV who underwent FU therapy. Of all effective cases, 89 (9.5%) recurred and most occurred within 3 years of treatment [13]. It is still unknown which treatment options should be used for relapsed patients. It is unclear whether it is effective to treat patients with FU therapy who have previously received FU therapy. For this reason, we considered it important to assess the safety and effectiveness of secondary FU therapy among women with NNEDV recurrence.

To the best of our knowledge, our study is the first to have explored these issues and determined that it is both efficacious and safe. In this study, 98 patients with NNEDV recurrence successfully underwent secondary FU therapy. The median time interval between the recurrence of the disease and the first FU therapy was 1.5 (0.5, 10.0) years and most patients (95.9%) had moderate or severe symptoms. The cure rate was 46.9% and the effective rate was 44.9% in the current study. Only 8 patients (8.2%) showed no improvement. Similar rates of total response have been reported in studies on the effectiveness of first FU therapy for NNEDV [13]. These results demonstrate that the second FU therapy is still effective for patients with recurrent NNEDV, and influential factor analysis has shown that there was no significant difference in the rates of therapeutic response when patients were grouped by age, disease duration, menopause status, lesion size, and pathological type. However, the effectiveness of secondary FU therapy for recurrent NNEDV was related to the interval between the recurrence of the disease and the first FU therapy. The efficacy was significantly higher among patients who experienced recurrence of NNEDV more than 1.5 years after their first FU therapy. The reason for this disparity is unclear. However, it is suggested that patients with short-term recurrence after FU therapy may benefit less from secondary FU therapy.

The safety of this technique for the treatment of patients with NNEDV recurrence is always a concern. Blisters developed in 16 (16.3%) patients, among whom 6 (6.1%) developed superficial skin ulcers, which is similar to that seen in previous studies of patients receiving FU therapy for the first time [9,23], meaning that secondary FU therapy did not appear to increase the risk of local skin burns. At the same time, no damage occurred in adjacent organs, such as the bowel and urinary tract. These results suggest that secondary FU therapy for recurrent NNEDV is relatively safe.

This study has several limitations. First, the study was single armed without control groups; therefore, prospective studies comparing FU therapy with topical corticosteroids therapy would be more helpful in confirming the efficacy of FU therapy. Second, the sample size of this study was relatively small, and a larger sample size would be more conducive to analyzing the factors influencing efficacy. Third, we do not yet know the underlying reasons why some patients do not respond to FU. In the future, we plan to conduct

### Table 3. Comparison of the therapeutic effect on different influential factors.

| Variable                        | Cure, % | Effective, % | Ineffective, % | p Value |
|---------------------------------|---------|--------------|----------------|---------|
| Age, years                      |         |              |                |         |
| <47                             | 26 (55.3) | 17 (36.2)   | 4 (8.5)        | 0.235   |
| ≥47                             | 20 (39.2) | 27 (52.9)   | 4 (7.8)        |         |
| Menopause                       |         |              |                |         |
| Pre-menopause                   | 26 (50.0) | 22 (42.3)   | 4 (7.7)        | 0.812   |
| Post-menopause                  | 20 (43.5) | 22 (47.8)   | 4 (8.7)        |         |
| Course of diseases recurrence, years |         |              |                |         |
| <1                              | 16 (42.1) | 17 (44.7)   | 5 (13.2)       | 0.332   |
| ≥1                              | 30 (50.0) | 27 (45.0)   | 3 (5.0)        |         |
| Time between relapse and initial treatment, years |         |              |                | <0.001  |
| <1.5                            | 8 (20.0)  | 25 (62.5)   | 7 (17.5)       |         |
| ≥1.5                            | 38 (65.5) | 19 (32.8)   | 1 (1.7)        |         |
| Symptoms                        |         |              |                | 0.404   |
| Mild                            | 3 (75.0)  | 1 (25.0)    | 0              |         |
| Moderate                        | 16 (51.6) | 12 (38.7)   | 3 (9.7)        |         |
| Severe                          | 27 (42.9) | 31 (49.2)   | 5 (7.9)        |         |
| Lesion size/vulva size          |         |              |                | 0.095   |
| <30%                            | 14 (63.6) | 7 (31.8)    | 1 (4.5)        |         |
| 30–50%                          | 20 (43.5) | 21 (45.7)   | 5 (10.9)       |         |
| >50%                            | 12 (40.0) | 16 (53.3)   | 2 (6.7)        |         |
| Pathological type               |         |              |                | 0.675   |
| lichen sclerosus                | 12 (38.7) | 17 (54.8)   | 2 (6.5)        |         |
| lichen simplex chronicus        | 34 (50.7) | 27 (40.3)   | 6 (9.0)        |         |
| Power                           |         |              |                | 0.420   |
| Level 2                         | 19 (47.5) | 15 (37.5)   | 6 (15.0)       |         |
| Level 3                         | 27 (46.6) | 29 (50.0)   | 2 (3.4)        |         |

Values are given as n (%) unless otherwise stated.
research on tissue samples from patients who failed to respond to FU treatment so as to identify the possible causes.

**Conclusion**

In conclusion, this study demonstrates that secondary FU therapy is still effective for patients with recurrent NNEDV and there are no obvious side effects. The response rate, however, is higher for patients who experience a recurrence of NNEDV after more than 1.5 years.

**Author contributions**

R.Z.L assembled the data and drafted the manuscript. J.F.J conceived the idea for the study, carried out the analyses, and reviewed and revised the manuscript.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

**Funding**

The Wisdom Accumulation and Talent Cultivation Project of the Third Xiangya Hospital of Central South University [No. YX202112].

**References**

[1] O’Connell TX, Nathan LS, Satmary WA, et al. Non-neoplastic epithelial disorders of the vulva. Am Fam Physician. 2008;77(3):321–326.

[2] Melnick LE, Steuer AB, Bieber AK, et al. Lichen sclerosus among women in the United States. Int J Womens Dermatol. 2020;6(4):260–262.

[3] Thorstensen KA, Birenbaum DL. Recognition and management of vulvar dermatologic conditions: lichen sclerosus, lichen planus, and lichen simplex chronicus. J Midwifery Womens Health. 2012;57(3):260–275.

[4] Li JY, Arkfeld CK, Tymon-Rosario J, et al. An evaluation of prognostic factors, oncologic outcomes, and management for primary and recurrent squamous cell carcinoma of the vulva. J Gynecol Oncol. 2022;33(2):e13.

[5] Kohn JR, Connors TM, Chan W, et al. Clinical outcomes and adherence to topical corticosteroid therapy in women with vulvar lichen sclerosus: a retrospective cohort study. J Am Acad Dermatol. 2020;83(4):1104–1109.

[6] Lewis FM, Tatnall FM, Velangi SS, et al. British association of dermatologists guidelines for the management of lichen sclerosus. Br J Dermatol. 2018;178(4):839–853.

[7] Nic Dhonncha E, O’Connor C, O’Connell G, et al. Adherence to treatment with prescribed topical corticosteroid therapy and potential barriers to adherence among female patients with vulvar lichen sclerosus: a prospective cross-sectional study. Clin Exp Dermatol. 2021;46(4):734–735.

[8] Mautz TT, Krapf JM, Goldstein AT. Topical corticosteroids in the treatment of vulvar lichen sclerosis: a review of pharmacokinetics and recommended dosing frequencies. Sex Med Rev. 2022;10(1):42–52.

[9] Li L, He S, Jiang J. Comparison of efficacy and safety of high-intensity focused ultrasound at different powers for patients with vulvar lichen simplex chronicus. Int J Hyperthermia. 2021;38(1):781–785.

[10] Wu C, Zou M, Xiong Y, et al. Short- and long-term efficacy of focused ultrasound therapy for non-neoplastic epithelial disorders of the vulva. BJOG: Int J Obstet Gy. 2017;124(Suppl 3):87–92.

[11] Zhou W, Zhu L, Zhou H, et al. The efficacy of high-intensity, focused ultrasound treatment for non-neoplastic epithelial disorders of the vulva. Cell Mol Biol. 2016;62(4):111–115.

[12] Li CZ, Bian DH, Wang L, et al. Short and long-term efficacy of focused ultrasound therapy for vulva dystrophy. Zhonghua Fu Chan Ke Za Zhi. 2007;42(1):9–13.

[13] Ye M, Deng X, Mao S, et al. High intensity focused ultrasound treatment for non-neoplastic epithelial disorders of the vulva: Factors affecting effectiveness and recurrence. Int J Hyperthermia. 2015;31(7):771–776.

[14] Günther AR, Limacher A, Beltraminielli H, et al. Efficacy of topical progesterone versus topical clobetasol propionate in patients with vulvar lichen sclerosus - A double-blind randomized phase II pilot study. Eur J Obstet Gynecol Reprod Biol. 2022;272:88–95.

[15] Corazza M, Schettini N, Zedde P, et al. Vulvar lichen sclerosus from pathophysiology to therapeutic approaches: Evidence and prospects. Biomedicines. 2021;9(8):950.

[16] Li Y, Shi J, Tan W, et al. Prospective observational study of the efficacy of mixed methylene blue compound injection for treatment of vulvar non-neoplastic epithelial disorders. Int J Gynaecol Obstet. 2020;148(2):157–161.

[17] Bizoń M, Maślińska D, Sawicki W. Influence of photodynamic therapy on lichen sclerosus with neoplastic background. JCM. 2022;11(4):1100.

[18] Zhang L, Lai Y, Wan T, et al. A randomized clinical study of the treatment of white lesions of the vulva with a fractional ultra-pulsed CO2 laser. Ann Palliat Med. 2020;9(4):2229–2236.

[19] Filippini M, Sozzi J, Farinelli M, et al. Effects of fractional CO(2) laser treatment on patients affected by vulvar lichen sclerosus: a prospective study. Photobiomodul Photomed Laser Surg. 2021;39(12):782–788.

[20] Kirtschig G, Cooper S, Aberer W, et al. Evidence-based (S3) guideline on (anogenital) lichen sclerosus. J Eur Acad Dermatol Venereol. 2017;31(2):e7–e83.

[21] Borghi A, Corazza M. Novel therapeutic approaches and targets for treatment of vulvar lichen sclerosus. Curr Pharm Biotechnol. 2021;22(1):99–114.

[22] Li C, Bian D, Chen W, et al. Focused ultrasound therapy of vulvar dystrophies: a feasibility study. Obstet Gynecol. 2004;104(5 Pt 1):915–921.

[23] Ruan L, Xie Z, Wang H, et al. High-intensity focused ultrasound treatment for non-neoplastic epithelial disorders of the vulva. Int J Gynaecol Obstet. 2010;109(2):167–170.