Medical Management of Penile and Urethral Lichen Sclerosus with Topical Clobetasol Improves Long-Term Voiding Symptoms and Quality of Life

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Abbreviations and Acronyms

AUASS = American Urological Association Symptom Score

LS = lichen sclerosus

LUTS = lower urinary tract symptoms

PROM = patient reported outcome measure

PU = perineal urethrostomy

Q_{max} = peak urinary flow rate

QOL = quality of life

RUG = retrograde urethrogram

Accepted for publication July 14, 2020.

No direct or indirect commercial, personal, academic, political, religious or ethical incentive is associated with publishing this article.

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† Financial interest and/or other relationship with Boston Scientific.

Editor's Note: This article is the fourth of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1391 and 1392.

Purpose: We evaluated the success of minimally invasive management of lichen sclerosus with topical and intraurethral clobetasol, as defined by improvement in patient reported outcome measures and nonprogression to surgery.

Materials and Methods: We conducted a review of our prospective ongoing quality improvement study to determine outcomes of our current standard practice for males with penile and urethral biopsy proven lichen sclerosus. Data were collected between 2011 and 2019, and included patient demographic information, medical and surgical histories, and location and extent of lichen sclerosus related pathology. The primary outcomes for this study were voiding function and voiding related quality of life, and were assessed using the AUASS (American Urological Association Symptom Score) and quality of life bother index, respectively.

Results: We identified 42 patients with biopsy proven lichen sclerosus related urethral stricture disease. Of these patients 85.7% were treated with intraurethral steroids alone and did not require surgical intervention. Median AUASS significantly improved from 12 to 8, and median quality of life bother index improved from 4 ("mostly dissatisfied") to 2 ("mostly satisfied"). Average stricture length of those with penile urethral disease and bulbar urethral disease was 4.8 cm (SD 3.0) and 16.2 cm (SD 6.5), respectively. Median followup was 8.4 months (IQR 2.6–26.4).

Conclusions: Lichen sclerosus related urethral stricture disease can be effectively managed with intraurethral steroids. This minimally invasive management strategy improves patient reported voiding symptoms and voiding quality of life.

Key Words: lichen sclerosus et atrophicus, balanitis xerotica obliterans, urethral stricture, clobetasol

LICHEN sclerosus is a chronic, progressive, lymphocyte mediated inflammatory skin disease. The etiology of LS is unclear, although it has been linked to autoimmune diseases and the Koebner phenomenon.[1] Recent evidence suggests that LS may evolve as part of a 2-hit mechanism which involves underlying risk factors (eg elevated body mass index, tobacco use) as well as urethral trauma (eg catheterization).[2]

LS afflicts up to 1.4 per 100,000 men and is predominantly diagnosed in white men after the third decade of life.[3] It most commonly presents as white plaques on the glans and prepuce that may cause pruritus, dyspareunia and phimosis. Microscopically, LS is characterized by hyperkeratosis and epidermal atrophy with effacement of the rete pegs.[4]

LS can extend to the meatus and the rest of the urethra at rates of up to 37% and 20%, respectively. Extension of LS into the urethra causes stricture and can present with obstructive symptoms that may ultimately progress to urinary retention.[5]

0022-5347/20/2046-1290/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000001304
Vol. 204, 1290-1295, December 2020
Printed in U.S.A.

Management of LS related urethral stricture consists of surgical and nonsurgical approaches. Historically, surgical procedures have included single and multiple stage substitution urethroplasty or diversion with perineal urethrostomy. These invasive procedures have varying degrees of reported success and recurrence and are an imperfect management strategy.[4,5]

Our previous observational research demonstrated an 89% success rate of intraurethral steroids for management of urethral LS, with success defined as not requiring operative management.[4] Based on these findings we hypothesized that patient reported outcome measures centered on symptoms of obstructive uropathy and quality of life would improve after an adequate treatment course with intraurethral steroids in patients with LS. Thus, we sought to evaluate the impact of intraurethral steroids on PROMs in an institutional cohort of patients with LS.

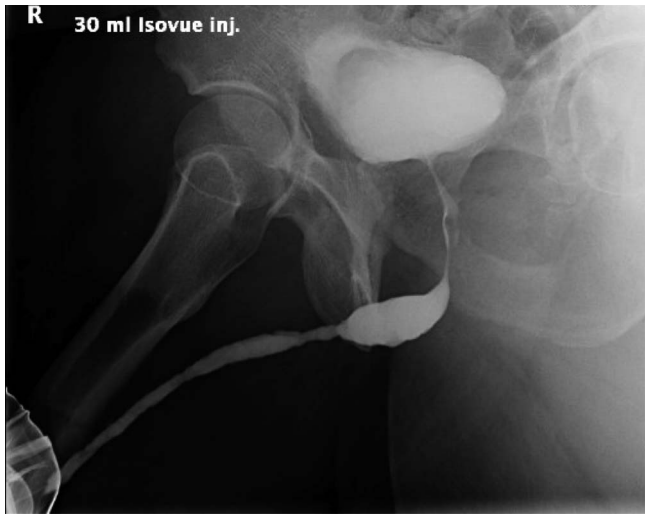

Figure 1. RUG demonstrating continuous stricture of penile urethra.

METHODS

Study Design

We reviewed our prospective ongoing quality improvement database to determine PROMs associated with intraurethral steroid application for males with penile and urethral biopsy proven LS. Inclusion criteria specified males 18 years or older who received care at our reconstructive urology clinic from 2011 to 2019 and for whom there was clinical suspicion for lichen sclerosus stricture. Patients were excluded from analysis if they were unable to give consent. Data included patient demographic information such as age, body mass index and medical comorbidities, and biopsy related information including pathology reports and prior medical and surgical treatment history. Specific histological criteria used to diagnose LS included hyperkeratosis, epidermal atrophy, rete effacement and lymphocytic infiltration. In order to perform the biopsy the urethral stricture was dilated, a cystoscope was introduced into the urethra, and biopsy was obtained with cold cup biopsy forceps under direct vision and no cautery. Extent of intraurethral manifestation of LS disease was determined by clinical imaging studies including RUG and cystoscopy (fig. 1). Urethral involvement was classified according to the most proximal aspect of stricture identified (ie a panurethral stricture with involvement from bulbar urethra to the meatus was classified as a bulbar stricture).

After diagnosis was confirmed, all patients were started on our institutional LS protocol. For patients with external manifestations of LS, the protocol includes application of topical 0.05% clobetasol cream twice daily for 4 to 8 weeks, then on an as needed basis (fig. 2). For those with urethral involvement the protocol mandates intraurethral application of 0.05% clobetasol cream with a lubricated delivery vehicle (ie straight catheter, meatal dilator) once daily for 1 week, every other day for 2 weeks, every third day for 3 weeks, every fourth day for 4 weeks, and then on an as needed basis for voiding symptoms. This method can also be considered periodic self-dilation with steroid application.[4] Catheter sizes ranged from 10 to 16Fr and most men chose to use a 14Fr straight catheter. This dosing and length of treatment are consistent with the U.S. Food and Drug Administration labeling of 0.05% clobetasol propionate cream for use for this type of skin disorder.[6] The current algorithm has been modified slightly from that previously reported by our group to reflect once daily application and to acknowledge the value of self-titration by the patient.[4]

Outcome Measures

The 2 primary outcomes for this study were voiding function and voiding related QOL. Voiding function was assessed using the AUASS, a validated measure of disease specific health status.[7] Voiding related QOL was assessed using the AUASS QOL bother index, which measures

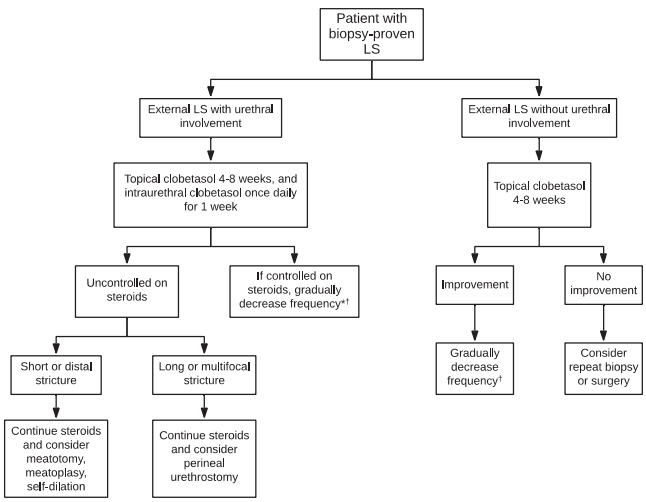

Figure 2. Algorithm to manage biopsy proven LS in males. Asterisk indicates decrease to every other day for 2 weeks, then every third day for 3 weeks, then every fourth day for 4 weeks, then on as needed basis for voiding symptoms. Dagger indicates decrease to as needed basis for external disease.

Table 1. *Study cohort characteristics*

Av age (SD)	51.3	(13.4)
Mean kg/m^2 body mass index (SD)	34.1	(6.7)
Mean mos followup (SD)	18.6	(24.2)
No. race (%):		
White	31	(73.8)
Black	4	(9.5)
Unknown	7	(16.7)
No. diabetes (%):		
Yes	8	(19.0)
No	34	(81.0)
No. hypertension (%):		
Yes	19	(45.2)
No	23	(54.8)
No. tobacco use (%):		
Current	7	(16.7)
Former	13	(30.9)
Never	22	(52.4)
No. operations before referral (%):		
Yes	35	(83.3)
No	7	(16.7)
No. medical therapy before referral (%):		
Yes	8	(19.0)
No	32	(81.0)
No. areas involved (%):		
Urethral meatus	5	(11.9)
Penile urethra	15	(35.7)
Bulbar urethra	22	(52.4)
Mean cm stricture length (SD):		
Penile urethra only	4.8	(3.0)
Bulbar involvement	16.2	(6.5)
Overall cohort	11.5	(7.7)

patient reported disease specific QOL on a Likert style scale from 0 ("delighted") to 6 ("terrible").

Data Analysis

Descriptive statistics were used to summarize the study cohort. Change in median AUASS and median QOL index before and after intervention was assessed with the Wilcoxon signed rank test. To better assess long-term impact we performed a subgroup analysis that excluded patients without at least 1 month of followup after biopsy. An alpha of 0.05 and 95% CIs were used as criteria for statistical significance. All analyses were performed using Stata® version 13.1.

RESULTS

Of the 60 patients who underwent biopsy for clinically suspected LS 52 (87%) had biopsy proven LS. Ten patients had LS involvement limited to the glans or foreskin, while the remaining 42 (80.8%) had urethral involvement. Demographic data are summarized in table 1. Average patient age was 51.3 years (SD 13.4), median age was 53 years and the majority (73.8%) were white.

Table 2. *Description of LS treatment*

	No.	(%)
External + intraurethral clobetasol only	36	(85.7)
Extended meatotomy	1	(2.4)
Perineal urethrostomy	3	(7.1)
Circumcision	1	(2.4)
Urethroplasty	1	(2.4)

Before referral 8 patients (19.0%) had received medical treatment for LS. Four (9.5%) were treated with topical clobetasol while 4 (9.5%) were treated with other topical agents (ie triamcinolone, testosterone). In contrast, the majority of patients (83.3%) had undergone surgical management for LS disease before referral. Prior procedures included direct vision internal urethrotomy, urethral dilation, circumcision and urethroplasty, among others.

Five patients (11.9%) in our cohort had urethral disease limited to the meatus, 15 (35.7%) had disease extending proximally to the penile urethra and 22 (52.4%) had strictures involving the bulbar urethra. Average stricture length in those with penile urethral disease and bulbar urethral disease was 4.8 cm (SD 3.0) and 16.2 cm (SD 6.5), respectively.

The majority of patients (85.7%) were treated with clobetasol alone without the need for further surgical intervention (table 2). One patient (2.4%) underwent circumcision and 1 (2.4%) underwent meatal dilation. In addition, 1 patient (2.4%) underwent urethroplasty for LS management. This patient had a remote history of anterior urethroplasty at another facility prior to referral. Three patients (7.1%) underwent PU for LS management. All had histories of recurrent strictures refractory to dilation and/or other invasive procedures (ie meatotomy, complex anterior urethroplasty) and none had tried intraurethral clobetasol prior to surgery. After surgery they were instructed to apply clobetasol to the glans and around the PU site for 4 weeks.

In the men treated with intraurethral steroids alone (85.7%) there was significant improvement in AUASS and QOL index (fig. 3). Median AUASS before starting clobetasol was 12 (IQR 5–23) and improved to 8 (IQR 4–16) with treatment ($p=0.017$). Median QOL score before clobetasol was 4 ("mostly dissatisfied," IQR 3–6) and improved to 2 ("mostly satisfied," IQR 1–3) with treatment ($p<0.001$). Questionnaires were completed by 84% of patients who presented for followup visits. Peak urinary flow rate increased after intervention with intraurethral steroids. Median Q_{max} rate improved from 6 ml per minute (IQR 3–9) to 12 ml per minute (IQR 7–14, $p=0.04$).

Median followup was 8.4 months (IQR 2.6–26.4). In the subgroup that excluded patients who did not complete at least 1 month of followup after biopsy, median followup increased to 15.6 months (IQR 5.8–33.0). In this subgroup AUASS improved from a median of 16 (IQR 6–26) to 7 (IQR 3–12) with treatment ($p=0.003$). QOL index improved from a median of 5 ("unhappy," IQR 3–6) to 2 ("mostly satisfied," IQR 1–3) after treatment ($p<0.001$).

Verrucous carcinoma of the glans developed in 1 patient (2.4%) during followup. After biopsy confirmation he was instructed to cease applying clobetasol topically but to continue applying intraurethrally.

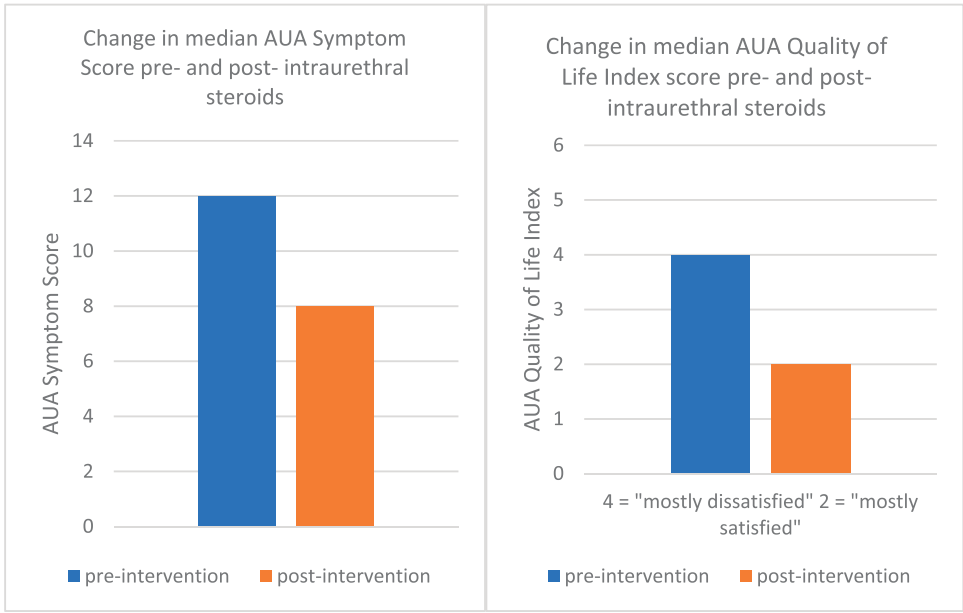

Figure 3. AUASS before and after intervention with intraurethral clobetasol

He ultimately underwent circumcision and laser ablation of penile tumors.

DISCUSSION

To our knowledge, this is the first report examining PROMs in patients with LS treated with topical and intraurethral clobetasol. We have previously shown that intraurethral steroids are an effective method for managing LS related urethral stricture.[4] However, no studies to date have assessed PROMs before and after intraurethral steroid management for LS. These data clearly indicate that voiding related QOL in these patients is significantly improved.

We used the AUASS as a measure of voiding symptoms and voiding QOL. The AUASS is a validated tool for the evaluation of LUTS common to conditions such as benign prostatic hyperplasia and urethral stricture. It is reliable and internally consistent, and has a significant association with other physiological parameters used to evaluate obstructive uropathy, such as urinary flow rate.[7] While not specific for urethral stricture disease or LS associated stricture, the AUASS can effectively predict recurrent urethral stricture in patients with a known stricture and can be used to guide stricture management.[8] Collecting AUASS data before and after intervention allowed us to track clinical improvement as well as improvement in patient reported QOL. Moving forward, we will use the USSIM (Urethral Stricture Symptoms and Impact Measure), a comprehensive PROM that better addresses the most important symptoms and aspects of urethral stricture disease that afflicts our cohort.[9,10]

Our results suggest that early identification of LS involvement in urethral stricture disease is critical to guide management and improve patient reported voiding symptoms and voiding QOL.

LS related stricture disease differs from urethral strictures that are idiopathic or traumatic in nature. Although the etiology of LS is incompletely understood at this point, it is known that LS is a chronic, progressive, inflammatory disease that has been linked to autoimmune diseases and the Koebner phenomenon. Therefore, it may be exacerbated by repeated physical insult (ie surgical manipulation).[2,11] LS typically arises at the meatus and progresses proximally in a continuous fashion, although lichen sclerosus can occasionally arise in isolated bulbar strictures.[4,12] Indeed, most of our patients with bulbar involvement had panurethral strictures and no patient in our cohort had significant skip lesions, meaning normal penile urethra but then a bulbar stricture that needed to be biopsied for LS. LS strictures typically involve the penile urethra, which increases the risk of stricture recurrence and necessitates more complex repair.[2] A recent systematic review highlighted LS in the ULTRA-L classification of anterior urethral stricture, suggesting the importance of identifying LS in order to properly manage these unique urethral strictures.[5,13]

The gold standard was previously considered surgical treatment with replacement of the entire involved area with extragenital skin grafts (ie buccal mucosa) thought to be resistant to LS.[5,14,15] However, more recent studies have shown that LS can manifest in extragenital skin grafts with high recurrence rates and that the adjusted odds of urethroplasty surgical

failure are higher for urethral stricture disease with LS involvement.[2,16,17] There are differences in reported surgical outcomes and recurrence rates associated with procedures such as single stage urethroplasty, 2-stage urethroplasty and PU.[5] Our experience is that urethroplasty in patients with LS has a much higher rate of stricture recurrence on long-term followup. Current evidence suggests that there is no overall surgical panacea for this relentlessly progressive process.

Although we offer intraurethral steroids to all men with evidence of LS associated urethral stricture, 3 of our patients ultimately pursued PU directly. PU may be a preferred option for older patients with longer strictures, men who are unwilling or unable to self-catheterize, or patients who have already adapted to seated voiding and who are less concerned with the impact of PU on sexual function.[18,19]

We have previously shown that treatment with intraurethral steroids has success rates comparable to those of surgical approaches.[4] Our success rate in the present study, defined as nonprogression to surgical intervention, was 85.7%. Moreover, the present study adds to the evidence supporting intraurethral steroids as effective management for LS by reporting patient reported satisfaction with this type of management. Using intraurethral steroids as the initial step in the management of LS related strictures does not exclude the possibility of future surgical interventions in the event of refractory disease or patient dissatisfaction. Thus, it is reasonable to attempt this conservative management option, which has also been shown to ameliorate histopathological features of LS, and spare patients a complex, often staged repair.[20]

Given the malignant potential of LS, biopsy is guideline recommended in cases of clinical uncertainty or atypical features on examination.[1] As such, we promote long-term annual followup for patients with LS. Annual physical examination should include thorough examination of the penis, meatus and inguinal lymph nodes. Repeat biopsy is warranted in the setting of new physical examination findings that are concerning for disease progression (ie suspicious lesion, growing lesion refractory to treatment, lymphadenopathy).[4] In patients with LS in whom penile carcinoma ultimately develops, topical steroids should be ceased.[21]

We present novel evidence that management of LS related urethral stricture with intraurethral steroids is an effective treatment strategy and improves voiding symptoms and voiding QOL. Based on our results, we recommend that clinicians adopt our algorithm when they clinically suspect LS as the etiology of urethral stricture disease.[22]

Strengths of the present study include use of an algorithmic approach with thorough evaluation of LS related pathology which included biopsy, physical examination and RUG. PROMs before and after intervention allowed us to evaluate patient reported improvement in disease burden. Limitations include the retrospective nature of our study, which relied on consistent coding and data entry. Our algorithmic approach may have reduced the number of patients who would have otherwise undergone surgical repair. Thus, there was insufficient power to statistically compare surgically and nonsurgically treated patients. Stratifying improvement in AUASS by LUTS severity (ie mild, moderate, severe) was also underpowered, although those with moderate and severe LUTS before intervention experienced improvement after steroid treatment. As a tertiary reconstructive urology clinic, we rely on patient referral and, thus, our results are at increased risk for referral bias. We initially sought to combine AUASS with Q_{max} to evaluate voiding function. While we did find an improvement in median Q_{max} after treatment, less than half of our patients (42%) had these data available, making this subgroup analysis difficult to relate to any definitive conclusions.[8] Ten patients in our cohort had followup times of less than 1 month, which negatively skewed median followup times. Our subsequent subgroup analysis excluding these patients (median followup 15.6 months) more accurately captures the consistent followup by the vast majority of our patients while maintaining significant improvement in AUASS and QOL index. Lastly, the AUASS and QOL index were designed for benign prostatic hyperplasia and, therefore, may not capture global QOL issues in patients with LS (voiding, cosmesis and sexual function).[7]

Future directions include a randomized controlled trial to evaluate the efficacy of intraurethral steroids alone vs control vs different types of surgical intervention with pre-urethral and post-urethral disease specific PROMs such as the USSIM.

CONCLUSION

Our study demonstrates that LS related urethral stricture can be effectively managed with intraurethral steroids, and that such management improves patient reported voiding symptoms and voiding QOL. In patients with biopsy proven LS an intraurethral steroid regimen as outlined in our algorithm should be considered first line therapy.

REFERENCES

1. Lewis FM, Tatnall FM, Velangi SS et al: British Association of Dermatologists guidelines for the management of lichen sclerosus. Br J Dermatol 2018; **178:** 839.
2. Erickson BA, Elliott SP, Myers JB et al: Understanding the relationship between chronic systemic disease and lichen sclerosus urethral strictures. J Urol 2016; **195:** 363.
3. Nelson DM and Peterson AC: Lichen sclerosus: epidemiological distribution in an equal access health care system. J Urol 2011; **185:** 522.
4. Potts BA, Belsante MJ and Peterson AC: Intraurethral steroids are a safe and effective treatment for stricture disease in patients with biopsy proven lichen sclerosus. J Urol 2016; **195:** 1790.
5. Chung ASJ and Suarez OA: Current treatment of lichen sclerosus and stricture. World J Urol 2019; doi: 10.1007/s00345-019-03030-z.
6. Clobex (clobetasol propionate) Lotion, 0.05% [drug insert]. San Antonio, Texas: DPT Laboratories, Ltd 2005.
7. Barry MJ, Fowler FJ Jr, O'Leary MP et al: The American Urological Association symptom index for benign prostatic hyperplasia. J Urol, suppl., 2017; **197:** S189.
8. Heyns CF and Marais DC: Prospective evaluation of the American Urological Association symptom index and peak urinary flow rate for the followup of men with known urethral stricture disease. J Urol 2002; **168:** 2051.
9. Breyer BN, Edwards TC, Patrick DL et al: Comprehensive qualitative assessment of urethral stricture disease: toward the development of a patient centered outcome measure. J Urol 2017; **198:** 1113.
10. Baradaran N, Hampson LA, Edwards TC et al: Patient-reported outcome measures in urethral reconstruction. Curr Urol Rep 2018; **19:** 48.
11. Powell JJ and Wojnarowska F: Lichen sclerosus. Lancet 1999; **353:** 1777.
12. Liu JS, Walker K, Stein D et al: Lichen sclerosus and isolated bulbar urethral stricture disease. J Urol 2014; **192:** 775.
13. Chen L, Hou R, Feng C et al: Establishment of the U.L.T.R.A. measurement rating system for anterior urethral stricture. Int Urol Nephrol 2017; **49:** 1201.
14. Kulkarni S, Barbagli G, Kirpekar D et al: Lichen sclerosus of the male genitalia and urethra: surgical options and results in a multicenter international experience with 215 patients. Eur Urol 2009; **55:** 945.
15. Hayden JP, Browning JT and Peterson AC: Lichen sclerosus: more than meets the eye. Urology 2020; **139:** 18.
16. Philippou P, Shabbir M, Ralph DJ et al: Genital lichen sclerosus/balanitis xerotica obliterans in men with penile carcinoma: a critical analysis. BJU Int 2013; **111:** 970.
17. Tausch TJ and Peterson AC: Early aggressive treatment of lichen sclerosus may prevent disease progression. J Urol 2012; **187:** 2101.
18. Barbagli G, De Angelis M, Romano G et al: Clinical outcome and quality of life assessment in patients treated with perineal urethrostomy for anterior urethral stricture disease. J Urol 2009; **182:** 548.
19. Peterson AC, Palminteri E, Lazzeri M et al: Heroic measures may not always be justified in extensive urethral stricture due to lichen sclerosus (balanitis xerotica obliterans). Urology 2004; **64:** 565.
20. Fistarol SK and Itin PH: Diagnosis and treatment of lichen sclerosus: an update. Am J Clin Dermatol 2013; **14:** 27.
21. von Krogh G, Dahlman-Ghozlan K and Syrjanen S: Potential human papillomavirus reactivation following topical corticosteroid therapy of genital lichen sclerosus and erosive lichen planus. J Eur Acad Dermatol Venereol 2002; **16:** 130.
22. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Urologic Diseases in America. Washington, D.C.: U.S. Government Printing Office 2012.