

## Peer Review File

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### Reviewer A

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#### *Abstract*

**Comment 1:** How was Lichen sclerosus (LS) identified, was it confirmed by biopsy of the urethral plate? Urethra? Or just by visualization?

**Reply 1:** Indeed, the diagnosis of LS was made clinically-histologically, with a biopsy of the urethral plate.

**Changes in the text (1):** lines 171-172 of corrected manuscript

**Comment 2:** Did the need for no further treatments determine success? This is not an objective measurement; success should be defined by flow rates or a verified symptomatic questionnaire. The absence of surgical intervention is not a valid outcome measurement.

**Reply 2:** Perhaps it is not entirely clear what is considered a successful urethroplasty, which is why we have changed the previous definition.

**Changes in the text (2):** lines 173-175 of corrected manuscript

**Comment 3:** When only two groups are present, rather than stating group A or B, it would be more helpful to delineate the groups by characteristics, e.g., LS or idiopathic.

**Reply 3:** The suggested change has been made throughout the manuscript

**Changes in the text (3):** lines 81-82 of corrected manuscript

**Comment 4:** The term PGI-I is used and not defined; this needs a definition for the reader to interpret the results.

**Reply 4:** This term is defined in the section “postoperative course and follow-up criteria”

**Changes in the text (4):** lines 254-256 of corrected manuscript

**Comment 5:** Unclear if the length of the strictures is the median or mean. In a study with small patient numbers, the median should be given with ranges in length listed in parenthesis.

**Reply 5:** For all variables, the mean with the standard deviation was used.

**Changes in the text (5):** lines 279-280 of corrected manuscript

**Comment 6:** Unclear if follow-up is median or mean; in this case, the median and ranges in follow-up should be given

**Reply 6:** The mean and standard deviations of all variables are shown in detail in the results.

**Changes in the text (6):** lines 286-287 of corrected manuscript

**Comment 7:** I am surprised by the findings specifically; the LS group had significantly longer strictures than the idiopathic group, and there was no difference in outcome?

**Reply 7:** Despite the fact that the length of the stricture has been shown to be an independent factor for recurrence of urethral stricture, in our study we did not observe differences.

**Changes in the text (7):** lines 346-351 of corrected manuscript

**Comment 8:** Just at face value, I find this difficult to accept. The longer the stricture, the more likely complications will develop. I would expect a difference between the two groups based on stricture length itself.

**Reply 8:** As mentioned in the previous answer, in fact the length of the stenosis has been shown to be an independent risk factor for recurrence of the stenosis. In the discussion, a reference is made to these results and a possible explanation for them.

**Changes in the text (8):** lines 346-351 of corrected manuscript

### *Introduction*

**Comment 1:** The grammatical construction of the Introduction specifically, lines 117-119. It could be improved to enhance readability.

**Reply 1:** reviewed and made the change

**Changes in the text (1):** lines 117-118 of corrected manuscript

**Comment 2:** The grammatical construction of the Introduction is basically reviewing a series of facts that are poorly tied together. The flow of this section could be improved to enhance readability and to elucidate the author's points and concerns better.

**Reply 2:** reviewed and made the change

**Changes in the text (2):** Introduction section

### *Material and methods*

**Comment 1:** The point that LS was confirmed by histology should be noted in the abstract.

**Reply 1:** reviewed and made the change

**Changes in the text (1):** lines 82-83 of corrected manuscript

**Comment 2:** I have a hard time with operative success as being defined as needing no further treatment. Ideally, success should be with either a normal flow rate and curve pattern, a valid subjective voiding questionnaire, repeat, retrograde urethrogram (RGUG) cystoscopy, etc.

**Reply 2:** previously answered in the section: Reviewer A / Abstract / Comment 2

**Changes in the text (2):** lines 173-174 of corrected manuscript

**Comment 3:** The authors in the abstract allude to the fact that tobacco use was a factor evaluated; this is not well delineated in the Materials and Methods section.

**Reply 3:** The smoking habit is included in the section of statistical analysis in materials and methods

**Changes in the text (3):** line 267 of corrected manuscript

**Comment 4:** Specifically, the authors should list all reviewed factors in this section, e.g., BMI, diabetes status, age, tobacco usage, etc.

**Reply 4:** All these parameters are included as baseline characteristics of the patients in order not to duplicate the information contained in the table and in the text.

**Changes in the text (4):** lines 182-83 of corrected manuscript

**Comment 5:** Since the authors used both one and two-stage techniques, they need to define their follow-up interval. I assume this was after the completion of the second stage.

**Reply 5:** reviewed and made the change

**Changes in the text (5):** lines 257-259 of corrected manuscript

**Comment 6:** Follow-up methodology should be reviewed; the patient is seen how often? The methods used in follow-up should be described: History and physical exam performed? Flow rate studies, RGUG, or urethral calibration performed?

**Reply 6:** included in the text

**Changes in the text (6):** lines 248-253 of corrected manuscript

**Comment 7:** Since both one and two-stage techniques were performed, the authors should clarify in the materials and method sections that the results will be separated by the type of technique performed. These results should be given separately and compared in the results section.

**Reply 7:** Since it was not the object of the study, a comparative study between both techniques was not carried out. The results are described in figure 1.

**Changes in the text (7):** figure 1

**Comment 8:** Since the LS study group had longer strictures than the idiopathic group, resulting in a significant difference in the operative techniques used between the two groups, e.g., is there a statistical difference in the surgical techniques employed between the two groups? If so this is imperative that this be pointed out.

**Reply 8:** As reflected in the surgical technique section, the type of technique used does not depend on the length, but on the urethral plate and spongiofibrosis.

**Changes in the text (8):** lines 190-193 of corrected manuscript

**Comment 9:** The authors should review the global patient impression of improvement questionnaire in the materials and methods section and reference its validity.

**Reply 9:** included in the text

**Changes in the text (9):** lines 255-257 of corrected manuscript. \*McKibben MJ, Rozanski AT, Fuchs JS, Sundaram V, Morey AF. Versatile algorithmic midline approach to perineal urethrostomy for complex urethral strictures. *World J Urol.* 2019 Jul;37(7):1403-1408. doi: 10.1007/s00345-018-2522-1. Epub 2018 Oct 17. PMID: 30334075.

**Comment 10:** Please clarify lines 255=256 regarding follow-up. Do you mean from the time of urethroplasty completion? Again, please state if the follow-up interval defined is after the completion of the second stage for the patient undergoing a two-stage technique) to the last clinical visit or failure?

**Reply 10:** answered previously

**Changes in the text (10):** lines 258-259 of corrected manuscript

## *Results*

**Comment 1:** In table one please notes, with small patient populations and broad SD, the median value accurately reflects the population under study; please redo with median values

**Reply 1:** reviewed and made the change

**Changes in the text (1):** table 1

**Comment 2:** The number of patients under observation for the plotted time period should be given on the Kaplan Meir survival curve.

**Reply 2:** Sent as a separate document called “Patients observation K-M curve”

**Changes in the text (2):** -

**Comment 3:** By my statistical evaluation, there is a significant difference in the two study groups (LS vs. idiopathic) between the use of single-stage and multistage repair,  $p=0.000531$ . I would be concerned that you cannot compare outcomes between two study populations when using significantly varied surgical techniques.

**Reply 3:** Indeed, the use of 2-stage urethroplasty is more frequent in the LS group, as described in the literature, although this is not the object of our study.

**Changes in the text (3):** -

**Comment 4:** If I interpret the graphs correctly, the overall graft patency rate (subjectively recorded) is approximately 20% for both groups at 60 months of follow-up. I am not sure how many patients were undervaluation at that time, but this is a poor long-term five-year patency rate compared to prior publications. Soave, A et al., Outcome of buccal mucosa graft urethroplasty: A detailed analysis of success, morbidity and quality of life in a contemporary patient cohort at a referral center, BMC Urology 19: 2019, doi.org/10.1186/s12894-019-0449-5

**Reply 4:** Indeed, given that a small percentage of patients reached up to 60 months of follow-up. If we look at the mean follow-up of around 40 months, 50-60% of the patients had graft survival. Follow-up period was defined as the time from urethroplasty to the last clinical control or failure event

**Changes in the text (4):** -

## *Discussion*

**Comment 1:** A large portion of the discussion is a repeat of the Introduction; please reduce duplication of material.

**Reply 1:** The introduction provides a description of the disease from a clinical point of view. In the discussion, a study is made about the treatment of urethral stricture in relation to SF, putting our study in context.

**Changes in the text (1):** -

**Comment 2:** My primary concern is that there is a significant difference in the surgical approach between the two study groups are present in this paper. I do not believe we can compare surgical outcomes in two groups that are so disparate regarding the surgical methodology used.

**Reply 2:** The comparison between both groups and the success of the urethroplasty is made from the second stage of urethroplasty (urethral tubing) in cases of multi-stage repair. Given that between the first and the second time in the 9 cases performed no additional surgery was needed that could influence the long-term results, we consider that they are comparable groups.

**Changes in the text (2):** -

**Comment 1:** The design however reminds me a little of an RCT, with patients being “allocated” to two groups. These groups are compared using t-test, Fischer’s test and Chi-square. In addition, the results are analysed with univariate and multivariate analyses. Why not do only the univariate and multivariate analyses, which as far as I understand, would answer the question of the impact from LS on the results.

**Reply 1:** t-test, Fischer's test and Chi-square were used to compare the variables between both groups.

**Changes in the text (1):** lines 264-266

**Comment 2:** Figure 1 shows the flow of patients included in the study, but how many patients were screened for participation but excluded (and why)?

**Reply 2:** The inclusion criteria were patients with idiopathic etiology penile urethral stricture or LS who underwent urethroplasty with oral mucosa graft, who had not undergone prior urethroplasties. We included only patients with complete clinical data. Patients with less than 12 months of follow-up were excluded from the study.

**Changes in the text (2):** lines 168-170 of corrected manuscript

**Comment 3:** Was the diagnosis of LS based on biopsies in all patients? Were the patients in the idiopathic group biopsied as well or was this diagnosis based on clinical examination only?

**Reply 3:** The diagnosis of patients with LS was made clinically and was confirmed with a biopsy in all patients, while in the idiopathic group the diagnosis was made only clinically.

**Changes in the text (3):** -

**Comment 4:** Table 1 is a mix of baseline demographics and results. In my opinion, it would be better to separate these data. It may be a question of preference, but I find it easier to visualize the distribution of the baseline data when they are presented with median and inter-quartile range. The p-values in table 1 is reported with unnecessary precision and should be corrected.

**Reply 4:** reviewed and made the change

**Changes in the text (4):** table 1

**Comment 5:** Line 337: “...shows a higher success rate in the LS vs idiopathic group”. As this is not significant, I would not state there is a higher success rate as this could be misinterpreted.

**Reply 5:** Indeed, reference is made to the difference between the two, but then it is detailed that such a difference is not statistically significant, although the difference does exist.

**Changes in the text (5):** lines 340-343 of corrected manuscript

**Comment 6:** The authors state the limitations of the study well, including the low sample size. I suggest that the small sample size is also discussed as an explanation for the results.

**Reply 6:** reviewed and made the change

**Changes in the text (6):** lines 349 and 407 of corrected manuscript