Peer Review File

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Reviewer A

Comment 1: Small Sample Size: The study involved only 15 patients, which is a relatively small cohort. This limits the generalizability of the findings to the broader population. A larger sample size would provide more robust data and help in establishing stronger correlations between idiopathic urethral stricture disease (IUSD) and its underlying causes.

Reply 1: The small sample size is mentioned as a limitation to this study and highlights the novel approach as a pilot study in the hope that other reconstructive surgeons follow this protocol to add a larger cohort to an international data base.

Changes in text: Added statement in limitations that this is a pilot study and hopes further adoption will improve sample size (Line 389-391 Page 15)

Comment 2: Lack of Control Group: The absence of a control group, such as patients without urethral strictures or with known causes of urethral stricture, limits the ability to draw comparative conclusions about the specific role of lichen sclerosus (LS) and other histopathological features in IUSD.

Reply 2: The difficulty with obtaining a control group is for patients to undergo sham procedure when no stricture is present that being said those with a confirmed diagnosis for their USD could also have been biopsied. The lack of control has been updated in the literature to read “enrolling control groups without stricture disease or with known etiologies for comparison,” (Line 402 Page 15)

Changes in text: Updated limitations to recommend enrolling control groups in future studies (Line 402 Page 15)

Comment 3: Geographic and Demographic Limitations: The study is geographically limited to an Australian population, which may not represent the global diversity in IUSD prevalence and characteristics.

Reply 3: The methods and limitations portion now include reference to Australian population and also makes reference to the higher incidence of iatrogenic USD as mentioned in the introduction. Line now reads within the limitation paragraph: “limited geographic diversity as an Australian population which may not represent global IUSD characteristics” (Line 389-390 Page 15)

Changes in text: Added statement about Australian population and global generalizability to limitations (Line 389-390 Page 15)

Comment 4: Histopathological Analysis Constraints: While the study provides insights into histopathological changes associated with IUSD, the interpretation of these changes can be subjective and varies based on the pathologist's expertise. Standardization in the assessment and interpretation of histopathological findings would enhance the reliability of the results. Additional photos/pictures of microscopic view would be a valuable addition.

Reply 4: The variability in histopathological diagnostic criteria is mentioned in the discussion. Images have now been included to highlight the histopathological changes consistent with LS as well as the other relevant changes noted.

Changes in text: Discussed variability in LS diagnostic criteria (Line 314-319 Page 12) and added images demonstrating histopathological changes (Figure 3 and 4, Line 666-677 Page 20)

Comment 5: Histopathological Analysis Constraints: While the study provides insights into histopathological changes associated with IUSD, the interpretation of these changes can be subjective and varies based on the pathologist's expertise. Standardization in the assessment and interpretation of histopathological findings would enhance the reliability of the results. Additional photos/pictures of microscopic view would be a valuable addition.

Reply 5: Follow up duration extended with average now 16 months and maximum 36 months. Ongoing follow up continues. Line reads: “The average follow up time was 16 months with maximum at 36 months. Ongoing follow up continues with yearly clinic reviews.” (Line 215-216 Page 10)

Changes in text: Updated follow up duration in results (Line 215-216 Page 10)

Reviewer B

Comment 1: 1. After performing the biopsy of the urethral mucosa and spongy tissue, is this area covered with a graft or is a muco-mucosal anastomosis of the defect performed?

Reply 1: The biopsies were taken at the edge of of urethrotomy and therefore the biopsy sites were incorporated into the buccal mucosa graft placement

Changes in text: None

Comment 2: 2. In patients who presented recurrence, a biopsy of the stenotic segments was performed to diagnose possible LS.

Reply 2: No. This is a good idea however our concern was that given the recurrence of stricture retaking samples may risk further stricturing and was not attempted. 1 patient with recurrence was resolved with a single episode of endoscopic dilatation; therefore, a biopsy would not have been possible.

Changes in text: None

Comment 3: In which patients do you consider performing double face urethroplasty? How do you define obliterative or semi-obliterative stricture? What type of approach is used in these patients, the technique described by Palminteri ventral onlay + dorsal inlay or dorsal onlay + ventral inlay?

Reply 3: Our criteria for double face urethroplasty are: 1) Near or obliterative strictures to maximise patency, 2) Obliterative defined as SPC dependent and near as <3Fr, 3) Utilize Palminteri approach

Changes in text: None

Comment 4: Another limitation of the study is the short follow-up of patients undergoing urethroplasty with graft. In the case of EPA, most recurrences occur in the first year after surgery, while in patients undergoing urethroplasty with graft, a follow-up of at least 5 years seems reasonable. Palminteri E, Lumen N, Berdondini E, Di Pierro GB, Cucchiarale G, Tenti G, De Nunzio C. Two-sided dorsal plus ventral oral graft bulbar urethroplasty: long-term results and predictive factors. Urology. 2015 Apr;85(4):942-7. doi: 10.1016/ j.urology.2015.01.013. PMID: 25817122.

Reply 4: Follow up extended with average now 16 months, maximum 36 months, and ongoing yearly reviews. Updated in results section: “The average follow up time was 16 months with maximum at 36 months. Ongoing follow up continues with yearly clinic reviews.” (Line 215-216 Page 10)

Changes in text: Updated follow up duration in results section (Line 215-216 Page 10)

Reviewer C

Comment 1: - Lines 247-249: the selected length categories are non-standard and the rationale for reporting in this manner is not apparent. I would recommend categorizing in a manner more consistent with existing literature, e.g. 2cm and 7cm [Erickson BA et al, 2020]

Reply 1: Stricture length categories have been updated to standard <2cm, 2-7cm and >7cm format with details now reading: “4 patients had stricture length below 2 centimetres, 10 patients had strictures between 2 and 7 centimetres and 1 patient had a stricture above 7 centimetres. The average length of stricture was 3.1 centimetres (1-8cm).” (Line 208-210 Page 10)

Changes in text: Updated stricture length categories (Line 208-210 Page 10)

Comment 2: The authors report clinical outcomes with urethroplasty in this cohort, but I do not think this is relevant to the clinical question explored in this paper. I would recommend removing information about the clinical outcomes from Methods and Results sections, or alternatively limiting this to a very brief review of outcomes.

Reply 2: You make an excellent point. Given the focus on histopathology, the clinical outcomes have been removed from methods and results to streamline the analysis. Thank you for this constructive feedback.

Changes in text: Removed clinical outcomes from methods and results

Comment 3: the authors report absence of pathologic evidence of cutaneous LS on circumcision when performed, but this is not discussed anywhere else in the paper. It should be expanded upon (succinctly) or removed. I do think this is relevant information and would encourage them to briefly expand on this reporting (comment in Methods on the indication and/or decision-making for simultaneous circumcision, report the number of patients who underwent simultaneous circumcision).

Reply 3: Appreciate you highlighting this oversight. To clarify, no patients underwent simultaneous circumcision. The line reading no macroscopic LS on glans/skin has been retained to preclude this as a confounder. Thank you for catching this ambiguity.

Changes in text:

Methods section updated to now include “, obvious macroscopic inflammatory disease (including a prior diagnosis of LS)” (Line 157-161 Page 8)

No macroscopic LS on examination in results (Line 214-215 Page 10)

Comment 4: Line 306: What is the parameter being evaluated in the reported NNT? This number is significantly too high to represent the number of patients with urethral stricture needed to treat with urethroplasty in order to achieve success. I’m not clear on what this result is referencing.

Reply 4: You have identified an excellent point. Upon review, NNT does not relate to this study's goals and has therefore been removed entirely. Thank you for catching this distracting statistic.

Changes in text: Removed NNT content

Comment 5: Line 326-327: The authors report new results using an alternative diagnostic criterion for LS. This is interesting info, but it should be in the results section. Consider restructuring the results to focus on the primary clinical question (pathologic findings) and report findings using two different standard definitions for LS.

Reply 5: We appreciate you highlighting this opportunity to enhance results interpretation. As the established criteria were predefined per methods to promote standardization, adopting alternative diagnostic guidelines post-hoc may increase subjectivity. However, to contextualize the observed incidence, the potential impact of using expanded LS criteria has been conservatively estimated through discussion. We aim for this to strengthen analysis

without compromising methodological rigor. Please advise if any clarification on this approach would further improve communication of the key insights.

Changes in text: None

Comment 6: tarting at line 368, the authors report limitations. These are spread over two paragraphs and should be consolidated. In addition to the two limitations reported (small number of subjects, method of pathologic staining/analysis), I would encourage consideration of other limitations, including: heterogeneity in stricture location (thus potential heterogeneity in underlying pathophysiology), technical limitations in tissue handling/ processing that yielded nondiagnostic pathologic evaluation in at least 3 cases. The other sections of these two paragraphs (discussion of establishing a pathologic database, use of immunohistochemical staining) are future directions and should be moved to a different section.

Reply 6: Thank you for encouraging critical evaluation of limitations to augment scientific discourse. In response, limitations have been synthesized into one comprehensive paragraph citing small sample size, lack of controls, inconsistent diagnostic pathology criteria, and more while separating future directions. We implemented your recommendation to consider heterogeneity in location and technical limitations that may have obscured microscopic disease patterns. Please let us know if further improvements could be made to transparently detail boundaries on inference.

Changes in text: Combined limitations into one paragraph and separated future directions (Line 386-404 Page 15)

Comment 7: In Table 1, the author refers to several cases in which the surgical approach was noted to be a “Kulkarni”. These are a mix of ventral and dorsal onlay approaches for short segment strictures. It is not clear what they are referring to as a Kulkarni here, and this may represent a misnomer (none sound like a Kulkarni dorsal onlay urethroplasty for long segment strictures)

Reply 7: We truly appreciate you taking the time to probe terminology usage; accuracy is vital in technical communication. You have helped identify an ambiguity requiring resolution – the “Kulkarni” descriptor we applied denotes single-sided urethral mobilization rather than graft positioning. As the priority is avoiding confusion, this non-essential procedural detail has been removed. Please advise if any outstanding queries on methods or results remain.

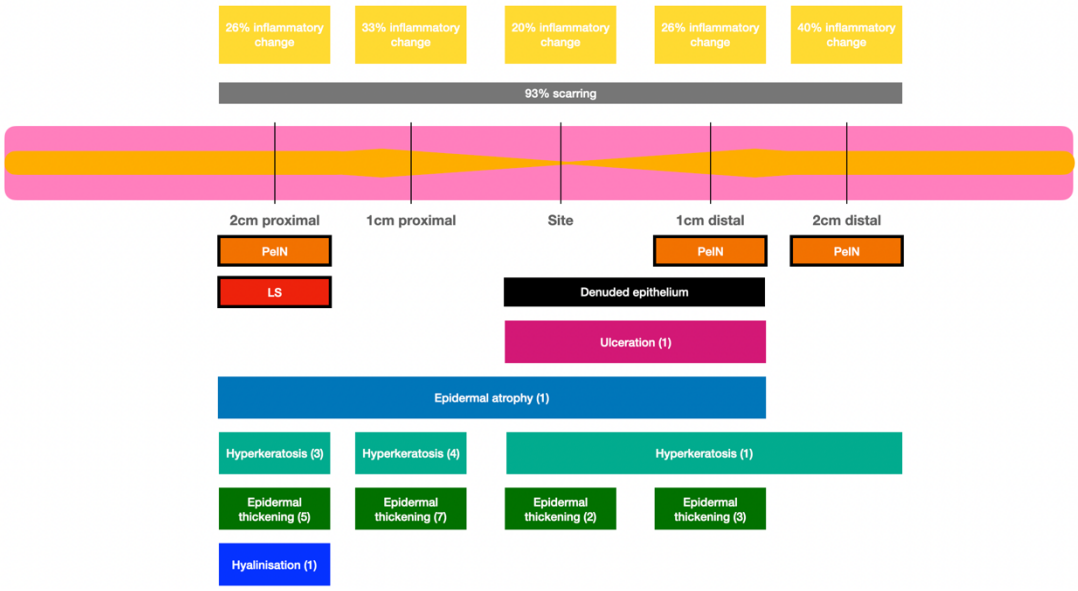
Changes in text: Removed “Kulkarni” label from table (Table 1)

Comment 8: I would encourage the authors to reimagine how they report out the pathologic characteristics included in Tables 2-6. As is, reporting each biopsy site separately is quite cumbersome and difficult for the reader to digest. Reporting out all sites in this manner could be consider as Online Supplements. One idea that may be more useful is to report out one

table with pathology at disease site, proximal (including 1 and 2cm proximal), and distal (including 1 and 2cm distal). At each site the authors could report the number (%) of patients with each feature, and could also report the number (%) with 2 features, 3 or more features, etc as relevant.

Reply 8: Your guidance on optimizing data presentation for digestibility and clarity is invaluable. In response, findings across biopsy locations have been synthesized into one figure highlighting key results while supplemental tables detail individual site pathology comprehensively. Paragraphs have been added guiding interpretation and calling attention to the unifying illustration. We sincerely appreciate you taking the time to strengthen communication of these novel findings through constructive input on information design. Please advise if you have any remaining suggestions on conveying these multidimensional results for maximal comprehension.

Changes in text: Added summarized figure of pathology findings across locations (Figure 3) and guided description in the text while moving granular tables to supplement (Line 217-270 Page 10-11)



Comment 9: Line 63-64: “is LS an underlying cause of some idiopathic strictures…” or “do idiopathic strictures show evidence of LS”Reply 9: The abstract has been refined to more precisely frame the pilot study aims examining 1) LS as an underlying etiology of some idiopathic strictures and 2) histological changes suggesting tissue predisposition to stricture formation.

Changes in text: Clarified research aims in abstract (Line 52-53 Page 4)

Comment 10: Line 126: “LS is increasingly recognized as AN underlying cause…” or “an important underlying cause…”

Reply 10: The phrasing highlighting LS as an underlying cause in stricture disease has been updated as you advised to now read “LS is increasingly recognised as an underlying cause of stricture disease...” (Line 14 Page 7).

Changes in text: Updated LS emphasis as underlying cause (Line 14 Page 7)

Comment 11: correct acronym to “USD” at end of sentence.

Reply 11: Thank you for catching this oversight in terminology usage. The USD acronym has been changed to USD

Changes in text: Standardized USD acronym (Line 119-120 Page 7)

Comment 12: Line 137-138: “can sometimes lead to the development of MORE COMPLICATED stricture disease” – the disease is present, so it won’t further develop but it can become more complex through treatment, as evidenced in prior literature

Reply 12: This paragraph has been removed in response to feedback on introduction length and focus. We appreciate you taking the time to strengthen quality through scope refinement.

Changes in text: Removed paragraph from introduction

Comment 13: Line 144-145: correct to “…length of the urethra, AND IS limited to the bulbar urethra.”

Reply 13: Thank you for catching this anatomical inaccuracy - the highlighted line has been updated to now definitively state EPA is limited to the bulbar urethra specifically. We appreciate you ensuring precision on these technical details.

Changes in text: Specified EPA limited to bulbar urethra (Line 123-125 Page 7)

Comment 14: Line 194: correct spelling of first word “enrollment”

Reply 14: We acknowledge and will maintain the British spelling of “enrolment” throughout for consistency.

Changes in text: None

Comment 15: Line 334-335: revise to “…in the underlying etiology of SOME idiopathic strictures”. Even with the alternative LS pathologic criteria, only 1/3 of candidates had LS findings.

Reply 15: You have rightly highlighted that the observed proportion of LS only accounts for a subset of idiopathic cases. As advised, the text has been updated to reference the etiology of “some” idiopathic strictures to accurately qualify the inference.

Changes in text: Qualified conclusions apply to some idiopathic strictures (Line 340-341 Page 13)

Comment 16: Line 337-338: correct to "…were observed both PROXIMAL and DISTAL to the site of stricture."

Reply 16: We appreciate you taking the time to ensure scientific rigor - the highlighted line has been revised to unambiguously state the pathological changes were proximal and distal to the anatomical site of stricture.

Changes in text: Clarified changes proximal and distal to stricture site (Line 342-343 Page 13)

Reviewer D

Comment 1: I do wonder if 1 year follow up is sufficient and a point where results are "durable" enough. While I understand recurrences are most likely within 18 months, 1 year does seem short. I will have to await the intermediate follow up period.

Reply 1: We appreciate you highlighting this opportunity to strengthen longitudinal insight. In response, reported follow-up has been extended with average duration now 16 months (previously 12), maximum follow-up now 36 months, and notation of ongoing yearly reviews. We agree robust surveillance over an adequate interval is vital for comprehensively understanding durability. Please let us know if you have any other suggestions on tracking long-term outcomes.

Changes in text: Updated follow-up details in results, including extending average and maximum duration (Line 215-216 Page 10).

Comment 2: An interesting finding was that the level of inflammation increased distally from the point of the stricture. 20 % at stricture, 27% at 1 cm distal to stricture and 40% at 2 cm distal to the stricture. I think this finding, though not really zeroed in on, warrants more attention and supports the notion that LS in idiopathic stricture disease is a spectrum, as stated in line 404. For instance, if a stricture is 1.8 cm, but the inflammation bridges several centimeters in either direction, should this stricture "field" warrant different treatment than just the strictured area itself? A way to evaluate this would be to see if IC green can be used to visualize the stricture area and something I hope is implemented in future iterations of this study.

Reply 2: Thank you for your astute observations on the nuances of inflammation distribution – we fully agree these warrant attention when considering therapeutic approaches. In response, a paragraph has been added discussing implications of inflammation potentially extending beyond visible stricture, including possible decreased EPA success joining still diseased urethral tissue segments. Indocyanine green imaging to assess extent is an excellent idea that has now been incorporated into planned research directions.

Changes in text: Added paragraph discussing inflammation patterns and implications on treatment decisions and outcomes (Line 340-352 Page 13). Included ICG imaging in future directions (Line 398-404 Page 15).

Comment 3: 1. Did all patients have uroflows less than 10 mL/s upfront? Or were these only obtained if recurrence was suspected?

Reply 3: Thank you for querying procedural specifics - uroflowmetry was performed routinely at each postoperative visit for all patients, not only if recurrence was suspected. This allows continual monitoring for detection of concerning trends. We appreciate you seeking clarity on measurement protocols; standardization is vital for reliability. Please advise if any other questions remain on follow-up methods.

Changes in text: None

Comment 4: 2. The authors discuss the need to standardize practice (and even definitions), as the LS rate would have jumped from 6.7% to 33%, yet no standardized protocol is offered. In short, have these findings changed the institution and senior urologist's practices at all since the study period concluded, and if, so, what would they propose as a starting point?

Reply 4: Thank you for raising this vital issue - we fully agree that variability in histopathological interpretation of LS introduces subjectivity that can impede standardization. In response, a discussion has been introduced framing LS as a disease spectrum given the lack of consensus diagnostic criteria. For patients exhibiting some LS features despite overall negative biopsies, incorporating clinical perspectives into individualized management is proposed. We believe contextualizing pathology within a broader clinical picture can help mitigate inter-observer variability until unified guidelines emerge. The unification process needs to come from the pathologists given they are the interpreters of the histological slides.

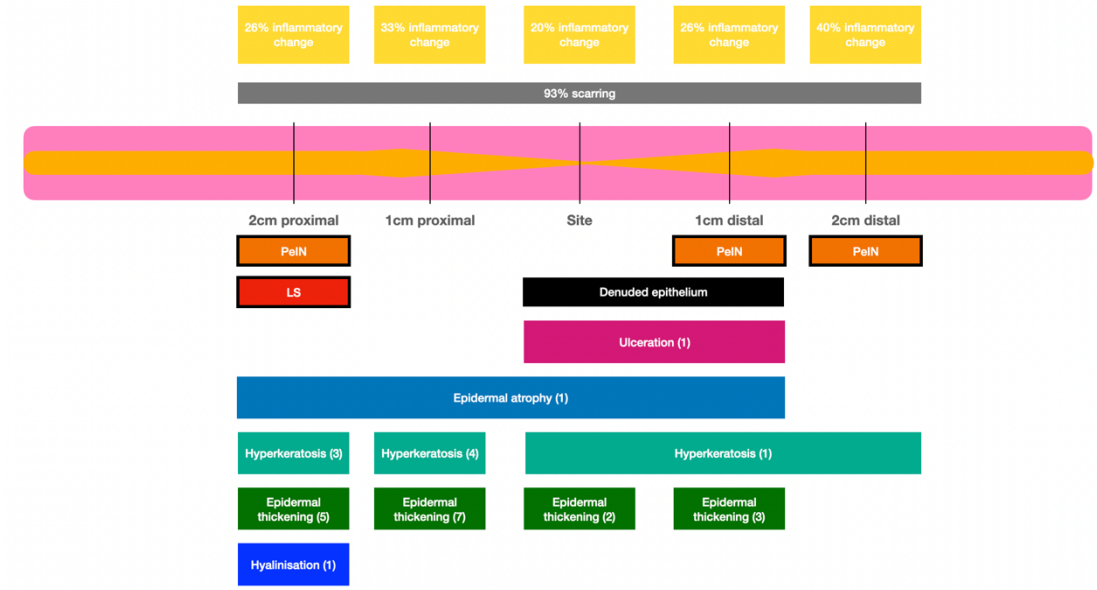
Changes in text: Proposed clinical correlation and expectant approaches for patients with some LS features to address standardization difficulties until unified criteria established. (Line 446-450 Page 16)

Reviewer E

Comment 1: Consider including illustrations of histologic features of the different findings.

Reply 1: Thank you for the insightful suggestion to incorporate microscopic images - this is an excellent opportunity to enhance reader comprehension through visualization of key pathological manifestations. In response, representative histology findings for lichen sclerosis, inflammation and other common features have now been compiled and displayed to demonstrate relevant morphology. We agree that the tables of histological outcomes are over detailed and difficult to read. We have amalgamated the findings into a single illustration for ease of reading and moved the tables to supplementary reading.

Changes in text: Added figure with histological images depicting LS, inflammation and other noted changes (Figure 3 and 4, Line 666-677 Page 20)). Changed biopsy tables to supplementary and combined into a single illustration (see below)



Comment 2: Is it possible to include more detailed information of the type of inflammatory infiltrate?

Reply 2: Our analysis characterized inflammation in a broad sense in terms of presence, acuity or chronicity and did not provide additional specificity which could be informative. The proposed immunohistochemical staining technique by Samarksa et al. to subtype immune cells provides an outstanding methodological advancement that has now been acknowledged in planned research directions.

Changes in text: Included specific staining proposal by Samarksa et al. in future directions to enhance inflammation subtype resolution (Line 400-402 Page 15).

Comment 3: The findings should be compared to a recent study titled "Histopathologic and clinical comparison of recurrent and non-recurrent urethral stricture disease treated by reconstructive surgery" by Samarska et al. and the study should be cited.

Reply 3: We sincerely appreciate you drawing our attention to this highly relevant recurrent stricture analysis - the ability to contextualize our results relative to postoperative outcomes is invaluable. In response, a paragraph has been added discussing their surgical cohort's association between fibrosclerotic histological patterns and elevated recurrence after EPA. This lends credence to our hypothesis that incorporating occult diseased tissue margins into repairs could seed failure.

Changes in text: Added paragraph comparing findings from Samarska et al. and interpreting their insights relative to EPA recurrence risk when joining occult diseased tissue. (Line 361-372 Page 14)

Reviewer F

Comment 1: The introduction in it's current form is too long. It doesn't serve the reader for example to review non-transecting v transecting urethroplasty as there is little relevance to the research questions being asked. All patients in the study underwent buccal graft urethroplasty making this discussion even less relevant. Paragraph starting 158 has abrupt change in topic line 163. Recommend parsing introduction to 3-4 paragraphs maximum and limiting the scope of the material reviewed.

Reply 1: We sincerely appreciate you taking the time to strengthen quality through constructive feedback on scope and concision - introduction length has been reduced by over 50% through summarization of key themes relevant to the study goals. Extraneous detail around specific techniques has been eliminated to maintain clear focus. We agree an economy of words serves comprehension and sincerely thank you for pushing clarity.

Changes in text: Reduced and focused introduction by summarizing pertinent themes and removing peripheral content (Line 121-133 Page 8)

Comment 2: Line 110: Recommend change to 1/1000 as a rate for ease of reading.

Reply 2: Thank you for catching this clumsy phrasing - as advised, the stricture rate has been updated to a more digestible 1 in 1000 format by eliminating decimal expansion.

Changes in text: Simplified stricture terminology as 1 in 1000 (Line 95 Page 6)

Comment 3: Would be worth clearly stating (if true) that patients who had undergone prior dilation for urethral stricture were excluded. Additionally, would recommend stating that a prior diagnosis of LS was an exclusion (versus just active inflammation/macroscopic disease)

Reply 3: Methods have been updated to explicitly state patients with prior urethral dilation were included while prior LS diagnoses were grounds for exclusion. Ensuring transparent portrayal of the cohort parameters is vital.

Changes in text: Specified prior dilation allowed for inclusion, prior LS diagnosis specifically mentioned as an exclusion criteria (Line 157-162 Page 8)

Comment 4: Was the same pathologist used for specimen review? Particularly important given study cited Line 314

Reply 4: The existing manuscript statement confirms the use of a single independent centralized uro-pathologist for all specimens has been retained.

Changes in text: None, single pathologist already stated (Line 181-182 Page 9)

Comment 5: Line 257 – Please comment in the discussion on why you think there was no LS at the stricture

Reply 5: Excellent point - discussion has been added proposing the scarred stricture specimens potentially represented burned out lichen sclerosis that obscured recognizable morphology, accounting for the unexpected lack of classic histological LS changes at the diseased sites.

Changes in text: Added hypothesizing burned out LS at stricture site explaining absent classic morphology (Line 390-392 Page 15)

Comment 6: Table 1: Given clinical LS was exclusion can remove column

Reply 6: Thank you for highlighting this as a redundant piece of information. The table has been updated to reflect this

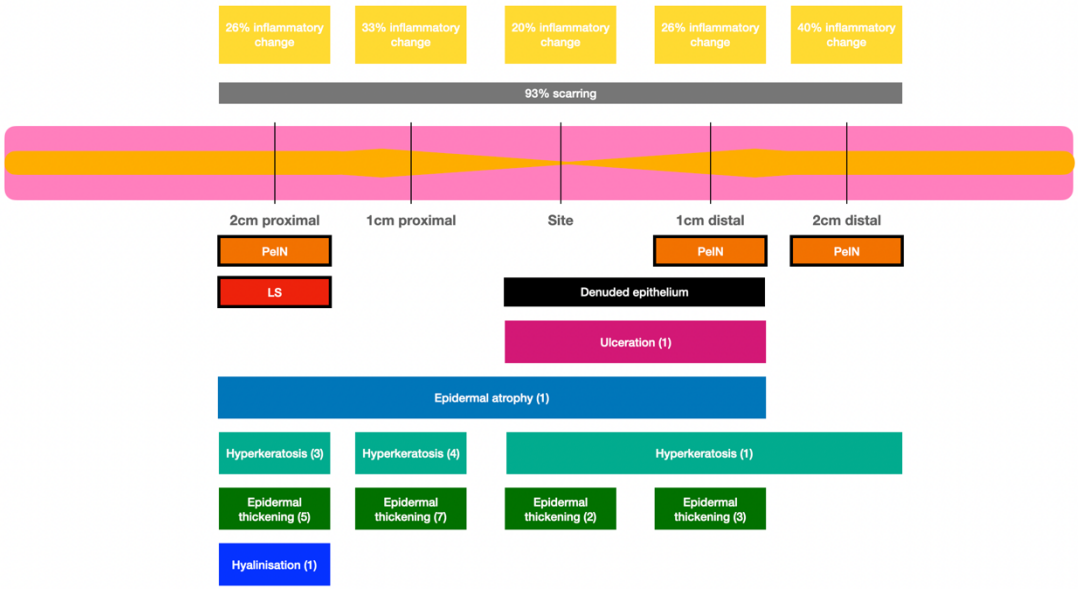
Changes in text: Table 1 column “Clinical LS” has been removed

Comment 7: Table 2-6: Reduce number of tables. Each biopsy site does not need its own table. May benefit from alternative data presentation

Patient #	Proximal 2cm	Prox 1cm	Stricture	Distal 1cm	Distal 2cm
14	LS, hyalin, scarring	Scarring	-	Scarring	Scarring

Reply 7: The multi-faceted histopathology results have been compiled into one summarized figure to enhance digestibility while the supporting granular tables have been moved to supplementary for peripheral reference.

Changes in text: Created a centralized visual figure compiling all pathology results across biopsy sites (see below). Moved granular tables to supplement (Line 217-270 Page 10-11).



Comment 8: Figure 1: Not sure RUG with stricture is relevant to study

Reply 8: The highlighted figure has been removed given lack of relevance to study goals. We appreciate your diligence ensuring only pertinent inclusion of visual elements to avoid distraction.

Changes in text: RUG Figure 1 removed

Comment 9: Line 339: Good point. Please comment on how this may impact decision making

Reply 9: A paragraph has been added proposing the non-visible proximal and distal inflammation potentially decreasing EPA success when joining still diseased tissue margins. These occult disease extensions should inform surgical decision-making.

Changes in text: Added proposed implications of pathology extending beyond stricture site in relation to heightened EPA recurrence risk (Line 350-353 Page 13)

Comment 10: Line 376: Is there a stain that would be recommended? Could help others repeat data and improve

Reply 10: The complementary immunohistochemical panel proposed by Samarksa et al. has been included to improve inflammation resolution. This has been cited in the planned research directions. The inclusion of Trichrome-blue stain for fibrosis assessment and immunohistochemistry for inflammatory markers CD3, CD20, CD68 have been included as further investigations to improve the study.

Changes in text: Cited Samarska et al. staining panel in future directions to standardize and subtype inflammation analysis (Line 400-402 Page 15)

Comment 11: Paragraph starting line 387: Given all patients underwent BMG unclear what role findings have in EPA. Recommend removing paragraph

Reply 11: Findings of occult proximal and distal disease have implications for EPA recurrence risk as we have indicated, so this paragraph has been retained. We agree the themes around inflammation patterns extending beyond visible stricture warrant inclusion given relevance to surgical decision making for balanced outcomes. BMG patients were only included in this study as this was the only way to facilitate biopsies at the urethrotomy as this is unable to be achieved with EPA as the diseased segment would only be available for histopathological assessment.

Changes in text: Retained paragraph discussing inflammation patterns in relation to heightened EPA failure risk requiring consideration in approach selection (No change)

Comment 12: Line 398: Worth emphasizing PeIN identification.

Reply 12: We sincerely appreciate you encouraging thorough interpretation of the singular detection of premature neoplastic transformation. As advised, the discussion has been expanded to further emphasize the identification of PeIN as underscoring i) the broader

malignancy risk inherent to inflammatory stricture disease and ii) the value of biopsies to prospectively screen for concerning cellular changes warranting intervention.

Changes in text: Augmented emphasis on highlighting PeIN case to underscore cancer risk and endorse early screening necessity (Line 441-445 Page 16)

Comment 13: Line 403: Introduce this idea in the introduction if you want to include. Please also cite diagnostic variability. This is worth noting and reviewing.

Reply 13: We appreciate you highlighting this opportunity to enhance results interpretation. As an established criteria were predefined for LS per methods to promote standardization, adopting alternative diagnostic guidelines post-hoc in the introduction may increase subjectivity. However, to contextualize the observed incidence, the potential impact of using expanded LS criteria has been conservatively estimated through discussion. We aim for this to strengthen analysis without compromising methodological rigor.

Change in text: No changes made

Comment 14: What group is this in your study? Macroscopic LS was excluded. It's a reasonable approach (treat LS symptoms as LS even with negative biopsy) but your data doesn't support a comment on this.

Reply 14: You raise an excellent point - the population exhibiting some LS features despite negative biopsies were the minority subset meeting alternative diagnostic criteria. As the cohort excluded overt LS diagnoses, directly generalizing recommendations could constitute overreach. As advised, this paragraph has been refined to frame the proposition as a hypothesis requiring validation. T

Changes in text: Qualified hypothetical extrapolation for patients with some LS features, removed implication of empirical generalization from cohort itself (Line 447-450 Page 16)

Comment 15: Line 407: Local skin flaps are recommended not to be used in LS.

Reply 15: Thank you for catching this unclear phrasing - as intended, the line has been updated to unambiguously state skin flaps should be avoided in LS cases.

Changes in text: Clarified skin flaps should be avoided in LS (Line 449-450 Page 16)

Comment 16: Line 413: Agree this is a pilot study. Recommend emphasizing this throughout paper.

Reply 16: We appreciate the reminder to prominently orient the reader regarding the preliminary nature of this initial inquiry. As advised, the pilot study design has now been clearly highlighted in the abstract, introduction, and conclusion sections to frame interpretations and future directions accordingly.

Changes in text: Further emphasized pilot study framework in abstract, introduction, and conclusion (Lines 52 Page 4, Line 134 Page 7, Line 439 Page 16)