



Histopathologic and clinical comparison of recurrent and non-recurrent urethral stricture disease treated by reconstructive surgery

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Background: Urethral stricture is a relatively frequent problem often requiring multiple surgical interventions. The objective of this study was to compare the clinicopathologic features of urethral resections from patients who underwent open end-to-end anastomotic urethroplasty and later recurred compared to those who did not.

Methods: A retrospective review of the pathology files identified 36 consecutive patients who underwent urethroplasty. The histopathological analysis included evaluation of the inflammatory infiltrate based on the predominant (>50%) cell type: lymphocyte-rich, neutrophil-rich, plasma cell-rich, and mixed; length and thickness of the fibrous plaque; and the cellularity of the fibrous plaque: cellular (>40 stroma nuclei/HPF) or paucicellular (<40 stroma nuclei/high power field).

Results: Ten (28%) patients recurred, and 26 (72%) did not. There was no significant difference between recurrent and non-recurrent cases in age, race, comorbidities, location of the stricture, and etiology. All patients with recurrent strictures showed dense paucicellular fibrotic plaques (10/10; 100%), while this was seen in 14/26 (53.8%) non-recurrent cases (P=0.01). Only one patient with cellular fibrosis showed recurrence during follow-up. The log-rank test shows that time to recurrence is significantly shorter in patients with paucicellular fibrosis compared to those with cellular fibrosis (P=0.036). The inflammation consisted of a mixed population of CD3(+) T-lymphocytes, CD20(+) B-lymphocytes, and CD68(+) histiocytes, and there was no difference in the composition of the inflammation between groups. All cases with plasma cell-rich infiltrate showed normal IgG4:IgG.

Conclusions: Our study supports reporting cellularity of the fibrous plaque as a potential predictor of outcome in patients undergoing reconstructive urethroplasty. Patients with paucicellular fibrosis are at increased risk of recurrence.

Keywords: Urethral stricture; urethroplasty; urethral obstruction

Submitted May 28, 2021. Accepted for publication Aug 26, 2021.

doi: 10.21037/tau-21-477

View this article at: <https://dx.doi.org/10.21037/tau-21-477>

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Introduction

Urethral stricture is a relatively frequent problem in urological practice with a relative comparable incidence of 0.6% of all urologic consults in the United States and other developed countries (1,2). The etiology includes idiopathic (unknown), iatrogenic (post-instrumental), congenital (hypospadias-related), inflammatory (sexually transmitted diseases-related), traumatic (pelvis fractures) and lichen sclerosus-related (formerly known as balanitis xerotica obliterans) (3-6). Idiopathic or unknown cause is the most common etiology in both bulbar and penile strictures (6,7).

The pathophysiology of urethral strictures is mostly unknown. Strictures may result due to ischemic spongiofibrosis occurring after infective, inflammatory, or traumatic injury (3,7). The pathogenesis includes excessive fibroblast proliferation, collagen synthesis, and extracellular matrix deposition (8). Recently IgG4-related disease was proved to be an etiological factor in ureteral stenosis (9), and BK-virus infection has been shown in relation to both ureteral and urethral stenosis (10).

The aim of this study is to describe the clinicopathologic features of the urethral stricture resections from patients who later recurred compared to those who did not recur on follow-up. We hypothesized that the pattern of inflammation and fibrosis pattern could be used to predict the outcome. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/tau-21-477>).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Johns Hopkins University (No. IRB00254688) and individual consent for this retrospective analysis was waived. We identified 36 consecutive patients with urethral stricture treated with surgical excision from the files of Department of Pathology of Johns Hopkins Medical Institutions in a period of 3 years. Since the goal of the study was to determine histopathologic predictors of recurrence, patients operated with flaps or grafts were excluded to decrease confounders. Only patients with available histopathological material were included. Patients with a history of radiation therapy to the pelvis were also excluded. A retrospective review was performed to collect patient demographics and history of

infection, trauma, previous urological procedures, pre- and postoperative urodynamic characteristics, and evaluate the postoperative value of the international symposium of prostate score (IPSS) and the sexual health inventory for men (SHIM) score. The non-recurrent strictures were defined as the first diagnosis with successful treatment during the documented follow-up period without requiring additional urological intervention. The recurrent strictures were classified as patients requiring internal urethrotomy and/or intermittent dilation. Surgical success was defined as absence of symptoms of lower urinary tract obstruction (LUTS) and no instrumentation after the resection. The status of recurrent or non-recurrent is at the time of last follow-up visit. When no anamnestic or documented cause was identified, the stricture was classified as idiopathic.

Histopathology and immunohistochemistry

Tissue samples were totally submitted for the histopathological evaluation. All tissue samples were first fixed in buffered formalin and processed to paraffin wax. The 3–4 μ m sections were stained with hematoxylin and eosin (H&E) for histologic evaluation. The histopathological analysis included assessing the inflammatory infiltrate based on the predominant (>50%) cell type, including lymphocyte-rich, neutrophil-rich, plasma cell-rich, and mixed infiltrate. The cellularity of the fibrous area was measured as a number of the stromal cells in 5 HPFs ($\times 40$ magnification) in the areas with the maximal stromal cellularity. Nuclei of inflammatory cells were not counted. The cellularity of the fibrous area was classified as cellular (>40 stroma nuclei/HPF) or paucicellular (<40 stroma nuclei/HPF), adapted from the previously published studies and confirmed by the number of the stromal cells in the cases with cellular fibrosis from this study (11,12). Trichrome-blue stain (Masson's trichrome stain) was performed to evaluate the extent of fibrosis below the urothelium or urethral lumen by measuring the thickness of deep blue staining in mm perpendicular to the lumen. The fibrotic plaque was defined as a dense fibrotic tissue, characterized by the packs of collagen fibers, strongly positive for Trichrome-blue stain, as previously described (11). In the samples with a prominent lymphoplasmacytic inflammation (lymphocyte rich cases), immunohistochemistry for CD3, CD20, CD68, IgG, and IgG4 was performed. Immunohistochemistry was performed using the Ventana Medical System Benchmark XT Ultra (Ventana, Tucson, AZ, USA) with the following

specific antibodies: anti-CD20 (clone MS/L26, Ventana; predilute), anti-CD3 (Dako polyclonal rabbit anti-human CD3; 1:100 dilution) anti-CD68 (clone KP-1, Ventana; predilute), anti-IgG (NCL-L-IgG, Leica Biosystems, Buffalo Grove, IL, USA; 1:500 dilution), and anti-IgG4 (catalog #A-10651; ThermoFisher Scientific, Waltham, MA, USA; 1:2,000 dilution). The number of positive cells was manually counted in 5 HPFs in hotspot and averaged. All samples were reviewed and measured by two pathologists (IS and AM) blinded to the recurrence/non-recurrence status of the patient.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA). The *p* values were calculated using the student's *t*-test and chi-square test. Results were reported in mean \pm SD. Statistical significance was considered if $P \leq 0.05$ and *P* values > 0.05 were reported as not significant (NS).

Results

Clinicopathologic findings

We identified 36 consecutive male patients who underwent reconstructive surgery and with a segment of urethral stricture excised and available for histologic studies. The surgical procedure performed was open urethroplasty with end-to-end anastomosis. Follow-up information determined that 26 (72%) patients were non-recurrent and 10 (28%) were recurrent. The average follow-up time was 68.2 months for the recurrent group (range, 28–184 months) and 53.0 months for the non-recurrent group (range, 25–134 months). The median time to recurrence was 15 months (range, 2–79 months), but 8/10 (80%) recurred within the first year after the urethroplasty, with a median time to recurrence of 4 months.

Age, race, etiology, stricture location, and the stricture size were similar in recurrent and non-recurrent groups (Table 1).

The average IPSS, which measures lower urinary tract symptoms, was 17.4 in the non-recurrent group and 22.14 in the recurrent group ($P=0.09$). The average SHIM score, which measures erectile function, was 14.4 for non-recurrent patients and 11.6 for recurrent patients ($P>0.05$).

Seventeen patients (65.5%) in the non-recurrent group and 9 (90%) in the recurrent group had at least one direct vision internal urethrotomy (DVIU) or dilatation procedure

prior to the urethroplasty ($P>0.05$). Three patients (11.5%) of the non-recurrent patients and 2 (20%) of the recurrent patients have had a previous urethroplasty ($P>0.05$) in a different location, and therefore, the current resection was not considered a recurrence. None of the patients had a pre-operative Foley catheter in either recurrent or non-recurrent group. One patient in each group was on intermittent catheterization prior to the resection and end-to-end anastomosis.

The average baseline voided volume was 309 mL in the non-recurrent group and 367 mL in the recurrent group ($P>0.05$). The post urethroplasty voided volume was 417 mL in the non-recurrent group and 457 mL in the recurrent group ($P>0.05$). The presurgical uroflow was 9.95 mL/s in the non-recurrent group and 11.66 mL/s in the recurrent group ($P>0.05$). The post urethroplasty uroflow was 28.89 mL/s in the non-recurrent group and 11.67 mL/s in the recurrent group ($P=0.001$).

Histopathology

Cases with non-recurrent stricture showed paucicellular fibrosis in 14/26 (53.8%, Figure 1) and cellular fibrosis in 12/26 (46.2%, Figure 2). In the cases with cellular fibrosis the average number of stromal cells was 42.8 ± 3.0 per HPF. Twelve patients (50%) with the non-recurrent disease had associated inflammation in the area of fibrosis, including lymphocyte-rich infiltrate in 11/26 (42.3%), and plasma cell-rich infiltrate in 1/26 (3.8%). All patients with recurrent urethral strictures showed paucicellular fibrotic plaques (10/10; 100%), defined as dense fibrotic tissue, characterized by the packs of collagen fibers, strongly positive for Trichrome-blue stain. The average number of stromal cells was 12 ± 1.8 per HPF in this group. The fibrous plaque in the recurrent disease was associated with inflammation in 3/10 (30%) patients, including lymphocyte rich infiltrate in 2/10 (20%) and plasma cell rich in 1/10 (10%). The inflammation showed a mixed infiltrate consistent with a reactive process composed of a mixed population of CD3(+) T-lymphocytes, CD20(+) B-lymphocytes, and CD68(+) histiocytes. The number of IgG(+) plasma cells varied greatly between cases; however, all cases showed a normal IgG4:IgG ratio ($<10\%$). There was no difference between the groups in the thickness of fibrotic area measured in slides stained with trichrome blue (0.92 ± 1.2 and 0.97 ± 1.4 mm, in recurrent and non-recurrent groups, respectively). Table 2 summarizes the histopathologic findings. The log-rank test for time to

Table 1 Clinicopathologic features of patients

Parameters	Non-recurrent	Recurrent	P value
Age, years	44 (range, 25–81)	44 (range, 32–55)	NS
Total number	26 (72%)	10 (28%)	NA
Race			
White	17 (65%)	6 (60%)	NS
Black	6 (23%)	4 (40%)	NS
Other	3 (12%)	0	NS
Etiology of disease			
Post-procedural	3 (12%)	2 (20%)	NS
Trauma	8 (30%)	2 (20%)	NS
Infectious	1 (4%)	0	NS
Congenital	1 (4%)	1 (10%)	NS
Unknown/idiopathic	13 (50%)	5 (50%)	NS
Location of stricture			
Bulbar	21 (81%)	10 (100%)	NS
Membranous	2 (8%)	0	NS
Penile	3 (11%)	0	NS
Size of stricture measured in preoperative urethrography (cm)	1.65 (range, 0.5–2.0)	1.5 (range, 1.0–2.0)	NS
Length of resected segment measured as part of the pathology report (cm)	2.78 (range, 1.3–4.8)	2.59 (range, 1.0–5.0)	NS
Comorbidities			
Diabetes	0	1 (10%)	NS
Obesity	2 (8%)	1 (10%)	NS
Hypertension	1 (4%)	2 (20%)	NS
Coronary artery disease	1 (4%)	0	NS
Erectile dysfunction	3 (11%)	0	NS
Smoking (current and past)	2 (8%)	2 (20%)	NS
Functional assessments			
IPSS (average)	17.40	22.14	0.09
Pre-surgical uroflow (mL/s)	9.95	11.66	NS
Post-surgical uroflow (mL/s)	28.89	11.67	0.001

NS, not significant, P values >0.05; NA, not applicable/not available; IPSS, international symposium of prostate score.

recurrence shows a significantly shorter time to recurrence in patients with paucicellular fibrosis compared to patients with loose fibrosis ($P=0.036$) and no difference between patients with and without inflammation ($P=0.47$, *Figure 3*).

Discussion

Urethral stricture disease requiring open urethroplasty has a negative impact on the quality of life of patients and is an important economic burden for the health care systems.

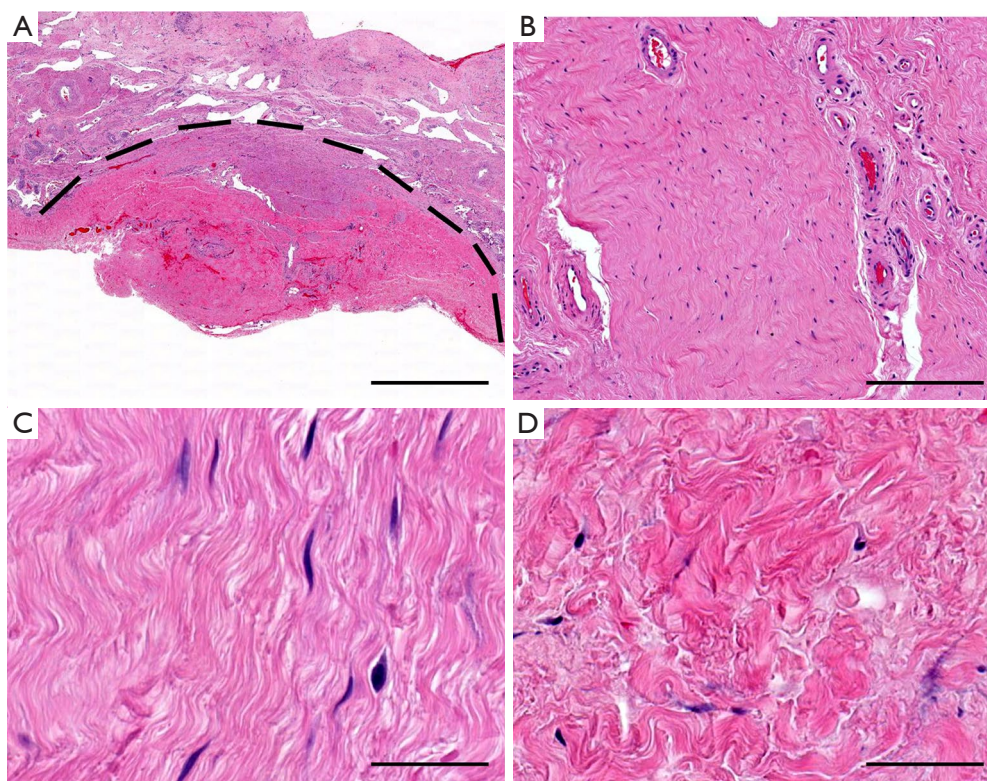


Figure 1 Histologic findings in urethral stricture with dense fibrosis. (A) Whole slide cross section of area of stricture. The area under the dotted line is the scarred tissue. (Hematoxylin-eosin; scale bar 2 mm). (B) Higher power of (A) in the area of fibrosis shows scattered stromal nuclei. (Hematoxylin-eosin stain; scale bar 200 μ m). (C,D) High power view of area of fibrosis with scattered stromal nuclei. Note the nuclei are elongated and surrounded by multiple layers of dense collagen deposition. (Hematoxylin-eosin stain; scale bar 100 μ m lower left and 30 μ m lower right).

Patients with this disease suffer symptoms of LUTS, including detrusor hypertrophy, diverticular bladder disease, urinary infections, urinary stones, and renal failure (7,13,14). Reconstructive surgery is the alternative for patients who fail DVIU or with obstructions larger than 1 cm. Open urethroplasty has a high success rate estimated to be around or higher than 75%. However, many patients still present with obstructive symptoms requiring continuous follow-up with uroflowmetry, dilatations, urethrotomy, or even repeat urethroplasty (15,16). The care of these patients is estimated at several hundred million U.S. dollars per year (13,17). Therefore, determining which patients are at increased risk of recurrence has been the subject of multiple studies. However, a significant problem comparing results of different studies, is that there are no well-established guidelines outlining the surveillance protocols for patients who have undergone urethral reconstruction surgery (18). Additionally, it is difficult to compare outcomes of studies

with a mixed population of patients, performed at different institutions, and with strictures of different urethral portions (17). Our study is a single institution study including patients operated with only one technique (end primary anastomosis) and almost exclusively bulbar urethral cases, limiting some of the variables with potential impact in outcomes and allows for a better comparison between recurrent and non-recurrent disease.

In this study, we investigated specific histopathologic features of the fibrous plaque removed during urethroplasty in patients undergoing end-to-end anastomosis. The features studied here are routine morphologic assessments, including the thickness of the fibrous area, the cellularity of the stroma, and the composition of the inflammatory response in cases with marked inflammation. Cases with non-recurrent stricture showed both hypocellular and cellular fibrosis. In contrast, all patients with recurrent urethral strictures showed paucicellular fibrotic plaques,

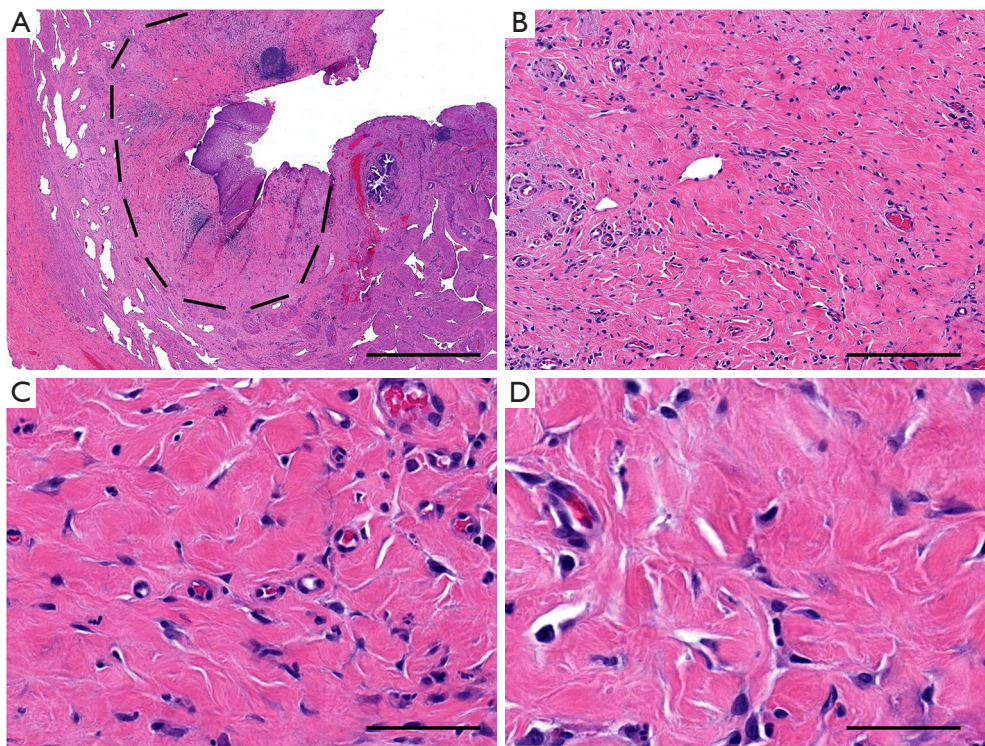


Figure 2 Histologic findings in urethral stricture with loose fibrosis. (A) Whole slide cross section of area of stricture. The area within the dotted line is the scarred tissue. The urothelium shows squamous metaplasia in the area overlying the stricture. (Hematoxylin-eosin; scale bar 2 mm). (B) Higher power of (A) in the area of fibrosis shows scattered stromal nuclei (Hematoxylin-eosin stain; scale bar 200 μ m). (C) Higher power of (A) in the area of fibrosis shows frequent stromal nuclei. Note the stromal nuclei are more rounded than the nuclei of the fibrosis of “dense fibrous plaques” shown in *Figure 1*. (Hematoxylin-eosin stain; scale bar 100 μ m). (D) High power of (A) showing area of fibrosis with frequent nuclei. In areas, the stromal nuclei appear to come in contact with one-another, a feature not seen in dense fibrous plaques. (Hematoxylin-eosin stain; scale bar 200 μ m).

Table 2 Fibrosis and inflammatory infiltrate analysis.

Parameter	Recurrent (n)	Non-recurrent (n)	P value
Paucicellular fibrotic plaque	10/10 (100%)	14/26 (53.8%)	0.01
Thickness of fibrosis (mm)	0.92 \pm 1.20	0.97 \pm 1.40	NS
Inflammatory infiltrate	2/10 (20%)	12/24 (50%)	NS
CD3	60.00 \pm 16.82	45.26 \pm 21.60	NS
CD20	49.2 \pm 38.0	46.5 \pm 68.8	NS
CD68	14.7 \pm 8.8	13.4 \pm 5.6	NS
IgG4/IgG	0.17 \pm 0.06	0.36 \pm 0.07	NS

NS, not significant; P values >0.05; IgG4, immunoglobulin G4; IgG, immunoglobulin G.

as indicated by the low number of stromal cells in the area of the stricture. We did not observe a difference in the thickness or extent of the fibrotic area between

groups suggesting that these are not as predictive of recurrence as cellularity is. It is possible that paucicellular plaques further affect the flexibility of the urethra and are,

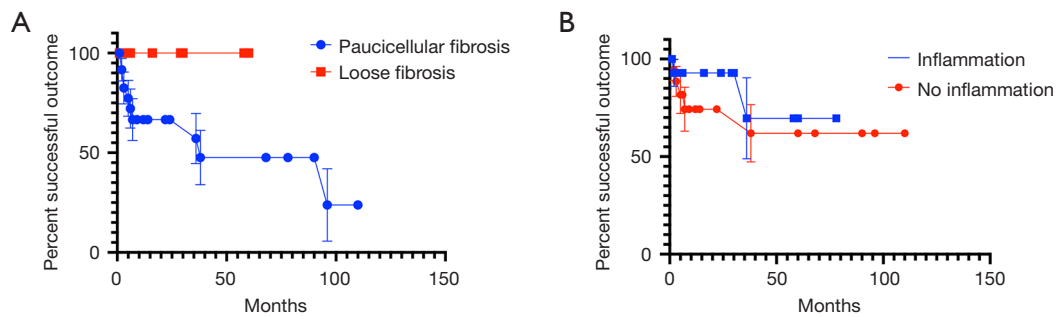


Figure 3 Kaplan-Meier analysis of time to recurrence. (A) Recurrence is only seen in patients with dense fibrous plaques ($P=0.04$). (B) There was no difference in time to recurrence in patients with and without inflammation.

therefore, associated with more symptoms of obstruction. Additionally, the cellularity of the fibrous plaque decreases as more collagen is deposited in the extracellular matrix. Consequently, it is likely indicative of the type of scar tissue that a given patient is predisposed to form.

We established a cut-off for cellularity of the fibrous area at <40 stroma nuclei/HPF. This limit was determined to achieve the highest possible specificity for paucicellular fibrosis as a predictor of recurrence. This could potentially spare patients without paucicellular fibrosis from frequent follow-up visits, should these findings be validated by further studies with more patients. All patients with recurrent strictures showed dense paucicellular fibrotic plaques, while this was seen in 53.8% non-recurrent cases.

We did not find an association between inflammation and recurrence rate. Similarly, a recently published study with emphasis on the histopathologic findings of anterior urethral strictures did not report the difference in recurrence rates based on inflammation (12). Furthermore, in cases with significant lymphoplasmacytic infiltration, we did not observe a high enough IgG4:IgG ratio to support IgG4-related disease as a potential etiologic factor.

Two studies by Breyer *et al.* identified smoking, obesity, diabetes mellitus, prior DVIU, prior urethroplasty, and stricture length >4 cm as risk factors associated with recurrence (19,20). A study of patients with bulbar urethroplasty also found a correlation between body mass index (BMI) higher than 35 and recurrence (21). Another study by Yalcinkaya *et al.* did not find an association between recurrence and etiologic factors or age but identified a direct correlation between the size of stricture and worse overall outcome (22). Among the clinical and epidemiologic data collected, we did not observe any association with recurrence. However, we acknowledge that our study

is underpowered to identify significant epidemiologic differences between groups.

Patients with recurrence disease were, on average, of the same age as patients with the non-recurrent disease. Several studies have previously reported that age negatively impacts outcomes of patients with urethral stricture disease undergoing urethroplasty. A multi-institutional study by Levy *et al.* compared the clinical characteristics of patients 60 years old or younger and older than 60 years old. The investigators identified that patients older than 60 years of age have significantly more comorbidities, including coronary artery disease, hypertension, hyperlipidemia, and cancer, than younger patients but did not find any difference in 3 months and 1-year functional outcomes between groups (23). However, a follow-up of only one year is insufficient to detect later symptomatic recurrence. In our study, we only had four patients who were older than 60 years old, including 1 with recurrent disease and 3 with non-recurrent stricture, which is insufficient to arrive at any conclusion as how age could impact the outcome. While there are multiple reports suggesting older individuals have a worse outcome after urethroplasty, these are thought to be related to a higher rate of comorbidities and worse blood supply. The current American Urologic Association (AUA) guidelines emphasize that an individual with recurrent urethral stricture is unlikely to result in a durable response if treated with minimally invasive techniques, including dilatation or DVIU. The guidelines do not support the use of age as a criterium to decide eligibility for urethroplasty, and therefore, the decision is left to the surgeon on a case-by-case approach.

Notably, the recurrent group did not show an improvement of the postoperative uroflow compared to the pre-surgical measure. This is markedly different to the non-recurrence

group that did experience significant increase in the uroflow post-surgically. This raises the possibility that the stricture was not completely removed during the excision. A follow-up study analyzing only patients with significant improvement in the uroflow could help to better determine the importance of histologic evaluation in predicting recurrence.

There are several notable limitations of this study. This was an exploratory, hypothesis generating study, that needs to be confirmed with larger number of patients and prospectively collected. A prospective collection would potentially improve the follow-up time. Almost half of the patients from the non-recurrent group also had paucicellular fibrotic plaque, and they may potentially have recurred if the follow-up was longer. Additionally, this study does not include histopathology of the normal urethra adjacent to stricture site and/or information on the resection margins. It is unclear whether fibrosis and/or inflammation, or their absence, have an impact on the postsurgical outcome. Our study showed a significant difference between two groups, since all patients with recurrent strictures and only 53.8% non-recurrent cases showed dense paucicellular fibrotic plaques. However, it is not clear whether the same results would be achieved in a larger cohort. Moreover, the occurrence of dense paucicellular fibrotic plaques should be studied in all types of urethroplasty. Therefore, a prospective study with a larger number of patients is necessary to improve methodological approach and test the hypothesis.

Conclusions

Our study suggests that the reporting of the cellularity of the urethral fibrosis and paucicellular fibrous plaques in the specimen of the urethral stricture could represent a potential predictor of symptomatic recurrence in patients undergoing reconstructive urethroplasty. Timely reporting of this easy-to-obtain finding can help postoperative management and follow-up. However, further research is necessary to validate this finding.

Acknowledgments

Funding: This study was supported by the Department of Pathology at Johns Hopkins Hospital.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://dx.doi.org/10.21037/tau-21-477>

[org/10.21037/tau-21-477](https://dx.doi.org/10.21037/tau-21-477)

Data Sharing Statement: Available at <https://dx.doi.org/10.21037/tau-21-477>

Peer Review File: Available at <https://dx.doi.org/10.21037/tau-21-477>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/tau-21-477>). ALB reports consulting fees from Astellas, from Comphya, from Futura Medical, from Lilly, LLC, from Myriad Genetics, from Novartis Pharmaceuticals, from Reflexonic, LLC, and from Urology Times Editorial Council, outside the submitted work, and leadership position in UroMissionsWorks. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Johns Hopkins University (NO. IRB00254688) and individual consent for this retrospective analysis was waived.

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Cite this article as: Samarska IV, Dani H, Bivalacqua TJ, Burnett AL, Matoso A. Histopathologic and clinical comparison of recurrent and non-recurrent urethral stricture disease treated by reconstructive surgery. *Transl Androl Urol* 2021;10(10):3714-3722. doi: 10.21037/tau-21-477