Delayed Reconstruction of Bulbar Urethral Strictures is Associated with Multiple Interventions, Longer Strictures and More Complex Repairs

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Purpose: Prior to urethral reconstruction many patients with stricture undergo a variable period during which endoscopic treatments are performed for recurrent obstructive symptoms. We evaluated the association among urethroplasty delay, endoscopic treatments and subsequent reconstructive outcomes.

Materials and Methods: We reviewed the records of men who underwent primary bulbar urethroplasty from 2007 to 2014. Those with prior urethroplasty, penile and/or membranous strictures and incomplete data were excluded from analysis. Men were stratified by a urethroplasty delay of less than 5, 5 to 10 or greater than 10 years from diagnosis.

Results: A total of 278 primary bulbar urethroplasty cases with complete data were evaluated. Median time between stricture diagnosis and reconstruction was 5 years (IQR 2−10). Patients underwent an average ± SD of 0.9 ± 2.4 endoscopic procedures per year of delay. Relative to less than 5 and 5 to 10 years a delay of greater than 10 years was associated with more endoscopic treatments (median 1 vs 2 vs 5), repeat self-dilations (13% vs 14% vs 34%), strictures longer than 2 cm (40% vs 39% vs 56%) and complex reconstructive techniques (17% vs 17% vs 34%). An increasing number of endoscopic treatments was independently associated with strictures longer than 2 cm (OR 1.06, $p = 0.003$), which had worse 24-month stricture-free survival than shorter strictures (83% vs 96%, $p = 0.0003$). Each consecutive direct vision internal urethrotomy was independently associated with the risk of urethroplasty failure (HR 1.19, $p = 0.02$).

Conclusions: Urethroplasty delay is common and often associated with symptomatic events managed by repeat urethral manipulations. Endoscopic treatments appear to lengthen strictures and increase the complexity of repair.

Key Words: urethral stricture; endoscopy; complications; failure to rescue, health care; reconstructive surgical procedures

Abbreviations and Acronyms

DVIU = direct visual internal urethrotomy

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In recently published guidelines endoscopic urethral manipulation has remained an acceptable primary treatment option for short (2 cm or less) bulbar strictures.[1,2] The practice patterns of most board certified urologists reflect these recommendations since 93% and 86% perform dilation and/or DVIU to treat anterior urethral strictures.[3,4] Despite the popularity of endoscopic stricture management these treatments have consistently been associated with an alarmingly high rate of failure.[5] A contemporary review of the literature highlighted the approximately 40%

variability in the primary success rate.[1] Further repetitive endoscopic treatments ultimately fail in most instances.[6,7]

In our practice we have observed that many men present for urethroplasty after a prolonged delay following the initial stricture diagnosis. These lengthy intervals are often punctuated by symptomatic events requiring repetitive and ultimately futile urethral manipulations in the form of endoscopic treatment or self-dilation. Evidence now suggests that these endoscopic measures may lengthen urethral strictures, resulting in the need for more complex repairs.[8] This is of particular importance given that lengthier strictures greater than 2 cm, especially those located in the distal bulb, may be more prone to urethroplasty failure.[9]

To our knowledge the impact of reconstructive delay on urethroplasty outcomes remains unknown but it may be quite deleterious. Histological evidence suggests that in addition to repetitive urethral trauma, chronic high pressure voiding may contribute to the progression of squamous metaplasia, spongiofibrosis and ultimately stricture complexity.[10,11]

We hypothesized that an increasing urethroplasty delay is associated with a greater number of urethral manipulations, resulting in longer strictures, more challenging repairs and worse reconstructive outcomes. The objective of this study was to characterize urethral stricture outcomes in a select group of men who underwent primary bulbar urethroplasty, stratified by the duration of the reconstructive delay.

PATIENTS AND METHODS

After receiving institutional review board approval we evaluated our prospectively maintained, single surgeon urethral stricture database to identify patients who underwent open urethral reconstruction from 2007 to 2014 at 1 of 3 academic hospitals, including 662 at University of Texas Southwestern Medical Center. To identify patients considered to be ideal candidates for endoscopic treatment this analysis was limited to 278 men with primary (first time) bulbar urethral stricture. Excluded from study were 346 patients with a history of previous urethroplasty, isolated penile or radiation induced membranous urethral strictures, pelvic fracture urethral disruption or posterior urethral stenosis. Also excluded were 38 primary bulbar cases with incomplete historical data.

Men were stratified by the duration (less than 5, 5 to 10 or greater than 10 years) between the initial urethral stricture diagnosis and formal urethroplasty. Reconstructive delay was calculated as the time between the initial stricture diagnosis and primary open urethral reconstruction. The date of stricture diagnosis was defined as the date of the initial diagnostic procedure, that is retrograde urethrogram, voiding cystourethrogram or cystoscopy. If not available, the date of the first transurethral treatment served as an alternative. When the date of diagnosis predated available records, the patient history was used to obtain the date of the original diagnosis.

Urethral stricture anatomical location and complexity were characterized by preoperative imaging. Bulbar stricture length was determined at the time of urethroplasty. In most patients a stricture length cutoff point of 2 cm, particularly in the mid to distal bulbar urethra,[9] was used to determine the reconstructive technique. This has generally been the point at which anastomotic urethroplasty vs more complex reconstruction (substitution techniques) is indicated.[12–14] Transurethral endoscopic treatments included DVIU or any endoscopic assisted urethral dilation with sounds or a balloon. Intermittent self-dilation was defined as patient reported use of disposable sounds or catheters before surgical reconstruction to maintain urethral lumen patency.

After urethroplasty patients were followed via an office evaluation at 3 months by AUA SS (American Urological Association symptom score) and then as determined by the complexity of the condition and urinary related concerns. Details regarding urethroplasty success were obtained by reviewing office examinations, operative reports, and written and/or telephone correspondence. Urethroplasty failure was defined as the need for recurrent urethral interventions such as endoscopic treatment, subsequent catheterization or repeat urethroplasty.

In the primary analysis we assessed urethral stricture characteristics and treatment outcomes stratified by the reconstructive delay. In the secondary analysis we evaluated outcomes stratified by a urethral stricture cutoff point of 2 cm. Continuous variables were evaluated by the nonparametric Wilcoxon rank sum or Kruskal-Wallis test and categorical variables were assessed by the Fisher exact test. Stricture-free survival following urethroplasty was estimated by the Kaplan-Meier method. Forward stepwise logistic regression analysis was used to identify factors associated with bulbar urethral stricture length greater than 2 cm at the time of reconstruction. Cox proportional hazard regression models were applied to identify variables associated with urethroplasty failure with $p < 0.05$ considered statistically significant. Statistical analyses were performed with SAS®.

RESULTS

A total of 1,287 urethral reconstructive procedures were performed by the senior surgeon from 2007 to 2014. For this analysis 278 of 316 men treated with primary bulbar urethroplasty at our tertiary academic referral center (1 of 3 institutions) who had complete data available were identified for analysis. Mean ± SD time between stricture diagnosis and formal reconstruction was 9.1 ± 11.6 years (median 5, IQR 2–10), during which patients underwent a mean of 0.9 ± 2.4 endoscopic procedures per year of delay (median 0.3, IQR 0–0.9). Median age at urethroplasty was 49 years (IQR 37–62). The most common urethral stricture etiologies were idiopathic in 148 cases (54%), trauma in 65 (24%) and iatrogenic in 45 (16%). When stratified by duration of reconstructive delay, there was no difference in clinical comorbidities between groups.

Reconstructive Delay

A total of 176 (49%), 71 (26%) and 71 men (26%) underwent urethroplasty less than 5, 5 to 10 and more than 10 years following diagnosis, respectively (table 1). Compared to those with a delay to reconstruction of less than 5 and 5 to 10 years, men with a greater than 10-year delay had longer urethral strictures (2 vs 2 vs 2.5 cm, p = 0.0009), which were more often longer than 2 cm (40% vs 39% vs 56%, p = 0.04) and frequently required complex substitution reconstructive techniques (17% vs 17% vs 34%, p = 0.02). Compared to those with a delay to reconstruction of less than 5 and 5 to 10 years, men with a longer than 10-year delay were also more likely to perform intermittent self-dilation (13% vs 14% vs 34%, p = 0.001) and undergo transurethral endoscopic manipulation (62% vs 73% vs 94%, p <0.0001), including a greater number of total endoscopic treatments (1 vs 2 vs 5), dilations and DVIUs (all p <0.0001).

Urethral Stricture Length

Urethral strictures longer than 2 cm at urethroplasty were associated with a greater reconstructive delay (median 5.3 vs 4.6 years, p = 0.02). These men underwent more endoscopic treatments (2 vs 1, p = 0.04), were more likely to perform intermittent self-dilation (25% vs 14%, p = 0.03) and more often required substitution urethroplasty (47% vs 1%, p <0.0001) than men with shorter strictures (supplementary table, http://jurology.com/). On univariable analysis each single year of reconstructive delay was associated with a 3% increased risk of a bulbar stricture length of greater than 2 cm (OR 1.03, 95% CI 1.01–1.05, p = 0.004). On multivariable analysis repeat endoscopic treatments remained associated with longer strictures. That is, each endoscopic procedure was associated with an incremental 6% increased risk of stricture length greater than 2 cm (OR 1.06, 95% CI 1.02–1.13, p = 0.003).

Bulbar Urethroplasty Failure Predictors

During a median followup of 64 months (IQR 40–84) 34 of the 278 men (12%) experienced urethroplasty failure. When stratified by the reconstructive delay of less than 5, 5 to 10 and greater than 10 years, there was a nonsignificant increase in treatment failure in men with a greater than 10-year delay (10% and 13%, respectively, vs 17%, p = 0.3). Regardless of the delay duration 24-month stricture-free survival was significantly worse among those with strictures longer than 2 cm (83% vs 96%, p = 0.0003) and in patients who underwent 2 or more vs 1 and 0 DVIUs (83% vs 95% and 95%, respectively, p = 0.009, figs. 1 and 2). Two or more urethral dilations alone did not impact stricture-free survival (p = 0.3). On multivariable analysis each DVIU procedure was associated with an incremental 19% increased risk of urethroplasty failure (HR 1.19, 95% CI 1.03–1.34, p = 0.02). Also, increasing stricture length trended towards clinical significance (HR 1.26, 95% CI 0.96–1.63, p = 0.09, table 2).

Table 1. *Clinical characteristics by delay between urethral stricture diagnosis and urethroplasty*

	Bulbar Urethroplasty Delay (yrs)						
	Less Than 5		5–10		Greater Than 10		p Value
No. pts	136		71		71		—
Prior endoscopic treatment:							
No. pts (%)	84	(62)	52	(73)	67	(94)	<0.0001
Median No. treatments (IQR)	1	(0–2)	2	(0–4)	5	(2–12)	<0.0001
Median No. dilations (IQR)	0	(0–1)	0	(0–2)	3	(0–9)	<0.0001
Median No. DVIUs (IQR)	0	(0–1)	0.5	(0–1)	1	(0–3)	<0.0001
No. self-dilation (%)	18	(13)	10	(14)	24	(34)	0.001
Stricture length (cm):							
No. greater than 2 (%)	53	(40)	28	(39)	40	(56)	0.04
Median (IQR)	2	(1.5–3)	2	(1.5–3)	2.5	(1.5–4)	0.0009
No. stricture type (%):							
Synchronous	8	(6)	1	(1)	5	(7)	0.2
Obliterative	22	(21)	8	(17)	10	(20)	0.9
No. technique (%):							0.02
Excision + primary anastomosis	112	(83)	59	(83)	47	(66)	
Substitution	23	(17)	12	(17)	24	(34)	

DISCUSSION

To our knowledge this is the first study to critically evaluate the natural history of delayed bulbar urethral reconstruction. Our data suggest that a symptomatic, prolonged reconstructive delay tends to be associated with symptomatic recurrences requiring repeat urethral instrumentation. These data suggest that the concept of endoscopic treatments being minimally invasive should be abandoned because this cumulative injury appears to lengthen strictures, increase the complexity of repair and ultimately impair urethroplasty success. Reconstructive delay with its concomitant repeated temporizing interventions often tends to change a simple, treatable condition into a chronic symptomatic disease with less certain outcomes.

The human urethra is delicate and highly susceptible to injury. A symptomatic urethral stricture will develop in 1 of 4 men who perform chronic clean intermittent catheterization.[15] This is in part due to the thin (60 to 80 μm) and fragile nature of the

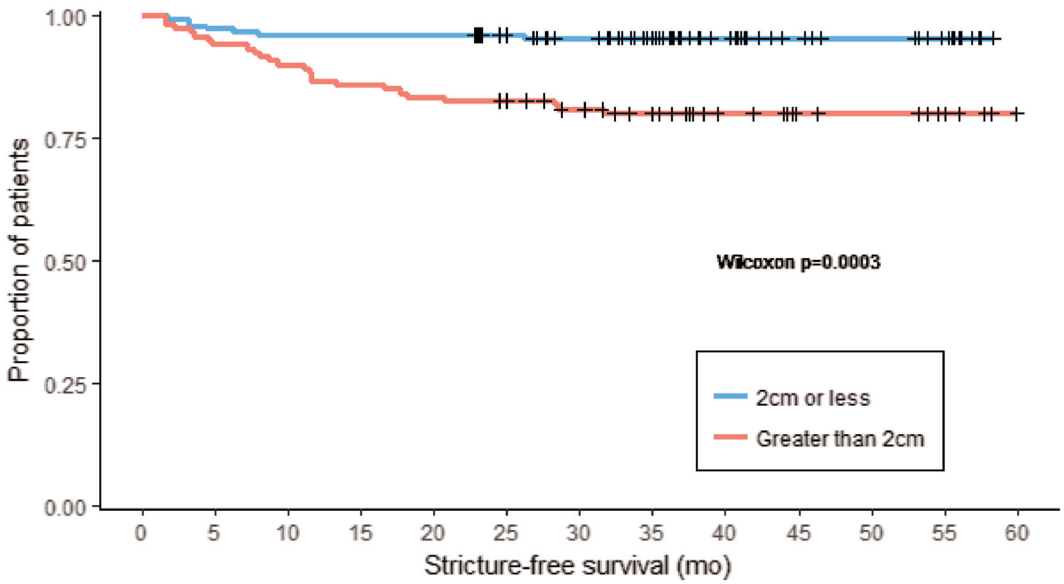

Figure 1. Bulbar urethroplasty stricture-free survival stratified by stricture length

bulbar urethral mucosa with its underlying, highly vascular, fibroblast rich extracellular matrix.[11] By contrast, this is largely different from other epithelial barriers such as buccal mucosa, which is characterized by a thick and robust (300 μm) non-keratinized squamous epithelium.[16]

With disruption of the urethral mucosal barrier urinary extravasation promotes abnormal collagen deposition, ultimately resulting in spongiofibrosis and stricture formation.[10,11] This can develop as a consequence of noxious stimuli (bacterial, chemical or physical) inducing squamous metaplasia, a

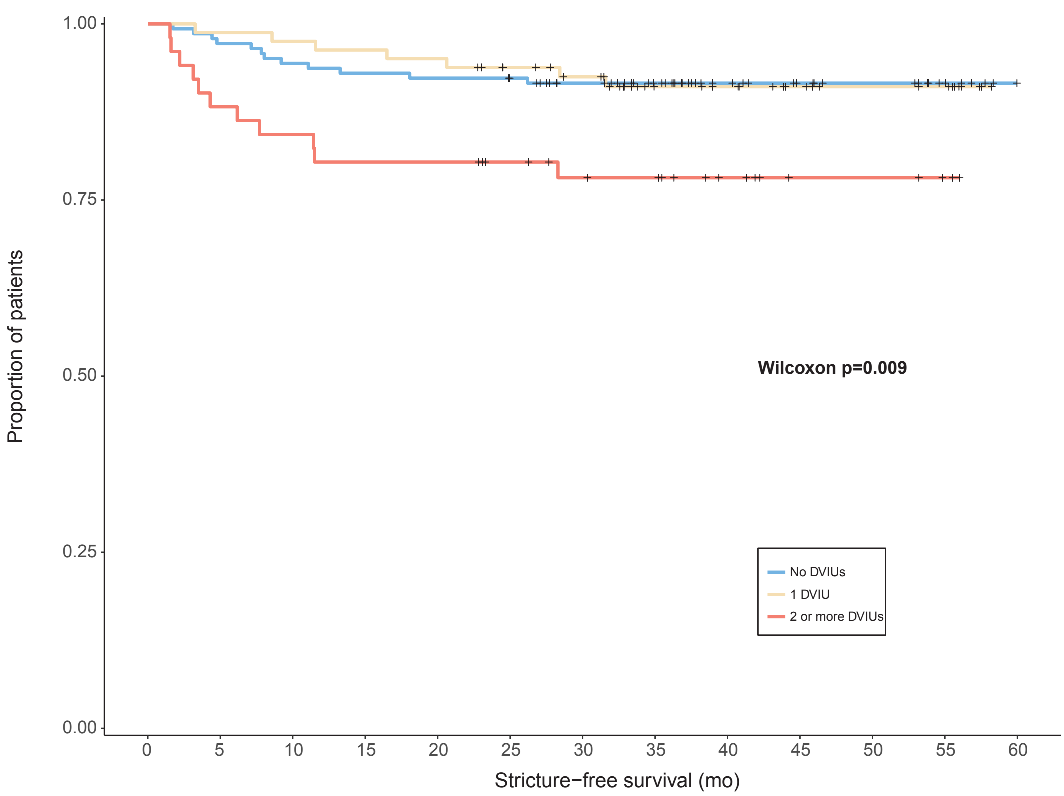

Figure 2. Number of DVIUs and bulbar urethroplasty stricture-free survival

Table 2. *Multivariable analysis of features associated with bulbar urethroplasty failure*

	Univariate		Multivariable	
	OR (95% CI)	p Value	OR (95% CI)	P Value
Age/yr	1.01 (0.99–1.04)	0.2	—	—
Body mass index/kg/m^2	1.03 (0.98–1.08)	0.2	—	—
Coronary artery disease	1.89 (0.79–3.99)	0.1	—	—
Diabetes	1.13 (0.78–2.55)	0.7	—	—
Smoking	0.79 (0.35–1.67)	0.5	—	—
Prior endoscopic treatments:				
Total No./treatment	1.01 (0.99–1.02)	0.2	—	—
No. dilations/dilation	1.01 (0.99–1.02)	0.3	—	—
No. DVIUs/DVIU	1.18 (1.06–1.32)	0.002	1.19 (1.03–1.34)	0.02
Self-dilation (yes/no)	1.34 (0.57–2.82)	0.5	—	—
Stricture type:			—	—
Obliterative	1.75 (0.72–3.83)	0.2		
Synchronous	2.82 (0.84–7.12)	0.09		
Urethral stricture length/cm	1.39 (1.20–1.60)	<0.0001	1.26 (0.96–1.63)	0.09
Substitution technique (referent excision + primary anastomosis)	3.91 (1.95–7.77)	0.0002	1.80 (0.52–5.62)	0.3
Urethroplasty delay:				
Greater than 10 vs less than 5 yrs	1.79 (0.80–3.94)	0.2	—	—
Greater than 10 vs 5–10 yrs	1.34 (0.59–3.40)	0.5	—	—
Continuous/yr	1.02 (0.99–1.04)	0.2	0.99 (0.96–1.02)	0.8

friable precursor lesion prone to fissure formation.[17] This pathological process is amplified in traumatic urethral mucosal injury, which is associated with greater fibrosis and loss of vascular density than atraumatic strictures.[11]

Given the pathogenesis of stricture formation, it is counterintuitive that endoscopic urethral manipulations have a curative role in stricture treatment. These interventions may in fact be detrimental. In an earlier analysis of 101 men who underwent bulbar reconstruction those with 2 or more prior transurethral manipulations were more likely to have longer strictures and be at fivefold greater risk for complex reconstruction.[8] Endoscopic treatments are based on the premise that re-epithelialization will develop before wound contracture. Accordingly DVIU was founded on a hypospadias model in which incising a healthy, well vascularized urethral plate resulted in normal re-epithelialization.[18] The faulty assumption is that the stricture and hypospadias models are identical. Actually DVIU of a poorly vascularized, fibrotic, bulbar urethral stricture produces greater fibrosis.[19] This process correlates with the dense dorsal scar frequently noted at the site of prior DVIU during bulbar mobilization.

Dilating bulbar strictures has also proved to have limited efficacy and be no better than DVIU. This is evidenced by the multiple publications[1] demonstrating low success with these methods since the original randomized, controlled trial by Steenkamp et al.[5] Notably the results of these studies have been heavily influenced by variability in stricture length, location and followup duration.[1] In a more contemporary, retrospective series of 76 patients without prior urethroplasty the success rate of first time DVIU was only 8% with a median time to failure of 7 months.[20] Concordant with our analysis these findings further support that endoscopic treatments only delay definitive reconstruction.

Urethral rest is a critical component of urethroplasty success as it allows for a period of stricture maturation and reliable identification.[21] The stricture predictably stabilizes 6 to 8 weeks after the cessation of urethral instrumentation, consistent with normal wound healing and contraction following injury. However, men are often placed on intermittent self-dilation to maintain patency[22] as a salvage method to temporize obstructive urinary symptoms after dilation or DVIU. Originally designed to prevent upper tract deterioration in those with neurogenic bladder, there is poor evidence supporting intermittent catheterization as a viable maintenance therapy for urethral stricture disease.[23] We have observed that self-dilation is often associated with additional urethral trauma (fig. 3). Evidence suggests that it is associated with poor quality of life[24] and masks the true extent of urethral stricture disease.[21] A reconstructive delay of greater than 10 years was associated with a threefold greater incidence of self-dilation in this series, suggesting that intervals between endoscopic

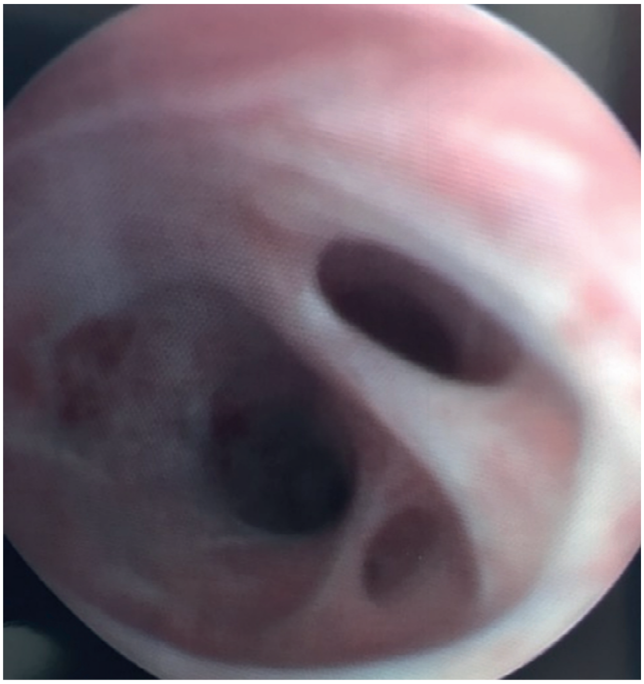

Figure 3. Endoscopic view of bulbar urethral stricture after chronic self-dilation. Note multiple traumatic false passages associated with repetitive self-dilation.

treatments are often symptomatic and these measures only prolong and complicate open surgical therapy.

We often observe extensive squamous metaplasia proximal to urethral strictures in men with long-standing disease. We propose that this is due to a high pressure, water hammer voiding effect which may further exacerbate urethral injury. Our analysis suggests that a prolonged reconstructive delay may in fact be associated with longer strictures. However, when controlling for other factors, this series was underpowered to detect an independent association between delay and treatment failure. It appears that this treatment is highly influenced by the extent of repetitive endoscopic therapy for the management of obstructive symptoms more so than the magnitude of the delay.

Each endoscopic treatment was associated with an incremental 6% increase in the risk of a stricture length greater than 2 cm. This is clinically relevant as strictures 2 cm or less are often amenable to anastomotic urethroplasty, which has repeatedly been associated with an excellent long-term success rate of 91% to 99%.[12–14] Others have routinely used buccal mucosa for bulbar reconstruction with a satisfactory 86% success rate at intermediate followup.[25] However, our preference has been to reserve substitution techniques for longer strictures when a tension-free anastomosis may not be feasible, especially in the mid and distal bulb.[9] Our findings remain consistent with previous studies suggesting that increasing bulbar stricture length may adversely impact reconstructive success.

Each DVIU procedure was associated with a 19% incremental increased risk of treatment failure. To date there remains a paucity of research exploring the adverse impact of endoscopic therapies on urethroplasty outcome. When controlling for length, location, type of repair and prior urethroplasty in a heterogeneous group of men, Breyer et al found that a history of prior DVIU was independently associated with a 1.7-fold greater risk of treatment failure.[26] Likewise in a select cohort treated with primary bulbar ventral graft urethroplasty Barbagli et al found that those with more than 4 DVIUs were more likely to experience stricture recurrence.[27] We propose that these endoscopic treatments contribute to progressive fibrosis and vascular compromise, which ultimately impair wound healing and urethroplasty success. Pending further validation, these observations suggest that early open surgical reconstruction is appropriate for recurrent bulbar urethral strictures.

Outside our tertiary reconstructive practice to our knowledge the total proportion of men who undergo endoscopic interventions elsewhere in the community remains unknown. The apparently limited efficacy of these interventions can only be ascertained in men who are ultimately referred for urethroplasty. Undoubtedly in select patients the careful and judicious use of endoscopic therapies is well tolerated and may effectively alleviate obstructive urinary symptoms without the need for open surgical reconstruction. Accordingly in our study the technique and type of endoscopic treatment was not standardized.

Although we were unable to explore the cost implications of repeat stricture treatments, we submit that the unmeasurable costs associated with these repetitive interventions (lost income, travel expenses and additional time) are disruptive and greatly impact quality of life. Finally, while an association appears to exist between increasing endoscopic treatments and the complexity of stricture disease, at this time we lack further quantitative radiographic or pathological evidence to support this observation.

CONCLUSIONS

Urethroplasty delay is often punctuated by symptomatic intervals characterized by repetitive urethral manipulations. With time the cumulative trauma of endoscopic urethral stricture management appears to lengthen strictures and increase the complexity of repair.

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EDITORIAL COMMENT

Endoscopic urethrotomy and self-dilation continue to be the most commonly performed treatments for urethral strictures despite dismal long-term success rates (reference 20 in article). Although urethroplasty is the definitive surgical treatment for urethral strictures, it continues to be underused, performed at less than 10% of all stricture procedures.[1]

This rigorous investigation characterizes the consequences of repetitive endoscopic manipulations in a large cohort presenting with bulbar strictures. An increasing number of endoscopic treatments was associated with an increased risk of urethroplasty failure, presumably due to the development of longer (greater than 2 cm) strictures.

Clearly urethrotomies and dilations come at a price. Despite the perception that they are safe and simple, they are not only cost inefficient and ineffective[2] but they also increase the complexity of future reconstruction, resulting in lower stricture-free rates. Future efforts should be focused on educating patients and general urologists alike on the need for early referral to a tertiary center, reserving repetitive endoscopic treatments only for medically frail patients with significant competing medical risks.

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