EUROPEAN UROLOGY FOCUS 6 (2020) 164–169

available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus

Focus on Internal Urethrotomy as Primary Treatment for Untreated Bulbar Urethral Strictures: Results from a Multivariable Analysis

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Article info

Article history:
Accepted October 23, 2018

Associate Editor:
Richard Lee

Keywords:
Urethral stricture
Direct visual internal urethrotomy
Multivariable analysis

Abstract

Background: The use of internal urethrotomy for treatment of urethral stricture remains a controversial topic in urology.
Objective: To investigate outcomes and predictors of failure for internal urethrotomy as primary treatment for untreated bulbar urethral strictures.
Design, setting, and participants: We performed a retrospective analysis of patients who underwent internal urethrotomy. Patients with bulbar urethral stricture who did not receive any previous treatment were included. Patients with traumatic, penile or posterior urethral strictures, lichen sclerosus, failed hypospadias repair, or stricture length >4 cm were excluded.
Outcome measurements and statistical analysis: The primary outcome was treatment failure. Kaplan-Meyer plots were used to depict treatment failure–free survival. Univariate and multivariable Cox regression analyses were used to test the association between predictors (age, body mass index, diabetes, history of smoking, etiology, stenosis type and length, preoperative maximum flow [pQ_{max}]) and treatment failure.
Results and limitations: Overall, 136 patients were included. The median stricture length was 2 cm. Median follow-up was 55 mo. At 5-yr follow-up the failure-free survival rate was 57%. On univariate analysis, diabetes, nonidiopathic etiology, stricture length of 3–4 cm, and pQ_{max} were significantly associated with treatment failure. These predictors were included in a multivariable analysis, in which pQ_{max} was the only significant predictor of treatment failure.
Conclusions: Failure of internal urethrotomy for untreated bulbar urethral strictures greatly depends on pQ_{max} flow at uroflowmetry. Patients with $pQ_{max\,>}$ 8 ml/s have a high probability of success, while patients with pQ_{max} <5 ml/s have a low probability of success.
Patient summary: The use of internal urethrotomy in patients with an untreated bulbar urethral stricture should only be considered in selected cases.

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https://doi.org/10.1016/j.euf.2018.10.014
2405-4569/

1. Introduction

Open urethroplasty is now regarded as the gold standard for treatment of urethral stricture diseases, as reconstructive urethral surgery has greatly improved in safety, variety, and effectiveness during the last three decades, mainly in expert reference centers where urologists performed a large number of cases annually [1–5]. The use of urethroplasty is also increasing in developing countries such as China [6]. Nevertheless, direct visual internal urethrotomy (DVIU) still represents the most common procedure used by urologists in the USA [7–12]. Compared to DVIU, open urethral surgery requires general anesthesia, more surgical expertise, and an adequate operating room and instruments, and is associated with a longer recovery period [13].

Evaluation of short- or long-term results of DVIU is challenging because patient selection, follow-up criteria, and success versus failure criteria are not homogeneous and it is sometimes difficult to identify a take home message from these reports. However, the failure rate after initial DVIU is reported to be at least 50%, and for the majority of patients this procedure should be considered as a temporizing measure until definitive reconstruction can be planned [14]. Moreover, some authors have reported that DVIU is neither clinically effective nor cost-effective [15]. A large series of 301 patients who underwent DVIU showed that the overall stricture-free rate at 36-mo follow-up was 8.3% [16]. In conclusion, DVIU is not the panacea for stricture management that we were previously led to believe [17]. In 1948, Davis and Lee [18] reported that in approximately 80% of a series of 36 patients who underwent internal urethrotomy, the urinary stream was satisfactory without dilatation for periods of time varying up to 3 yr; they concluded: "We have, however, avoided the use of the word cure". This old sentence skillfully summarizes the topic we present here for discussion. However, such negative conclusions often originate from a nonhomogeneous series, including strictures with remarkable differences in site, etiology, pathology, and previous treatments, or with relative small cohorts with poor follow-up [14,16,19–22]. Moreover, some articles do not report the site, etiology, or pathology for strictures treated with DVIU [23,24]. There is a lack of information for a highly homogeneous subset of patients treated in high-volume centers, which could offer new insights into DVIU.

Here we report our experience with DVIU in a homogeneous series of patients with bulbar urethral stricture who underwent strict follow-up, and present a multivariable analysis of the results to identify significant predictors of treatment failure.

2. Patients and methods

2.1. Patient population and study design

We performed a retrospective descriptive analysis for a cohort of patients who underwent DVIU at the Center for Reconstructive Urethral Surgery in Arezzo, Italy. The study was approved by the institutional review board. Patients were requested to read and sign informed consent explaining the surgical procedure and the complications. Patients were fully informed that the current literature suggests that DVIU should be considered only as a temporizing measure in the majority of patients until definitive reconstruction can be planned. The inclusion criteria were patients who underwent DVIU for untreated bulbar urethral strictures with minimum follow-up of 12 mo. Patients with traumatic, penile, or posterior urethral strictures, lichen sclerosus, failed hypospadias repair, stricture length >4 cm, or incomplete clinical records or follow-up were excluded. The primary outcome of the study was treatment failure, defined as any postoperative instrumentation.

2.2. Preoperative evaluation and definition of variables

Preoperative data included age at surgery, body mass index (BMI), smoking status (no vs yes vs former), diabetes, and cardiovascular diseases. Stricture-related data were stricture etiology (idiopathic, catheter, instrumentation, infection), length, and preoperative maximum flow rate (pQ_{max}). All patients underwent preoperative evaluation using urine culture, uroflowmetry, post-void residual (PVR), retrograde urethrogram (RUG), voiding cystourethrogram (VCUG), and urethral ultrasonography. In patients presenting with urinary tract infection (UTI), surgery was delayed according to urine culture results after adequate antibiotic therapy. DVIU was performed in all patients using a cold-knife cut at the 12 o'clock position. A silicon grooved 16F Foley catheter was left in place for 7 d.

2.3. Follow-up protocol

Follow-up was scheduled every 4 mo in the first year and every 6 mo thereafter and included urine culture, uroflowmetry, and PVR. Patients who were not able to comply with the follow-up protocol were excluded from the study.

2.4. Success versus failure criteria

The clinical outcome was classified as a success if uroflowmetry showed $Q_{max} > 12$ ml/s, PVR <50 cm^3, no UTI in the last 4 mo, and an improvement in symptom score. For patients showing symptoms of a decreased force of stream and $Q_{max} < 12$ ml/s, PVR >50 cm^3, or a UTI in the last 4 mo, we suggested repeat RUG, VCUG, and urethral ultrasonography. The clinical outcome was considered a failure when patients underwent a new surgical procedure for stricture recurrence.

2.5. Statistical analysis

The statistical analyses consisted of three steps. First, the median and interquartile range (IQR) and the frequency and proportion were reported for continuous and categorical variables, respectively. Second, failure-free survival rates were described using Kaplan-Meier curves. Third, a multivariable Cox regression analysis predicting treatment failure was fitted. Predictors consisted of age at surgery, BMI, smoking status, diabetes, stricture etiology (idiopathic vs nonidiopathic), type of stenosis (nonobliterative vs obliterative), stenosis length, and pQ_{max}. All statistical analyses were performed using Stata v.12.0 (StataCorp LP, College Station, TX, USA). All tests were two-sided and significance was set at $p < 0.05$.

3. Results

Overall, 136 patients were included. Descriptive characteristics for the population are reported in Table 1. The stenosis length was 1–2 cm in 60 (45%), 2–3 cm in 55 (40%), and 3–4 cm in 21 patients (15%). Median follow-up was 55 mo (IQR

Table 1 – Descriptive characteristics for 136 consecutive patients treated with endoscopic urethrotomy for anterior urethral stenosis[a].

Parameter	Result
Age (yr)	37 (25–48)
Body mass index (kg/m^2)	24 (23–27)
Smoker	
No	82 (60)
Yes	33 (25)
Former	21 (15)
Diabetes	
No	130 (96)
Yes	6 (4)
Type of stenosis	
Obliterative	53 (39)
Nonobliterative	83 (61)
Etiology	
Idiopathic	110 (81)
Instrumentation	11 (8)
Catheter	14 (10)
Infection	1 (1)
Stenosis length	
1–2 cm	60 (45)
2–3 cm	55 (40)
3–4 cm	21 (15)
Preoperative maximum flow (ml/s)	6.8 (5.0–9.1)
Follow-up (mo)	55 (36–92)

[a] Data are reported as median (interquartile range) for continuous variables and as n (%) for categorical variables.

36–92). At 5-yr follow-up the failure-free survival rate was 57% (95% confidence interval 47–66%). The failure-free survival rate over time for the overall population in shown in a Kaplan Meier plot in Fig. 1.

On univariate analysis, diabetes (hazard ratio [HR] 3.25; $p = 0.024$), nonidiopathic etiology (HR 1.89; $p = 0.043$), stricture length 3–4 cm (HR 2.37; $p = 0.029$), and pQ_{max} (HR 0.73; $p < 0.00001$) were significantly associated with treatment failure (Table 2). These predictors were then included in a multivariable analysis, in which pQ_{max} was the only significant predictor of treatment failure (HR 0.76; $p < 0.00001$).

Patients were stratified into three groups according to pQ_{max} (≤5 vs 5–8 vs ≥8 ml/s). Failure-free survival at 5 yr after surgery was significantly different in the three groups: 31% versus 53% versus 83% ($p < 0.00001$; Fig. 2). Similarly, when patients were stratified according to stricture length (1–2 vs 2–3 vs 3–4 cm), a significant difference in failure-free survival was observed at 5 yr (71% vs 51% vs 39%; $p < 0.00001$; Fig. 3).

3.1. *Treatment of failures*

Out of 136 cases, 51 (38%) were classified as failures. The success rate gradually decreased according to the follow-up length (Fig. 1). The recurrences were homogeneously distributed over time, and the majority occurred in the first (35%) or second (27%) year after urethrotomy. The mean time to recurrence was shorter after a second (15 mo) than after a first urethrotomy (25 mo). A flow chart of the treatment failures and successes is shown in Fig. 4. Out of 51 failures, 19 (37%) were treated with oral mucosa graft urethroplasty, of which 18 (95%) were successful; 32 were treated with urethrotomy, of which 20 (63%) were failures and 12 (38%) were successful. The 20 failures after the second urethrotomy were treated with oral mucosa graft urethroplasty and all were successful.

4. Discussion

Our study of a homogeneous series of patients with long and strict follow-up confirms the American Urological

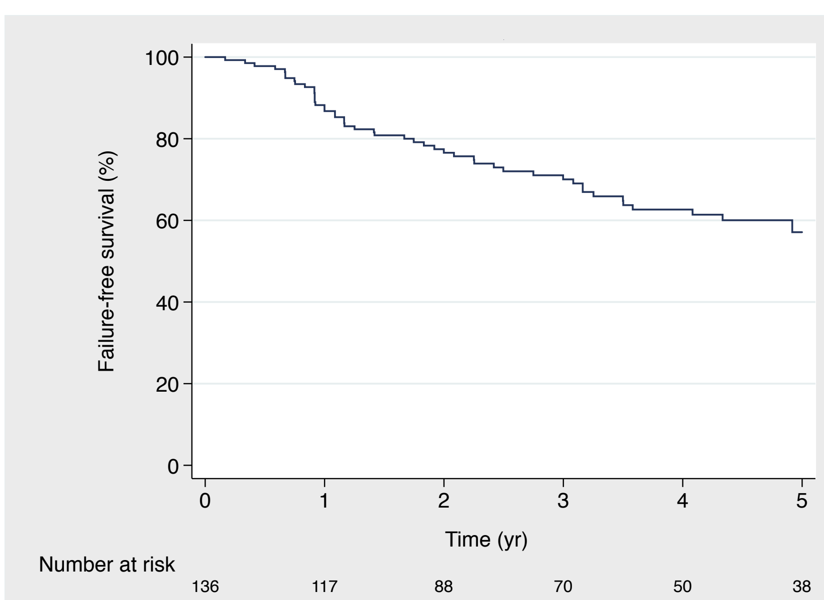

Fig. 1 – Kaplan-Meier plot depicting failure-free survival in the overall population.

Table 2 – Univariate and multivariable Cox regression analyses predicting treatment failure following urethrotomy for anterior urethral stenosis.

Variable	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age in years	1.01 (0.99–1.03)	0.3		
Body mass index	1.00 (0.91–1.10)	0.9		
Diabetes				
No	Reference		Reference	
Yes	3.25 (1.16–9.07)	0.024	1.83 (0.55–6.08)	0.3
Smoker				
No	Reference			
Yes/former	1.18 (0.68–2.07)	0.6		
Etiology				
Idiopathic	Reference		Reference	
Nonidiopathic	1.89 (1.02–3.51)	0.043	1.49 (0.74–2.99)	0.3
Type of stenosis				
Nonobliterative	Reference			
Obliterative	1.45 (0.81–2.59)	0.2		
Stenosis length				
1–2 cm	Reference		Reference	
2–3 cm	1.60 (0.85–3.01)	0.15	1.17 (0.60–2.28)	0.6
3–4 cm	2.37 (1.09–5.12)	0.029	1.83 (0.83–4.04)	0.13
Preoperative Q_{max}	0.73 (0.64–0.84)	<0.0001	0.76 (0.66–0.86)	<0.0001

HR = hazard ratio; CI = confidence interval; Q_{max} = maximum flow rate.

Association guidelines on male urethral stricture diseases: DVIU success depends on the stricture length, with the highest success rate found for short bulbar strictures [25]. We report here that the DVIU success rate was 71% for short strictures (1–2 cm) and only 47.6% for longer strictures. In our series of patients, the overall success rate of 62.5% is higher than other in reports in the literature, because we excluded navicularis, penile, posterior, traumatic, lichen sclerosus, and failed hypospadias repair strictures, which negatively influence DVIU outcomes.

We selected DVIU as the primary treatment for untreated bulbar urethral strictures. The most cost-effective treatment for short bulbar urethral strictures is a controversial topic. Some authors reported that primary urethroplasty for short bulbar strictures with is less costly than treatment with DVIU, while others have suggested that the most cost-effective strategy is to reserve urethroplasty for patients in whom primary DVIU fails [26,27]. In our study, 60 patients (44.1%) had strictures of 1–2 cm in length and the success rate of DVIU as primary treatment on these patients was 73.3%. We don't performed evaluation of the cost-effective approach but we believe that, as far as the clinical point of view is concerned, this data justifies the use of DVIU as primary approach in short bulbar stricture. Some authors reported that age at presentation, obesity, and idiopathic strictures were independent factors of failure after DVIU for short bulbar strictures [28]. In our present series patients, maximum flow at preoperative uroflowmetry was the only significant predictor of surgical failure at multivariable analysis.

Of 51 failures (37.5%) after primary DVIU, 32 (62.7%) were treated with a second urethrotomy, for which the success rate was very poor (37.5%). These data strongly suggest that after a primary DVIU failure, open urethroplasty should be considered. Of the 51 primary DVIU failures, 19 (37.3%) were treated with one-stage oral mucosa urethroplasty, with a very high success rate of 94.7%. The success rate for oral mucosa graft urethroplasty was also high for patients with stricture recurrence after a second urethrotomy. Moreover, we need consider that repeated transurethral manipulation of a bulbar urethral stricture is associated with an increase in stricture complexity and prolonged disease duration, as reported by Hudak et al. [29]. We repeated DVIU in one patient who underwent one-stage oral mucosa urethroplasty after failure of primary DVIU and the procedure was successful. We cannot draw any conclusion because only one case represents an anecdotial report, but other

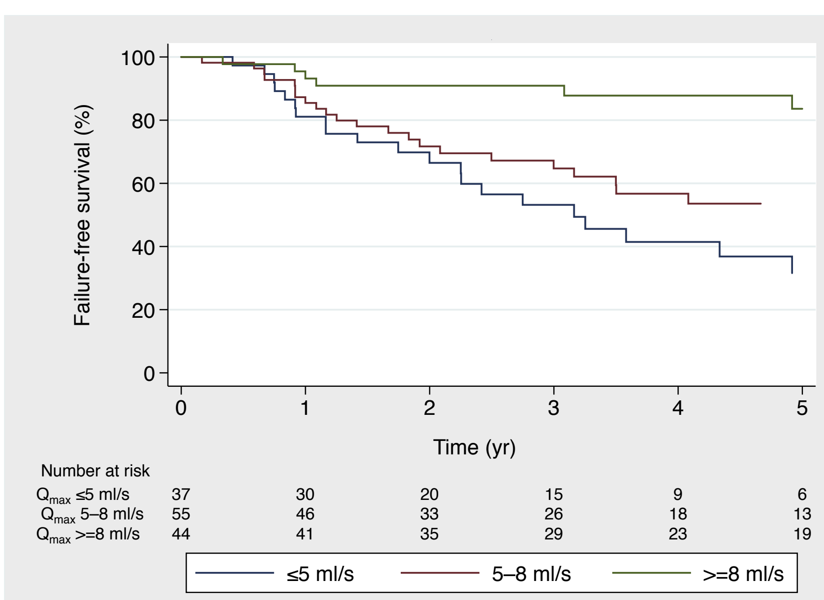

Fig. 2 – Kaplan-Meier plot depicting failure-free survival according to preoperative maximum flow (Q_{max}) at uroflowmetry (≤5 vs 5–8 vs ≥8 ml/s).

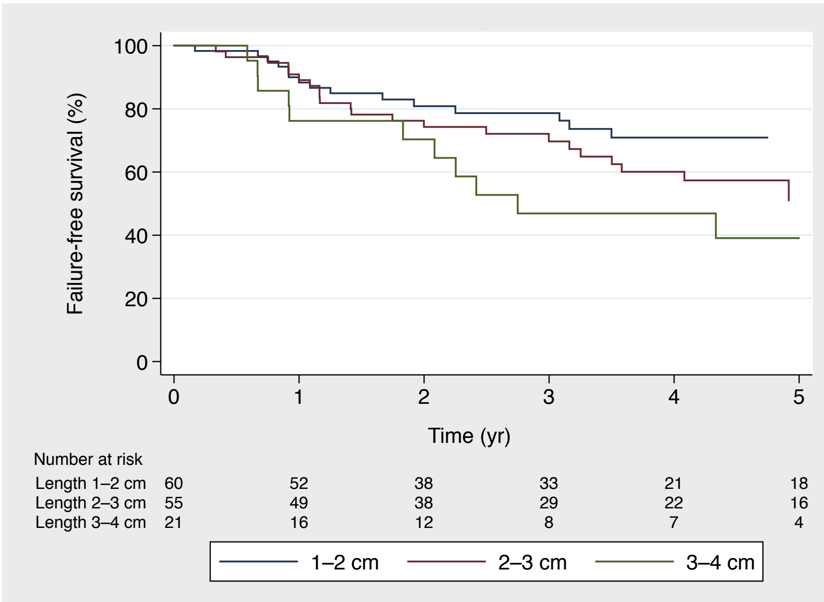

Fig. 3 – Kaplan-Meier plot depicting failure-free survival according to stricture length (1–2 vs 2–3 vs 3–4 cm).

authors reporting on a series of 43 patients suggested that DVIU might be a viable treatment option in selected patients with very short strictures after failure of oral mucosa urethroplasty [30].

It is interesting to note that the time of failure recurrence after primary DVIU is homogeneously distributed over time and patients may develop stricture recurrence after many years.

The main limitation of our study is the small sample size for some of the data reported. Only one patient had stricture etiology due to infection, only four patients were older than 70 yr, only eight were obese, and only five had follow-up >10 yr (Table 1). A concern about the Q_{max} cutoff of >12 ml/s we used might arise. Q_{max} normally differs by age and gender and with pathologic conditions. Younger men present with higher Q_{max} than their older counterparts, while women have a higher Q_{max} than males. In cases of benign prostatic hyperplasia, urinary flow generally decreases. The Q_{max} lower acceptable limit is typically set to approximately 15 ml/s, but an arbitrary lower limit is often considered for patients with urethral stricture disease.

Finally, we did not perform any correlation analysis using a quality of life (QoL) questionnaire and no patient-reported outcomes were considered, which limits the possibility of a "partial success" category for patient satisfaction with Q_{max} >12 ml/s but poor QoL

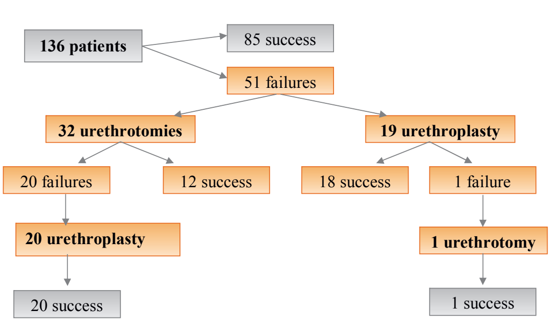

Fig. 4 – Flow chart of the treatment successes and failures.

5. Conclusions

The risk of surgical failure of internal urethrotomy for untreated bulbar urethral strictures greatly depends on preoperative maximum flow at uroflowmetry. Patients with a pre-operative maximum flow greater than 8 ml/s have a high probability of success when treated with internal urethrotomy. The success rates of DVIU as a primary treatment in patients with stricture lengths of 1–2 cm as compared to longer strictures was really impressive and statistically significant. On the contrary, patients with a preoperative maximum flow smaller than 5 ml/s have a low probability of success and may be considered for alternative treatments such as urethroplasty, especially when affected by long urethral strictures.

Author contributions: Massimo Lazzeri had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Barbagli, Lazzeri.
Acquisition of data: Balò, Rimondi, Sansalone, Butnaru, Larcher.
Analysis and interpretation of data: Barbagli, Fossati, Lazzeri.
Drafting of the manuscript: Barbagli, Fossati, Lazzeri.
Critical revision of the manuscript for important intellectual content: Montorsi.
Statistical analysis: Fossati, Larcher.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Montorsi, Lazzeri.
Other: None.

Financial disclosures: Massimo Lazzeri certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

References

[1] Waxman SW, Morey AF. Management of urethral strictures. Lancet 2006;367:1379–80.

[2] Morey AF. Urethral stricture is now an open surgical disease. J Urol 2009;181:953–5.

[3] Santucci RA. Should we centralize referrals for repair of urethral stricture? J Urol 2009;182:1259–60.

[4] Fossati N, Barbagli G, Larcher A, et al. The surgical learning curve for one-stage anterior urethroplasty: a prospective single-surgeon experience. Eur Urol 2016;69:686–90.

[5] Faris SF, Myers JB, Voelzke BB, et al. Assessment of the male urethral reconstruction learning curve. Urology 2016;89:137–43.

[6] Xu YM, Song LJ, Wang KJ, et al. Changing trends in the causes and management of male urethral stricture disease in China: an observational descriptive study from 13 centres. BJU Int 2015;116:938–44.

[7] Bullock TL, Brandes SB. Adult anterior urethral strictures: a national practice patterns survey of board certified urologists in the Unites States. J Urol 2007;177:685–90.

[8] Ferguson GG, Bullock TL, Anderson RE, et al. Minimally invasive methods for bulbar urethral strictures: a survey of members of the American Urological Association. Urology 2011;78:701–7.

[9] Anger JT, Buckley JC, Santucci RA, et al. Trends in stricture management among male Medicare beneficiaries: underuse of urethroplasty? Urology 2011;77:481–6.

[10] Anger JT, Scott VCS, Sevilla C, et al. Patterns of management of urethral stricture disease in the Veterans Affairs system. Urology 2011;78:454–8.

[11] Burks FN, Salmon SA, Smith AC, et al. Urethroplasty: a geographic disparity in care. J Urol 2012;187:2124–7.

[12] Lacy JM, Cavallini M, Bylund JR, et al. Trends in the management of male urethral stricture disease in the veteran population. Urology 2014;84:1506–10.

[13] Buckley JC, Heyns C, Gilling P, et al. SIU/ICUD consultation on urethral strictures: dilation, internal urethrotomy, and stenting of male anterior urethral strictures. Urology 2014;83:S18–22.

[14] Santucci R, Eisenberg L. Urethrotomy has a much lower success rate than previously reported. J Urol 2010;183:1859–62.

[15] Greenwell TJ, Castle C, Andrich DE, et al. Repeat urethrotomy and dilation for the treatment of urethral stricture are neither clinically effective nor cost-effective. J Urol 2004;172:275–7.

[16] Al Taweel W, Seyam R. Visual internal urethrotomy for adult male urethral stricture has poor long-term results. Adv Urol 2015;2015:1–4. http://dx.doi.org/10.1155/2015/656459.

[17] Boccon Gibod L, Le Portz B. Endoscopic urethrotomy: does it live up to its promises? J Urol 1982;127:433–5.

[18] Davis E, Lee LW. Lasting results following internal urethrotomy for urethral stricture. J Urol 1948;59:935–9.

[19] Pansadoro V, Emiliozzi P. Internal urethrotomy in the management of anterior urethral strictures. J Urol 1996;156:73–5.

[20] Albers P, Fichtner J, Bruhl P, et al. Long-term results of internal urethrotomy. J Urol 1996;156:1611–4.

[21] Steenkamp JW, Heyns CF, De Kock MLS. Internal urethrotomy versus dilation as treatment for male urethral strictures: a prospective, randomized comparison. J Urol 1997;157:98–101.

[22] Heyns CF, van der Merwe J, Basson J, et al. Treatment of male urethral strictures – possible reasons for the use of repeated dilatation or internal urethrotomy rather than urethroplasty. S Afr J Surg 2012;50:82–7.

[23] Brodker A, Ostri P, Rye-Andersen J, et al. Treatment of recurrent urethral strictures by internal urethrotomy and intermittent self-catheterization: a controlled study of a new therapy. J Urol 1992;148:308–10.

[24] Heyns CF, Steenkamp JW, De Kock, et al. Treatment of male urethral strictures: is repeated dilation or internal urethrotomy useful? J Urol 1998;160:356–8.

[25] Wessells H, Angermeier KW, Elliot S, et al. Male urethral stricture: American Urological Association guideline. J Urol 2017;197:182–90.

[26] Rourke KF, Jordan GH. Primary urethral reconstruction: the cost minimized approach to the bulbous urethral stricture. J Urol 2005;173:1206–10.

[27] Wright JL, Wessells H, Nathens AB, et al. What is the most cost-effective treatment for 1 to 2 cm bulbar urethral strictures: societal approach using decision analysis. Urology 2006;67:889–93.

[28] Harraz AM, El-Assmy A, Mahmoud O, et al. Is there a way to predict failure after direct vision internal urethrotomy for single and short bulbar urethral strictures? Arab J Urol 2015;13:277–81.

[29] Hudak SJ, Atkinson TH, Morey AF. Repeated transurethral manipulation of bulbar urethral strictures is associated with increased stricture complexity and prolonged disease duration. J Urol 2012;187:1691–5.

[30] Rosenbaum CM, Schmid M, Ludwig TA, et al. Internal urethrotomy in patients with recurrent urethral stricture after buccal mucosa graft urethroplasty. World J Urol 2015;33:1337–44.