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The Impact of Age on Urethroplasty Success

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OBJECTIVE To determine if age is an independent predictor of surgical success in patients undergoing urethroplasty. Urethroplasty performed by excision and primary anastomosis depends on vascular collateralization. Successful augmented urethroplasty depends on graft neovascularization. Older patients have more comorbid conditions including peripheral vascular disease associated with reduced penile blood flow.

METHODS This is a retrospective review of urethroplasties from 11 institutions. Primary outcome was functional success at 1 year from surgery, defined as freedom from post-urethroplasty procedures. Secondary outcome was freedom from cystoscopic evidence of stricture recurrence at 3 months. Study outcomes were compared between 2 age cohorts (<60 years old and ≥60 years old). Multivariable logistic regression analysis evaluated the influence of patient factors on our primary and secondary outcomes, using age as a continuous variable.

RESULTS Of 322 urethroplasties, 258 were performed in patients <60 years and 64 in patients ≥60 years. Median follow-up was 1.8 years. The following were not significantly different between groups: stricture length or location, smoking status, number of previous urethrotomies or dilations, and urethroplasty type. The following were more common in patients ≥60 years: diabetes, hypertension, hyperlipidemia, coronary artery and peripheral vascular disease, chronic obstructive pulmonary disease, and cancer. There was no difference in need for repeat procedures or anatomic recurrence between age groups or with increasing age. Stricture length was the only statistically significant clinical factor.

CONCLUSION Urethroplasty success may be affected by comorbidities but not age. Age alone should not be used as an absolute exclusion criterion for men needing urethral reconstruction. UROLOGY 107: 232–238, 2017.

The prevalence of urethral stricture disease increases steadily with age.[1] Additionally, rates of hospital stays, procedures, and outpatient physician visits for urethral stricture disease also increase with age.[1] Yet several studies have shown that regardless of insurance status or proximity to a urethral reconstruction surgeon, age is a consistent barrier to urethroplasty.[2,3] Older men are more likely to undergo repeat dilation or urethrotomy, and the rates of urethroplasty in older men with urethral strictures are less than 1%.[2-4] Indeed little is known about outcomes of urethroplasty in older men because most urethroplasty series report on outcomes in populations overrepresented by younger men.[4-6]

Although reasoning is likely varied, perhaps most importantly, older men may be less likely to receive urethroplasty because of surgeon reluctance on the accord of the perceived negative impact of age on urethroplasty outcomes. Successful bulbar urethroplasty requires a well-vascularized urethra for a transecting excision and primary anastomosis (EPA), whereas a non-transecting bulbar urethroplasty with buccal mucosa graft (BMG) requires a healthy, well-vascularized graft bed for subsequent neovascularization. Older patients have an increased comorbid burden that may result in decreased penile and urethral blood flow. However, it is unclear whether age is an independent predictor or simply a surrogate for such comorbidities. The only study to focus on age as a primary predictor of urethroplasty outcome demonstrated similar success rates regardless of age.[7] Although Santucci et al's study[7] suggests no difference, they did not conduct a multivariable regression analysis to determine possible

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demographic influences. Additionally, Santucci et al reported on only 7 patients out of 70 who underwent BMG, making conclusive comparisons among surgical approaches challenging.

In our study, we sought to determine whether age is an independent predictor of urethroplasty success. Further, the collateral blood supply that is necessary for a successful outcome in EPA led us to hypothesize that older men may have inferior outcomes (urethroplasty success) than younger men when both groups undergo EPA, but similar outcomes to younger men when both groups undergo non-transecting augmentation urethroplasty. Herein, we present a multi-institutional study evaluating the effect of age on urethroplasty success, stratified by transecting bulbar EPA compared with non-transecting bulbar urethroplasty with BMG.

METHODS

From 2007 to 2014, men aged 18 years or older with urethral stricture disease were recruited to participate in a prospective, longitudinal, institutional review board-approved, outcomes database. The database includes enrollment from 8 participating institutions, which all participate in Trauma and Urologic Reconstructive Network of Surgeons. Demographic data, operative, and perioperative details were collected, as well as objective and subjective measures based on a standardized protocol, as previously described.[8] For the current study, we included men who underwent a single-stage urethroplasty. Surgical techniques included EPA and non-transecting augmentation urethroplasty with BMG. We excluded non-transecting EPAs and augmented anastomotic BMG urethroplasties as these groups would confound our evaluation of outcomes—it would be unclear whether any differences would be due to the transection or to the use of a graft. For similar reasons, we excluded men who had augmentation urethroplasty with tissue other than BMG. We further excluded men with a history of prior urethral reconstruction, prior pelvic radiation, a history of hypospadias or history of reconstruction for hypospadias, and those with less than 1 year of in-clinic or telephone follow-up subsequent to urethroplasty (Fig. 1).

Outcomes

We sought to determine if age is an independent predictor of both anatomic and functional success following urethroplasty. First, we divided our study population into 2 cohorts—those <60 years old and those ≥60 years old—and compared urethroplasty results within urethroplasty types; that is, EPA and BMG results were compared between older and younger men. We also evaluated the impact of increasing age, used as a continuous variable. Our primary outcome was functional success at 1 year from the date of surgery. We defined functional success as the freedom from additional procedures after urethroplasty. These procedures included urethral dilation, urethrotomy, or urethroplasty. Secondary outcomes included functional success for the entire study period, as well as anatomic success at 3 months, 1 year, and for the entire study period following surgery. We defined anatomic success as the ability to atraumatically pass a flexible adult cystoscope through the area of urethral reconstruction at a postoperative visit. Cystoscopy is performed per protocol at 3 months and 1 year and then as needed based on symptoms and flow rate thereafter. These definitions of success have been described previously.[8]

Statistical Analysis

Demographic and clinical characteristics as well as study outcomes were compared between the 2 age cohorts using

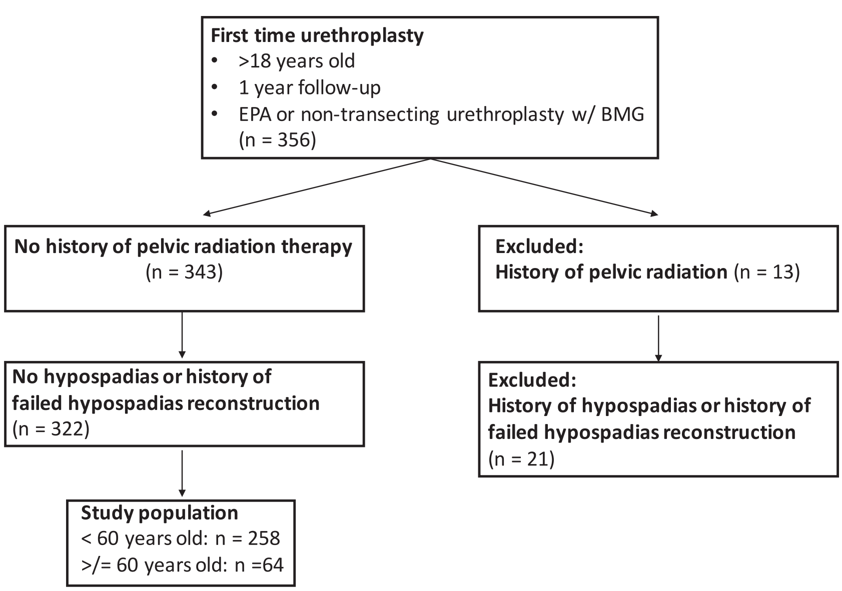

Figure 1. Study population accrual.

a Student *t* test or chi-square test, as appropriate. We then performed a multivariable logistic regression analysis to evaluate the influence of patient factors on our primary and secondary outcomes. The outcomes of these models were the odds of freedom from repeat surgery at ≥1 year (model 1) or the odds of freedom from cystoscopic evidence stricture recurrence at 3 months (model 2). The entire cohort was included in both models, with primary predictors of interest being both increasing age and age ≥60 years vs <60 years. Urethroplasty type was included as a predictor rather than creating separate models for each type of urethroplasty. All statistical analysis was performed using SAS 9.3. Statistical significance was considered a *P* value <.05 for all calculations. Our cohort size allowed 80% power to detect a >10% difference between the cohorts undergoing an EPA, and a >15% difference between cohorts undergoing BMG.

RESULTS

Demographic and Clinical Factors

Of the 322 men who met inclusion criteria, 258 (80%) were <60 years old, and 64 (20%) were ≥60 years old (see Fig. 1). Each institution contributed a median of 31 men (range 4-160, standard deviation 50.4). Overall, median was 43.5 years (Q1: 32.0 years, Q3: 57.0 years). When categorized into 2 age groups (<60 and ≥60 years), the median age in the younger group was 39 years (Q1: 30.0 years, Q3: 49.0 years) and the median age in the older group was 67.0 years (Q1: 62.0 years, Q3: 73.0 years). Median follow-up was 1.8 years (range 1.0-7.5, standard deviation 0.86), with no difference between the age cohorts. Follow-up was defined at the period from surgery to last clinic encounter. Regarding clinical characteristics, there was no difference in stricture length, location of stricture, number of prior DVIUs, or type of surgical approach for urethral reconstruction between the 2 age groups. However, the ≥60-year-old population had statistically significant higher rates of diabetes, hypertension, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, peripheral vascular disease, and cancer (Table 1). The ≥60-year-old group also had a higher rate of smoking history, but this did not reach statistical significance (*P* = .06).

Table 1. Patient characteristics

	Age <60 (n = 258)	Age >60 (n = 64)	*P* Value
Stricture length			.74
≤2.5 cm	48.8	46.9	
>2.5 cm	46.1	50.0	
Location of stricture (%)			
Bulbar	95.2	91.7	.61
Meatus or fossa	0	3.3	
Membranous	2.0	1.7	
Penile	2.8	3.3	
Etiology (%)			
Trauma	25.4	7.9	<.0001
Iatrogenic	13.6	41.3	
Idiopathic	55.1	47.6	
Infectious	3.8	0	
Lichen sclerosis	2.1	3.2	
Comorbidities (%)			
Diabetes	8.9	21.9	.004
Hypertension	19.4	53.1	<.0001
Hyperlipidemia	10.1	42.2	<.0001
Coronary artery disease	3.9	28.1	<.0001
HIV	0.4	0	.62
COPD	0.4	6.3	.0007
Peripheral vascular disease	0.4	7.8	<.0001
Cancer	3.1	23.4	<.0001
Smoking status (%)			
Nonsmoker	73.3	61.9	.06
Current smoker	11.1	9.5	
Previous smoker	15.6	28.6	
No. of previous DVIU			**.03**
0-1	62.8	54.7	
>1	25.2	20.3	
Surgery type (%)			
EPA	50.0	45.3	.50
BMG	50.0	54.7	

BMG, buccal mucosa graft; COPD, chronic obstructive pulmonary disease; DVIU, direct vision internal urethrotomy; EPA, excision and primary anastomosis; HIV, human immunodeficiency virus. Bold values indicate statistical significance ($P < 0.05$).

Table 2. Study outcomes stratified by age group

	Age <60 (n = 258)	Age >60 (n = 64)	*P* Value
Functional success at 1 y (%)			
EPA	98.4	100.0	NS*
BMG	86.8	91.4	0.46
Anatomic success at 3 mo (%)			
EPA	94.9	100.0	0.58
BMG	71.7	84.0	0.21

* *P* value approaches 1. This is owing to how close the 2 groups are to 100% and the small difference between them.

Functional and Anatomic Success

There was no difference in 1-year functional success rates between age groups, regardless of surgical approach: EPA was successful in 98% of men <60 years old and in 100% of men ≥60 years; similarly, BMG was successful in 87% of men <60 years old and in 91% of men ≥60 years (*P* = .46). Similarly, anatomic success was not different at 3 months between age groups (Table 2). Other outcomes, including anatomic success at 1 year and long-term functional success, were also not different by age.

On multivariable logistic regression analysis, being ≥60 years of age was not a significant predictor of 1-year functional success (odds ratio [OR] = 1.68; confidence interval [CI] = 0.44-6.35; Table 3). Additionally, when evaluating the impact of age as a continuous variable, increasing age was not a significant predictor of 1-year functional (OR = 0.99; 95% CI = 0.97-1.03; *P* = .95) or 3-month cystoscopic success (OR = 1.00; 95% CI = 0.99-1.01; *P* = .79). The only statistically significant clinical factor was stricture length (OR = 0.18; CI = 20.04-0.91 for ≤2.5 cm vs

Table 3. (a) Model 1—odds of functional success at 1 year by multivariable logistic regression. (b) Model 2—odds of anatomic success at 3 months by multivariable logistic regression

	Odds Ratio Estimate	95% Wald Confidence Limit	*P* Value
Age ≥60 vs age <60	1.68	0.44-6.35	0.45
Type of repair:			
EPA vs BMG	3.12	0.75-13.03	0.12
Prior DVIU vs no prior DVIU	0.79	0.31-2.05	0.63
Location of stricture:			
Bulbar vs non-bulbar	1.18	0.20-6.85	0.86
Stricture length			
>2.5 cm vs <2.5 cm	0.18	.04-0.91	**.04**
Etiology of stricture:			
Iatrogenic vs trauma	0.64	0.12-3.4	0.60
Idiopathic vs trauma	0.46	0.11-2.02	0.31
Other vs trauma	0.24	.05-1.25	.09
Comorbidities (Yes vs No)			
Diabetes	3.25	0.52-20.18	0.21
Hypertension	0.61	0.21-1.78	0.36
Hyperlipidemia	1.48	0.37-5.95	0.59
Coronary artery disease	0.27	.05-1.34	0.11
Cancer	0.51	0.10-2.51	0.40
Smoking status			
Current smoker vs nonsmoker	0.85	0.20-3.54	0.81
Previous smoker vs nonsmoker	1.61	0.47-5.49	0.45

	Odds Ratio Estimate	95% Wald Confidence Limit	*P* Value
Age ≥60 vs age <60	1.77	0.49-6.35	0.38
Type of repair:			
EPA vs BMG	5.27	1.67-16.65	**.005**
Prior DVIU vs no prior DVIU	1.14	0.45-2.86	0.79
Stricture length			
>2.5 cm vs <2.5 cm	0.39	0.13-1.15	.09
Etiology of stricture:			
Iatrogenic vs trauma	1.54	0.39-6.06	0.54
Idiopathic vs trauma	0.84	0.28-2.51	0.76
Other vs trauma	1.42	0.31-6.55	0.65
Comorbidities (Yes vs No)			
Diabetes	2.75	0.57-13.35	0.20
Hypertension	0.42	0.16-1.11	.08
Hyperlipidemia	1.26	0.37-4.27	0.71
Coronary artery disease	0.37	.08-1.80	0.22
Cancer	2.48	0.31-19.94	0.39
Smoking status			
Current smoker vs nonsmoker	0.34	0.10-1.15	.08
Previous smoker vs nonsmoker	3.07	0.75-12.52	0.12

Bold values indicate statistical significance ($P < 0.05$).

>2.5 cm). A similar multivariable logistic regression analysis with an outcome of 3-month anatomic success also showed that older age was not an independent predictor of success (OR = 1.77; CI = 0.49-6.35; Table 3). Here, EPA had significantly higher odds of success than BMG (OR = 5.27; CI = 1.67-16.65). Stricture length, hypertension, and current smoker vs nonsmoker were the only other predictors that were close to being statistically significant. Of note, previous smoker vs nonsmoker was not predictive.

DISCUSSION

In 2016, the American Urological Association published current guidelines for the management of urethral stricture disease.[9] For individuals with recurrent urethral strictures, minimally invasive techniques for treatment such as dilation or internal urethrotomy are unlikely to result in a durable response. As a result, those affected should be offered definitive treatment in the form of urethroplasty owing to higher rates of success. The guidelines do support the use of chronic dilation in men who are not candidates for urethroplasty. In light of our findings, surgical candidacy for urethroplasty should be left to surgeon discretion, but age alone should not limit or dictate the use of urethroplasty.

To date, most urethroplasty series have been relatively small with wide heterogeneity in populations, limiting the feasibility of subgroup analyses based on specific demographic and clinical characteristics. Case series from institutions performing higher numbers of urethroplasties comprise a wider breadth of clinical and demographic information but are generally limited to a single surgeon and technique and not representative of outcomes in the reconstructive community as a whole.[10-16] Most available series have not found a significant impact of age on urethroplasty outcome.[4,7,11,12,15-18] Of the previously published studies investigating age with relation to urethroplasty, Schwentner et al found a higher urethroplasty failure rate in older patients.[10] However, this study investigated only 42 patients and did not account for differences in comorbidities between groups. Other studies include more patients and find no difference between age groups, but similarly often do not account for comorbidities or provide no definitive answers for the feasibility of different urethroplasty surgical approaches in older patients.[7,11,12,15,16] Santucci et al[7] evaluated 70 patients ≥65 years. Although the surgical approach was varied in their study, only 7 patients underwent BMG. Additionally, their control group of individuals <65 years was from a single site and, aside from age, the patients' demographic information was not included or reported in the analysis. Although an important study, the limited data regarding control demographics, lack of multivariable regression analysis, and small surgical approach subgroups limit the scope and applicability of the study's conclusions.

With the data available in the present study, we are able to describe the management of urethroplasty in age group subsets that comprise significantly sized age-specific populations on the order of the largest previously published case series. The breadth of data collected from our multi-institutional cohort facilitates the analysis of urethroplasty across and among age groups. In addition to an extensive investigation of ages included on urethroplasty overall, we were able to determine that age itself does not influence outcomes from different surgical approaches. Older men should be offered the style of urethroplasty that best suits their pathology.

It is important to understand why we included both functional and anatomic success as end points. Functional success is the definition used most widely in the urethroplasty literature[6,19-23] and allows for comparison between our series and others. Further, it can be argued that freedom from repeat surgery matters more to patients than cystoscopic evidence of stricture recurrence. However, it is possible that age could bias the freedom from repeat procedures. Perhaps older men have inferior outcomes, but either they or their surgeons are disinclined to proceed with a repeat surgery owing to advanced age. Thus, anatomic success serves as an important objective confirmation that outcomes are not different in older and younger men.

The results of this study support the feasibility of urethroplasty including EPA and BMG approaches in patients >60 years of age. Outcomes were not significantly affected by age with respect to functional or anatomic surgical success. These statistically similar results are despite the significantly higher rates of comorbidities we found in the older group. In fact, hypertension was significantly more common in older men and was a borderline significant predictor of inferior success rates. Yet even without controlling for this factor, older men fared equally well. It should be noted that although the *P* value for hypertension was >.05 in the multivariable models, the confidence interval only barely crossed 1, and the effect size was large (OR = 0.42). Statistically, this suggests that with larger sample size the large effect would be consistent and the difference would be statistically significant. With regard to surgical approach, EPA was superior to BMG for 3-month anatomic success after controlling for other factors. However, this was not our outcome of interest, simply a confounder for which we controlled. Furthermore, the superiority in anatomic success did not translate into any difference in functional success at 1 year. We did find that stricture length was predictive of functional success. This is intuitive in that longer strictures were more likely to require additional procedures. Further subdivisions of the included cases showed no difference in outcome between the groups when comparing type of urethroplasty or location of stricture for functional success. As such, our study suggests that taken alone, age should not be an independent consideration in the decision to perform urethroplasty.

As we provide further evidence that age should not be used as an independent variable to forego urethroplasty, one must consider alternative explanations for the lack of application in this group of patients. Although there are countless 60-year-old men who functionally and biologically may appear to be much "younger than their age," the epidemiological phenomenon of comorbidities increasing with age is a reality. Other possible explanations include barriers to surgery in older patients such as preoperative cardiology or anesthesia evaluation. A recent review of factors associated with dropout from pursuing bariatric surgery noted need for preoperative cardiology evaluation, and laboratory testing independently predicted surgery dropout.[24] Additionally, a higher percentage of patients >60 years old are on anticoagulant or antiplatelet medications, requiring careful perioperative cessation or bridging strategies. Finally, despite increasing availability of fellowship-trained reconstructive surgeons, travel to and from centers of excellence is a significant barrier for older patients, many of whom may rely on prearranged transportation or support from friends and family. Together, all of these compounding factors often reduce the palatability of pursuing urethral reconstruction in lieu of "simpler" endoscopic techniques.

There are limitations to the present study. Although extracted from a large series of individuals undergoing urethroplasty and coming from multiple centers, case numbers of urethroplasty in older men are still limited compared with younger individuals. Additionally, the referral nature of most urethral surgeons introduces inherent selection bias that should be acknowledged. Follow-up time was at least 1 year in all patients, but extended follow-up will be required to speak to the comparative long-term durability of repairs in each group.

CONCLUSION

The present study suggests that urethroplasty is a durable solution over moderate-length follow-up for urethral stricture in all age groups. Although older men are more likely to have more comorbidities, their suitability for urethroplasty should be judged based on their overall health, not their age. Given the overwhelmingly consistent data, urethroplasty should be offered to more men older than 60 years old.

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EDITORIAL COMMENT

Urethroplasty is the definitive surgical treatment for strictures with a success rate of 85-90% for simple procedures and about 80% for extremely complex repairs.[1]

Anastomotic urethroplasty and graft urethroplasty are the most common techniques with similar long-term success rates.

The up-to-date definition of success is anatomical (if a flexible cystoscope can pass easily through the reconstructed urethra) and functional (if patient-reported improvement in voiding symptoms and urinary quality of life).[2]

Despite the incidence of urethral strictures increases with age, there are few reports on urethroplasties in elderly patients.

The corpus spongiosum surrounds the urethra from the meatus to the bulbar segment and provides the vascular supply. A urethral stricture is formed when the spongiosal tissue is replaced by dense non-elastic collagen fibers interspersed with fibroblasts. The degree of fibrosis in corpus spongiosum relates directly to the extent and severity of the stricture.[3]

Many insults can induce fibroblastic changes to the urethra, including inflammatory causes (infections or lichen Sclerosus) and traumatic causes (iatrogenic injury or pelvic fracture).

Since spongiofibrosis is based on a vascular injury, age is certainly a main driver of urethral stricture development. At the same time, age *per se* might drive surgical outcomes of urethroplasty, due to the weakness of vascular collateralization and graft neovascularization that are supposed to be the main causes of failure after anastomotic and augmented urethroplasty, respectively.[3]

Contrasting evidences are available on the successful outcomes of urethroplasty in elderly population.[4-6]

In a report by Scwentner et al, a lower success rate in elderly patients was reported; however the study did not take into account different comorbidities between groups.[4]

On the contrary, in a series of 604 urethroplasties performed in a tertiary referral centre, stricture length (HR 5.9, [2.1-16.5]; $P \leq .001$), Lichen sclerosus (HR 3.4 [1.2-10]; $P = .02$), iatrogenic and infectious etiology (HR 7.3 [2.3-23.7]; $P \leq .001$), but not age >50 yrs (HR 0.8 [0.5-1.5], $P = .53$), were independently associated with stricture recurrence.[5]

Similarly, Santucci et al showed in a multicentric series, including different urethroplasty techniques, comparable incidence of postoperative complications and treatment failure in patients older than 65 years old compared with the younger (<65 years old) counterpart.[6]

Finally, in the present study the Authors examined if age is an independent predictor of surgical success after either anastomotic or augmented urethroplasty. Obviously, the two groups of patients (<60 and ≥60 years old) were not homogeneous for comorbidities, since older patients had significantly higher rates of diabetes, cardiovascular or pulmonary disease and cancer.

At multivariable regression, age failed to be an independent predictor of both anatomical and functional success, while stricture length was the only significant predictor of functional failure ($P = .04$).[7]

The reader must be aware of the lack of strong evidences on this topic; besides, this study did not overcome selection bias and limitations of previous reports.[4-6] Notwithstanding, based on available evidences, older age should no longer be considered a contraindication to urethroplasty in favour of minimally invasive techniques, such as simple dilatation or endoscopic urethrotomy.

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AUTHOR REPLY

The above commentary nicely crystallizes the basic pathophysiological tenants of stricture formation and explains how increasing age is theorized to place patients at risk of poor outcomes. Our collective experience demonstrates that patients are often indiscriminately subjected to age bias when counseled on the various treatment options for urethral stricture disease. There appears to be a decidedly lower threshold to employ repetitive, even scheduled endoscopic treatments for older patients in an effort to avoid "major surgery." Heyns et al analyzed pre-referral stricture management for patients who eventually underwent urethroplasty, noting that patients with 5-6 endoscopic interventions before referral had an average age of 60.2 years vs 46.6 years in those receiving 1-2 interventions.[1] The unintended consequence from this phenomenon is strictures that are unnecessarily more complex when they are eventually referred for reconstruction.

The commenting authors highlight several important papers supporting urethroplasty in older patients; our work augments the existing literature by providing adequate power to decouple age from comorbidity, demonstrating age alone does not portend a poor prognosis. Our findings galvanize reports from previous authors, providing ample evidence that should serve to encourage, irrespective of patient age, the referral of patients with urethral stricture disease to those capable of providing definitive treatment.

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