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Risk factors for subsequent urethral atrophy in patients undergoing artificial urinary sphincter placement

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ABSTRACT

Objective: Artificial urinary sphincter (AUS) device failure or revision can be due to multiple etiologies including erosion, infection, mechanical malfunction, and urethral atrophy. However, few studies have evaluated factors that predispose patients to urethral atrophy. Here, we sought to identify preoperative and perioperative risk factors associated with urethral atrophy in men undergoing primary artificial urinary sphincter (AUS) placement for stress urinary incontinence.

Material and methods: From 1987 to 2013, 1829 AUS procedures were performed at our institution. A total of 1068 patients underwent primary AUS placement and were the focus of our study. Multiple clinical and surgical variables were evaluated for a potential association with revision for atrophy. Those found to be associated with atrophy and relevant competing risks were further evaluated on multivariable analysis.

Results: With a median follow-up of 4.2 years (IQR 1.3-8.1), 89 men (8.3%) had urethral atrophy requiring reoperation. Median time to revision was 4.5 years (IQR 1.9-7.6). On univariable analysis, only smaller cuff size (4.0-cm versus 4.5-cm; HR 3.1, p=0.04) was associated with an increased rate of urethral atrophy. Notably, patient age at the time of surgery (p=0.62), body mass index (0.22), and smoking status (p=1.00) were not associated with a risk of atrophy. On multivariable analysis smaller urethral cuff size remained significant (HR 2.8, 95% CI 1.1-7.1; p=0.01).

Conclusion: Revision surgery for urethral atrophy was performed in approximately 8% of men undergoing primary AUS placement. Utilization of a smaller AUS cuff size appears to be an independent factor associated with increased rate of urethral atrophy.

Keywords: Atrophy; AUS; incontinence; male sling; post-prostatectomy.

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Introduction

Stress urinary incontinence after radical prostatectomy or other urologic procedures can have a devastating impact on a man's quality of life.[1] While various treatment modalities including urethral bulking agents and male urethral slings have been developed over the last several decades, the artificial urinary sphincter (AUS) implantation has remained the gold standard treatment for male stress urinary incontinence since its introduction in 1972.[2] The literature is limited by the lack of prospective data, but a pooled-analysis of outcomes in patients undergoing primary AUS placement showed that over 25% of patients required surgical intervention.[3] Similarly, in our cohort of 1,082 patients who underwent primary AUS placement over a 28-year period, we found a device revision-free survival rates of 74% and 57% at 5-, and 10-year years, respectively.[4] The etiologies underlying the need for device revision are variable, and include urethral erosion and/or infection, mechanical failure, and urethral atrophy.[3]

Urethral atrophy, characterized by recurrent episodes of stress incontinence after a period of symptomatic improvement in the absence of erosion/infection and mechanical failure, is thought be caused by chronic compression resulting in a hypoxic insult to the underly-

ing urethra and spongy tissue.[3,5,6] Previous reports have suggested that urethral atrophy is a leading cause for secondary intervention after primary AUS placement, and Van der Aa et al.[3] found that nearly 9% of patients underwent device revision for urethral atrophy. Despite its high prevalence, relatively few studies have evaluated the impact of preoperative risk factors on the subsequent development of urethral atrophy requiring revision surgery.[5,7-10] Discussing risk factors for urethral atrophy is important for counseling patients preoperatively, in order to promote informed decision-making. We hypothesized that preoperative risk factors could be used to identify patients at increased risk for a subsequent development of urethral dilation. Here, we sought to identify preoperative risk factors for the subsequent development of urethral atrophy in patients undergoing primary AUS placement.

Material and methods

After obtaining institutional review board and organizational ethics committee approval (13-0019200), we retrospectively reviewed our experience with AUS placement at our institution. We identified 1829 AUS procedures performed at our institution, including 1068 who underwent primary AUS placement. Our analysis was limited to procedures performed between 1987 and 2013 in order to allow for adequate patient follow-up. Exclusion criteria of the study were as follows: age <18 years, history of prior AUS placement, history of AUS placement secondary to neurogenic bladder, and refusal to participate in research studies. A total of 1068 patients who met our inclusion criteria and had complete medical data were included in the study Three consecutive prosthetic surgeons performed the AUS implantations within the time frame of the study. All implanted AUS devices were of AMS 800 brand (Boston Scientific Marlborough, MA, USA).

A perineal approach is utilized for all AUS placements at our institution, with the urethral cuff placed at the level of the proximal bulbar urethra after circumferential dissection and measurement of the appropriate cuff size by the performing surgeon. A transcorporal approach is utilized when urethral dissection is difficult secondary to prior pelvic radiation or previous urethral sling placement.[11,12] A separate abdominal incision is made to place the abdominal reservoir (we most commonly utilize at 61-70 cm H_20 reservoir) which is filled with 22 cc of iso-osmotic contrast material.

A retrospective chart review was performed to identify relevant clinical and surgical comorbidities, along with intraoperative and postoperative data after primary AUS placement. While a standardized protocol could not be designed secondary to the retrospective nature of this study, all patients were evaluated at six-weeks postoperatively. Device activation and patient training was performed, along with a follow-up visit. Patients were then seen on an as-needed basis. However, as part of our Department of Urology AUS registry, patients

Table 1. Cohort demographics

	Total cohort n=1,068	Atrophy (+) n=89	Atrophy(-) n=979
Age, median (IQR) (years)	71 (66;75)	69 (66;74)	71 (6;75)
BMI, median (IQR) (kg/m^2)	28 (26;31)	28 (25;30)	28 (26;32)
Coronary artery disease, n (%)	195 (27)	16 (25)	179 (27)
Diabetes mellitus, n (%)	121 (17)	9 (14)	112 (17)
Hypertension, n (%)	443 (61)	37 (59)	406 (62)
Cerebrovascular disease, n (%)	41 (6)	2 (3)	39 (6)
Tobacco use, n (%)	43 (6)	3 (5)	40 (6)
Pelvic radiation, n (%)	367 (34)	34 (38)	333 (34)
Radical prostatectomy, n (%)	847 (79)	78 (88)	769 (79)
Bladder neck contracture, n (%)	205 (29)	18 (30)	187 (29)
Androgen deprivation therapy, n (%)	100 (14)	7 (11)	93 (14)
Cuff size, n (%)			
4.0 cm	26 (3)	6 (7)	20 (2)
4.5 cm	986 (97)	79 (92)	907 (97)
5.0 cm	3 (0.3)	1 (1)	2 (0.2)

BMI: body mass index

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received periodic mail-in surveys to monitor device function and outcomes.

Urethral atrophy was defined based on recurrent or worsening of stress urinary incontinence in patients who underwent prior primary AUS placement after a period of significant symptom improvement. A full evaluation was performed including history and physical examination, device activation by the surgeon to rule out operator error, and inflate/deflate abdominal x-ray to evaluate for the presence of contrast in the system. Cystoscopy was also performed to rule out cuff erosion and visualize signs of urethral atrophy such as poor coaptation with activation of the device and change in tissue turgor. During revision surgery for urethral atrophy, the cuff was removed and subsequently replaced after measuring the circumference of the urethra either at the location of the original cuff, or, if deemed appropriate, at a new area of healthy-appearing urethra.

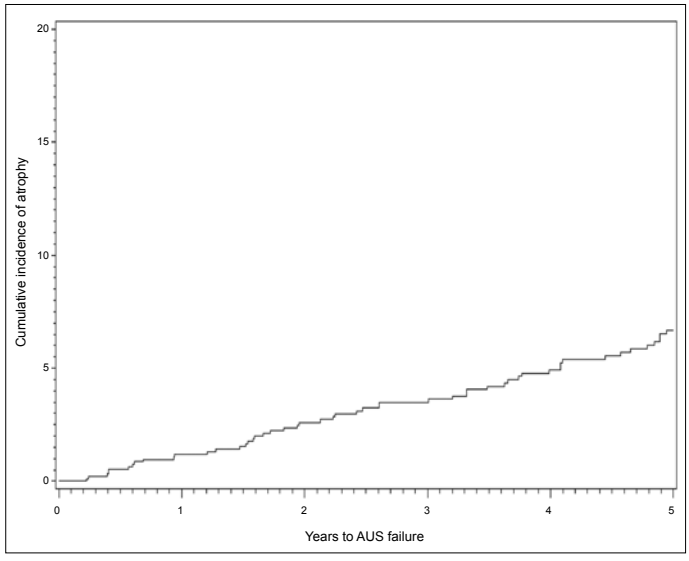

Figure 1. Cumulative incidence plot for urethral atrophy after primary AUS placement
AUS: artificial urinary sphincter

Our primary outcome in this study was to assess the impact of preoperative clinical and demographic variables on the rate of subsequent surgical intervention for urethral atrophy. Continuous features were summarized with medians and interquartile ranges (IQRs), while categorical features were summarized with frequencies and percentages. Univariable and multivariable statistical analyses were performed to evaluate the impact of various clinical and demographic variables on device outcomes, specifically re-intervention for urethral atrophy. Factors were included in multivariable analysis if they were significant in univariable analysis ($p<0.05$) or have previously been reported to be associated with the risk of urethral atrophy.[5] Cumulative incidence was estimated as time from AUS implantation to subsequent repeat surgery for urethral atrophy using the competing risk analysis method. All statistical tests were 2-sided, with a p-value <0.05 considered statistically significant. Statistical analysis was performed using the SAS software package (SAS Institute, Inc.: Cary, NC, USA).

Table 2. Univariable and multivariable analysis

	Univariable analysis				Multivariable analysis			
	HR	**95% CI**		**p**	**HR**	**95% CI**		**p**
Age†(years)	0.98	0.95	1.01	0.25	0.98	0.95	1.01	0.22
BMI (kg/m^2)	0.96	0.91	1.02	0.18				
Coronary artery disease	1.06	0.60	1.86	0.84				
Diabetes mellitus	0.91	0.44	1.90	0.80				
Hypertension	1.06	0.63	1.73	0.86				
Cerebrovascular disease	0.64	0.16	2.60	0.53				
Tobacco use	1.03	0.32	2.36	0.97				
Pelvic radiation†	1.42	0.90	2.23	0.13	1.50	0.96	2.33	0.07
Radical prostatectomy	1.26	0.64	2.47	0.50				
Bladder neck contracture	1.12	0.64	1.94	0.70				
Androgen deprivation therapy	0.89	0.41	1.95	0.78				
Cuff size†								
4.0 vs. 4.5 cm	3.11	1.39	6.94	0.006	3.09	1.38	6.90	0.006
5.0 vs. 4.5 cm	3.23	0.40	26.4					

†Included in multivariable analysis. BMI: body mass index

Results

Patient demographics for the 1068 primary AUS placements at our institution from 1987 to 2013 stratified by whether or not patients underwent revision surgery for urethral atrophy are shown in Table 1. In this cohort of primary AUS placements, the majority of urethral cuffs were 4.5cm, and no patients underwent 3.5 cm-cuff placement. Median follow-up for the entire cohort was 4.2 years (IQR 1.3-8.1), when 89 patients (8.3%) underwent revision surgery for urethral atrophy. Median time to revision for urethral atrophy was 4.5 years (IQR 1.9-7.6). The cumulative incidence curve for urethral atrophy is shown in Figure 1.

As shown in Table 2, on univariable analysis only smaller cuff size (4.0 cm vs. 4.5 cm) was associated with a higher incidence of revision for urethral atrophy (HR 3.1; p=0.006). While radiation trended towards an increased risk for urethral atrophy, these results did not reach statistical significance (HR 1.4; p=0.13). In order to further evaluate the impact of cuff size on the need for subsequent revision surgery after primary AUS, we performed a multivariable analysis that included the parameters of cuff size (4.0 cm vs. 4.5 cm), prior radiation therapy, and age. Again, on multivariable analysis only smaller cuff size was associated with a significantly increased risk of urethral atrophy (HR 3.1; p=0.006), although radiation trended towards significance (HR 1.5; p=0.07).

Discussion

Here, with a median of 4.2 years of follow-up, we found that over 8% of our patients who underwent primary AUS placement required revision surgery for urethral atrophy. While the majority of available studies do not report the timing of urethral atrophy, it is likely that with further long-term follow-up the atrophy rate would be even higher.[3] Additionally, the current data capture only those who underwent revision surgery for urethral atrophy and an underestimation of the true prevalence is likely. This information is useful when counseling patients on treatment options for male stress urinary incontinence.

In the current cohort, those patients who had a smaller cuff-size (4.0 cm vs. 4.5 cm) utilized at the time of primary AUS placement were more likely to undergo revision for urethral atrophy. These results are not surprising, as the most-prevalent hypothesis surrounding the mechanism underlying atrophy involves ischemia from compressive force applied to the underlying urethra.[10] In 2001, Elliott et al.[13] evaluated outcomes in patients undergoing AUS revision surgery at two institutions. The authors found that patients who performed nocturnal device deactivation had a 10% rate of reoperation for urethral atrophy, compared to 21% in those who did not deactivate their device at night. While these results did not reach statistical significance, they underlie the concept of chronic compression in the development of recurrent incontinence. We do not routinely recommend device deactivation at night, although patients are not discouraged from doing this should deactive it if they desire.

Viers et al.[5] recently evaluated their experience with primary AUS placement in 305 patients from a single-surgeon series. Rather than reporting on revision rates, the authors used placement of a 3.5 cm-cuff as a surrogate for urethral atrophy. This was based on previous work from the same group, wherein they found a decreased rate of device revision in patients with a 4.0 cm-cuff after introduction of the 3.5 cm-cuff in 2010.[14] We do not routinely utilize the 3.5 cm-cuff due to concerns for increased complication rates. Similarly, in a multi-institutional study evaluating risk factors for AUS explantation, Brant et al.[15] found that utilization of a 3.5-cm cuff resulted in a significantly greater rate of explantation (16% vs. 7%), and this remained significant on multivariable analysis (OR 3.3, p=0.02). It is conceivable that placement of a smaller cuff at the time of primary AUS placement in our cohort could result in a decreased rate of subsequent urethral atrophy diagnosis albeit at an increased risk of complications as noted by Brant et al.[15].

In their study, Viers et al.[5] also found that prior radiation and increased time between prostate cancer treatment and incontinence surgery were associated with an increased risk for urethral atrophy (utilization of a 3.5 cm cuff). Interestingly, data from the same institution suggested that patients undergoing placement of a 3.5 cm cuff with a history of prior radiation also had a higher rate of cuff-erosion compared to those without a history of radiation.[16] Similarly, while not statistically significant, we did appreciate a trend towards an increased rate of revision surgery for urethral atrophy in patients with a history of radiation therapy (HR 1.5; p=0.07). The lack of significance may be due to the relatively small total number of events (n=89 with atrophy) and we advocate for further research into the impact of radiation therapy on outcomes. In contrast, data regarding the impact of radiation on overall device survival is mixed.[17]

It should be noted that the concept of urethral atrophy has been questioned by some. In 2015, Bugeja et al.[7] reported on 50 patients who, at an average of 10.1 years after primary AUS placement underwent AUS revision after excluding infection, erosion, and complete loss of fluid within the system. In 19 of these patients, no device abnormality was identified. At revision, 14 patients (74%) had the same cuff-size placed at the same location as the explanted device, including 6 patients who underwent adjunctive "capsulectomy/capsulotomy" of an inner fibrous sheath overlying the corpus spongiosum. Concurrent device pressure studies suggested the reduction of the pressure-regulating balloon (PRB) pressure. Continence was restored in 12/14 (86%) of these patients. Based on these results, the authors concluded that urethral atrophy may actually represent

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decreased pressure transmission from changes to the PRB or restriction from a fibrous capsule surrounding the corpus spongiosum. While interesting, further work is required to determine the true pathophysiologic mechanism underlying recurrent stress incontinence in the absence of other causes.

Our study has several notable limitations including its nonrandomized, retrospective design. The data also represent a single-institution series at a tertiary referral center, which impacts follow-up as some patients elect to pursue ongoing care locally. To account for this, our AUS registry periodically contacts patients by mail to obtain ongoing follow-up to elicit information such as re-operation. For the current report, we did not specifically evaluate outcomes data such as postoperative efficacy and leakage rates, and we look forward to further studies evaluating these outcomes. Also, the impact of adjunctive intraoperative maneuvers such as transcorporal cuff placement on outcomes is unclear. Finally, the relative number of urethral atrophy events was low (n=89) which may impact our ability to detect smaller but clinically significant differences in device outcomes.

In conclusion, in one of the largest cohorts of patients undergoing primary AUS placement, we found a urethral atrophy rate of 8.3%. Those patients who had a 4.0 cm cuff placed at the time of primary placement were significantly more likely to undergo revision surgery for urethral atrophy. Also, while not statistically significant, we identified a trend towards increased urethral atrophy in patients with a history of radiation therapy for prostate cancer. This information is useful when counseling patients on treatment options for male stress urinary incontinence.

Ethics Committee Approval: Ethics committee approval was received for this study from the institutional review board of Mayo Clinic (#13-001920).

Informed Consent: Written informed consent was obtained from all patients who elected to participate in retrospective research at our institution.

Peer-review: Externally peer-reviewed.

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