The impact of androgen deprivation on artificial urinary sphincter outcomes

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Background: Androgen deprivation therapy (ADT) causes systemic tissue atrophy. It is unclear if this tissue atrophy adversely impacts artificial urinary sphincter (AUS) outcomes. We sought to evaluate the effect of ADT on adverse AUS outcomes.

Methods: We retrospectively identified 518 men undergoing primary AUS placement at our institution between 1998 and 2014. Rates of device explant for infection/erosion, mechanical failure, and urethral atrophy in men with >6 months of ADT use within 2 years prior to AUS placement were compared to ADT naive men.

Results: Fifty of the patients (50/518, 9.7%) had >6 months of ADT use within 2 years prior to AUS placement while 442 were ADT naive. Multivariable survival analysis of AUS events by competing risks failed to show any effect of ADT on device explantation for infection/erosion (HR 1.12, P=0.68), replacement for mechanical failure (HR 0.92, P=0.77), or urethral atrophy (HR 0.77, P=0.46).

Conclusions: This study did not show evidence supporting differences in adverse AUS outcomes between men with ADT use and ADT naive men.

Keywords: Antiandrogen; artificial urinary sphincter (AUS); incontinence; outcomes

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Introduction

Since introduction of the artificial urinary sphincter (AUS) in 1972, the AUS has become the gold standard for alleviating severe stress urinary incontinence after prostatectomy (1-3). Notably, post-prostatectomy prostate cancer survivors make up a significant proportion of AUS candidates (4-6) and many men treated for prostate cancer will eventually be treated with androgen deprivation therapy (ADT) (7-9). While ADT is associated with systemic tissue changes, including genital atrophy (10,11), muscle loss and increased adiposity (12,13), as well as metabolic changes such as insulin-resistance (14), its effect on periurethral tissues is unknown. Likewise, there is a paucity of data evaluating the impact of ADT on AUS outcomes.

This is an important consideration given that urethral atrophy and device infection/erosion are common causes for repeat AUS surgery. Thus, if ADT comprises the periurethral tissues, it may alter AUS outcomes. This paucity of data poses challenges to patients and providers weighing the risks and benefits of treatment options for men with AUS and biochemical prostate cancer recurrence.

Here, we evaluated the impact of ADT exposure on AUS outcomes.
Methods

After obtaining Internal Review Board approval, we retrospectively identified 1,263 men undergoing AUS surgery between 1998 and 2014 at our institution. Of these, 518 patients had primary AUS placement and represented our study cohort. Patients were excluded from the analysis if they underwent AUS placement secondary to neurogenic bladder, were younger than 18 years, or declined research consent. All AUS devices were American Medical Systems 800 (AMS 800; American Medical Systems, Inc., Minnetonka, MN, USA) and implanted via perineal approach.

In terms of surgical technique for AUS placement in males, we use a perineal approach with placement of the urethral cuff around the proximal bulbar urethra. Following circumferential dissection of the proximal bulbar urethra between the corpora cavernosum and corpora spongiosum, the appropriate-sized cuff is selected. In cases of severely atrophic urethral tissues (measurement <3.5 cm) or difficult dissection planes (e.g., in some cases with prior pelvic radiation therapy or urethral sling placement), we use a transcorporal approach, as previously described (15,16). In addition, we prefer to implant a 61–70 cm abdominal reservoir through a separate abdominal incision. The reservoir is filled with 22 cm$^3$ isosmotic contrast to assist with identification of mechanical failure during future evaluations.

Individual medical records were abstracted for demographic information, relevant past medical history, and surgical outcomes. Surgical outcomes measured included rates of AUS removal for erosion/infection, mechanical failure, and urethral atrophy. ADT exposure was defined as documented use of GnRH agonist, GnRH antagonist, antiandrogen, or orchiectomy for >6 months in the 2 years prior to AUS placement and were therefore excluded from analysis, while 50 patients had clearly documented dates of >6 months of ADT use within the 2 years preceding AUS placement.

The retrospective design of this study precluded a comparison of secondary AUS surgery events by competing risks methodology. We identified 1,263 patients undergoing AUS surgery at Mayo Clinic between 1998 and 2014, with 518 patients having undergone primary AUS placement. Overall, 76 patients (15%) with ADT exposure were identified. Of these, 26 patients had ADT use that could not be quantified (i.e., without clearly documented start/end dates of ADT use) or had <6 months of ADT in the 2 years preceding AUS placement and were therefore excluded from analysis, while 50 patients had clearly documented dates of >6 months of ADT use within the 2 years preceding AUS placement.

Demographic and clinical characteristics of men with ADT use compared to ADT naive men are outlined in Table 1. Notably, men with ADT use had a higher incidence of pelvic radiation (P<0.0001). Of the men on ADT, 44 (88%) were managed with a GnRH agonist, 6 (12%) were managed by orchiectomy. Within the ADT cohort, 43 (86%) men were on ADT at the time of AUS placement.

Median (IQR) follow up for ADT naive men and those on ADT was 4.6 (1.2, 7.9) and 2.9 (1.7, 5.6) years, respectively. In ADT naive men, AUS removal due to infection/erosion, mechanical failure, and urethral atrophy occurred in 35, 36, and 31 men, respectively. By comparison, men with ADT use had AUS removal due to infection/erosion, mechanical failure, and urethral atrophy in four, four, and two men, respectively. The rates of device survival for any secondary surgery, removal for infection/erosion, revision for mechanical failure, and revision for urethral atrophy were not significantly different between these groups (Figures 1–4).

Multivariate analysis of secondary AUS surgery events adjusting for competing risks can be seen in Table 2. As shown, when evaluating for the impact of ADT on device outcomes, while controlling for pelvic radiation, there was...
Table 1  Patient demographics and clinical characteristics

| Characteristics                        | ADT naive | ADT    | P value |
|----------------------------------------|-----------|--------|---------|
| N                                      | 442       | 50     |         |
| Median age at AUS surgery (IQR)        | 70.9 (66.2, 75.5) | 73.3 (66.1, 78.4) | 0.06    |
| Median BMI (IQR)                       | 28.2 (26.1, 31.2) | 29.1 (26.6, 32.5) | 0.24    |
| Pelvic radiation (%)                   | 124 (28.1) | 39 (78.0) | <0.0001 |
| Robotic radical retropubic prostatectomy (%) | 22 (8.4)  | 2 (5.7)  | 0.59    |
| Radical retropubic prostatectomy (%)   | 344 (86.0) | 42 (89.4) | 0.53    |
| Diabetes (%)                           | 66 (15.0) | 9 (18.0) | 0.57    |
| Coronary artery disease (%)            | 102 (23.1) | 17 (34.0) | 0.07    |
| Cerebrovascular disease (%)            | 18 (4.1)  | 2 (4.0)  | 0.98    |
| Congestive heart failure (%)           | 7 (1.6)   | 1 (2.0)  | 0.81    |
| Hypertension (%)                       | 276 (62.6) | 37 (74.0) | 0.11    |
| AUS Cuff size (%)                      |           |        | 0.23    |
| 4 cm                                   | 9 (2.1)   | 2 (4.1)  |         |
| 4.5 cm                                 | 423 (97.0) | 47 (95.9) |         |
| 5 cm                                   | 1 (0.2)   | 0       |         |
| >5 cm                                  | 3 (0.7)   | 0       |         |
| Not available                          | 6 (1.4)   | 1 (2.0)  |         |

ADT, androgen deprivation therapy; AUS, artificial urinary sphincter; IQR, interquartile range.

Figure 1  K-M survival curve of AUS with and without >6 months of ADT use within 2 years of AUS surgery. AUS, artificial urinary sphincter; ADT, androgen deprivation therapy.

Figure 2  Cumulative incidence curve of AUS infection/erosion with and without >6 months of ADT use within 2 years of AUS surgery. AUS, artificial urinary sphincter; ADT, androgen deprivation therapy.
no difference in rates of secondary surgery for infection/erosion, mechanical failure, or urethral atrophy.

**Discussion**

We found here that ADT for >6 months within 2 years preceding AUS placement was not associated with an increased risk of secondary surgery for AUS infection/erosion, mechanical failure, or urethral atrophy. To our knowledge, this is the first study evaluating the effect of ADT on AUS explantation rates for infection/erosion, mechanical failure, and urethral atrophy.

Multiple other studies have evaluated risk factors associated with urethral tissue integrity and their association with adverse AUS outcomes. McGeady *et al.* evaluated outcomes in AUS placement in compromised urethras (prior radiation, prior AUS placement, or prior urethroplasty). This retrospective analysis of 86 AUS placements found that compromised urethras had a significantly higher AUS failure rate. Each of the features evaluated in this study significantly increased risk of failure (17). While one may suspect that ADT use, with the potential attendant risk of urethral atrophy, would also be a factor in higher AUS failure rates, we did not observe this. In another study, Brant *et al.* evaluated explantation rates in a multi-institutional cohort of 386 men and identified radiation and prior infection/erosion as risk factors for AUS erosion. Furthermore, they hypothesized that a smaller size urethra was a marker for potential tissue compromise (18). While men on ADT have a measurable loss of penile length as soon as 3 months after initiating therapy (11), our results do not suggest that ADT use translates into an increased risk of AUS removal.

ADT is known to cause genital atrophy, however ADT was not associated with adverse AUS outcomes. This finding is unique when compared to studies evaluating other

**Table 2 Multivariable survival analysis**

| Variable               | Hazard ratio (95% CI) | P value |
|------------------------|-----------------------|---------|
| AUS secondary surgery  |                       |         |
| ADT >6 months          | 0.89 (0.63–1.25)      | 0.50    |
| Pelvic radiation       | 1.31 (0.89–1.92)      | 0.17    |
| Infection/erosion      |                       |         |
| ADT >6 months          | 1.12 (0.65–1.94)      | 0.68    |
| Pelvic radiation       | 1.21 (0.61–2.42)      | 0.59    |
| Mechanical failure     |                       |         |
| ADT > 6 months         | 0.92 (0.54–1.57)      | 0.77    |
| Pelvic radiation       | 1.17 (0.61–2.42)      | 0.66    |
| Urethral atrophy       |                       |         |
| ADT >6 months          | 0.77 (0.38–1.55)      | 0.46    |
| Pelvic radiation       | 1.62 (0.81–3.27)      | 0.18    |

AUS, artificial urinary sphincter; ADT, androgen deprivation therapy.
urethral risk factors and AUS outcomes (17,18). The tissue atrophy seen in ADT does not seem to be severe enough to put patients at an increased risk of infection/erosion or urethral atrophy requiring AUS revision. Many men experience genital atrophy after robotic prostatectomy even without ADT (19-21). It may be that any additional atrophy incurred as a result of ADT after prostatectomy does not significantly worsen urethral integrity.

Limitations of this study include its retrospective design, lack of randomization, and lack of functional outcome measurements. Patients were presumed to be hypogonadal as a result of their ADT use, but regular testosterone measurements were not available to verify this. Additionally, this cohort represents patients seen at a high volume AUS surgical center, so these results may not reflect outcomes at smaller volume practices. Despite the study’s limitations, this study represents the largest cohort of men with ADT and AUS placement and the novel results have important implications for patient counseling.

ADT is not associated with higher rates of infection/erosion, mechanical failure, or urethral atrophy in men with AUS. ADT use should not discourage physicians from offering AUS to otherwise appropriate surgical candidates. ADT can be initiated in patients with a history of AUS without increasing the patient’s risk of explant for infection/erosion, mechanical failure, or urethral atrophy.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the internal review board (No. 14-007243).

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