Review Article: Oncology: Genitourinary Cancer

Literature review on the efficacy of treatments for urinary incontinence in irradiated *vs*. non-radiated men treated for prostate cancer

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Background and Objective: Prostate cancer is one of the most common non-dermatologic cancers. Management of localized prostate cancer can include surgical resection, radiation therapy, or a combination of both. One of the most common side effects of prostate cancer treatments is urinary incontinence (UI). However, the pathophysiology of incontinence secondary to radiation and surgery can differ. Therefore, the efficacy of treatments between the two cohorts may also differ. This paper aims to review the current treatment modalities for incontinence and their efficacy in irradiated patients treated for prostate cancer.

Methods: Review articles, meta-analysis articles, and cohort studies published between Jan 1990–Apr 2022 that addressed treatment efficacy/outcomes for incontinence following radiation therapy and/or prostatectomy for prostate cancer were identified and reviewed using the PubMed database, no language restrictions applied.

Key Content and Findings: Treatments for incontinence are differentiated by the type, i.e., stress UI (SUI), urge UI (UUI), and overflow UI. Generally, surgery is associated with stress incontinence, while radiation can cause urge incontinence secondary to overactive bladder (OAB). Patients may also suffer from overflow incontinence, secondary to urethral strictures or anastomotic obstruction. Stress incontinence can be conservatively managed with pelvic floor physical therapy (PFPT) and/or penile clamps. Surgical management includes urethra bulking agents (BA), male slings (MS), or an artificial urinary sphincter (AUS). Urge incontinence can be conservatively managed with PFPT and/or pharmacologic agents. Surgical management includes Botox and sacral nerve modulation. Overflow incontinence is largely caused by urethral strictures, which can be managed via a urethral or anastomotic repair.

Conclusions: The efficacy of treatment modalities for incontinence in radiated patients has not been extensively studied. The AUS and the MS are among the most studied surgical interventions for stress incontinence in radiated populations, with the AUS remaining the gold standard of treatment in both populations. Radiation has also been linked to urge incontinence, which can be managed with medication to help alleviate symptoms; surgical options are not well studied in radiated patients. Radiated patients also have a higher incidence of urethral strictures, which can cause overflow incontinence. Patients may undergo a urethroplasty but should be aware that there is a higher risk of recurrent strictures given their history of radiation.

Keywords: Radiation; incontinence; prostatectomy; prostate cancer

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Introduction

Prostate cancer is one of the most common non-dermatologic cancers. Early diagnosis and treatment are associated with long-term survival outcomes. Clinically localized prostate cancer is managed in a variety of ways, including active surveillance (AS), radical prostatectomy (RP), interstitial brachytherapy (BT), external beam radiation therapy (EBRT), or a combination of RP and radiotherapy (RT) depending on patient preference and severity of disease (1). Urinary incontinence (UI) is one of the biggest factors that patients consider when deciding between treatments. Many studies, as discussed in this review paper, have evaluated and compared the risk of urinary dysfunction after RP and/or radiation (1). While studies report a predominance of urge UI (UUI)/overactive bladder (OAB) symptoms in radiated patients, and stress UI (SUI) in patients with RP alone, mixed incontinence is also frequent (1). Overflow incontinence, secondary to urethral strictures, may also be seen in both treatment modalities (2).

A RP involves surgically removing the prostate and is one of the most common sources of male SUI. Dropkin *et al.* references reported rates of post-prostatectomy SUI (PP-SUI) ranging from 2.9–87% (3). Additionally, the article states that with the introduction of robotic surgery, this range has narrowed to 4–31% (3) with variation in prevalence attributed to differences in inclusion/exclusion criteria, definitions, and data acquisition. Sphincter insufficiency is the most important etiology of SUI following RP (2). Many studies demonstrate that within the RP cohort adverse urinary events occur within 2 years after surgery. In contrast, adverse urinary outcomes following RT accrue over time (4).

Radiation causes cell death through direct ionization and indirect free radical formation, resulting in cellular apoptosis and subsequent fibrosis. It also causes vascular damage and ischemia to the tissues via obliterative endarteritis (5). This causes dysfunction of the bladder, specifically the bladder trigone, and urethra due to impairment in blood circulation, which leads to OAB symptoms and lower urinary tract symptoms (LUTS). Irradiated patients can also experience bladder outlet obstruction (BOO) secondary to urethral strictures, with symptoms such as weak stream, hesitancy, urinary retention, and intermittency. Fridriksson *et al.* reported that RT had an increased incidence of storage LUTS, compared to the patients with RP alone (6). Boettcher *et al.*, reported 30% of patients treated with RT had OAB symptoms at 3 years, compared to the 11% of patients who had RP alone (7).

Current literature reports a wide range of UI following prostate cancer treatment. A majority of the studies, report the highest incidence of UI in patients treated with a combined treatment of RP and RT. Hosier *et al.*, reported an increased hazard of 5.44 for the development of *de novo* OAB in patients treated with both RP and RT, compared to RP alone. An increase in SUI with adjuvant RT was also reported (8). This paper aims to review the current treatment modalities for UI and their efficacy in radiated patients.

This paper is a retrospective literature review that aims to synthesize currently published data on the efficacy of treatment modalities for UI in radiated patients. We present the following article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-22-5/rc).

Methods

We searched PubMed for "prostate cancer", "urinary incontinence", " radiation", "irradiated", and "treatments" among other terms stated in *Table 1* from 1990–2022 and this returned 448 results. Of this, 112 articles were relevant to the topic of this review paper. We selected 65 papers for inclusion based on the quality and applicability of the content. The majority of papers were published in English. However, a small minority required online translation that was provided by the publishing site. Literature review papers, cohort studies, randomized control studies, and meta-analysis were reviewed. Primary review of studies that were cited in review papers, and/or the discussion or introduction of relevant papers were also reviewed.

SUI

SUI is the involuntary leakage of urine with an increase in intraabdominal pressure. Individuals with SUI may experience urinary leakage with coughing, laughing, sneezing, or vigorous effort. SUI may be secondary to insufficient strength of the pelvic floor muscles (PFMs), or sphincter dysfunction (9). Per American Urological Association (AUA) guidelines, patients who have undergone a RP should be offered pelvic floor physical therapy (PFPT) in the immediate postoperative period (Grade B). If conservative management fails, surgery can be considered for bothersome SUI at 6 months postoperative (Grade C) and should be offered at 1 year postoperative (Grade B) (10).

Table 1 The search strategy summary

Items	Specification
Date of search	August 2020
Database searched	PubMed
Search terms used	"prostate cancer" AND "radiation" (MeSH); "urinary incontinence" (MeSH); "radiation" (MeSH); "irradiated" (MeSH); "treatments", "male slings" AND "radiation"; "artificial urinary sphincter" AND "radiation" AND "urinary incontinence"; "penile clamps" AND "radiation" AND "urinary incontinence"; "pelvic floor physical therapy" AND "radiation" AND "urinary incontinence"; "urethral bulking agents" AND "radiation" AND "urinary incontinence"; "pharmacology" AND "radiation" AND "urinary incontinence"; "overactive bladder" AND "radiation" AND "urinary incontinence"; "ARGUS sling" AND "radiation" AND "urinary incontinence"; "ReMeex sling" AND "radiation" AND "urinary incontinence"; "ATOMS sling" AND "radiation" AND "urinary incontinence"; "Advance sling" AND "radiation" AND "urinary incontinence"; "ProACT" AND "radiation" AND "urinary incontinence"
Timeframe	January 1990–April 2022
Inclusion criteria	Discussed treatment modalities and their efficacy for UI following radiation therapy for prostate cancer; no language restrictions as long as translation available
Exclusion criteria	Case reports and studies/articles that did not meet the above criteria. Two studies were not reviewed, as a translation was not available

MeSH, Medical Subject Headings; UI, urinary incontinence.

Conservative management

Conservative management for SUI can include pelvic floor muscle training (PFMT), behavioral modification, and/or urethral compression (penile clamps).

PFMT

PFMT is one of the first-line therapies for SUI and OAB (11). Frequently, men with SUI have damage to, or decreased integrity of, the internal sphincter within the vesical neck, as seen in post-prostatectomy patients. PFMT is believed to increase muscle strength and blood flow to the sphincter to aid in healing, which helps in the treatment of SUI (10). It can also aid in the treatment of OAB/UUI, by teaching patients to recognize and inhibit their involuntary bladder contractions (2). Unfortunately, not everyone responds to PFMT. In a Cochrane review for post-prostatectomy incontinence (PPI), 2,736 patients were reviewed and only a moderate benefit of PFMT was found (12). A meta-analysis by Fernández *et al.*, indicated that PFMT can help a patient reach their maximum improvement threshold faster, but results plateaued with time. They indicated a RR of UI of 2.16 at 3 months, and 1.23 at 12 months when comparing PFMT to a control group (13). Limitations of the studies included differing regimens of PFPT, amount of contact with caregivers, and differing definitions of SUI. Overall, the data suggests that if performed early in post-prostatectomy patients, PFPT improves time to continence [improving quality of life (QoL)] but not overall continence at 12 months (10,12).

No studies were found evaluating PFMT in patients who underwent radiation therapy. However, a systematic review by Bernard *et al.* reported that RT can have detrimental effects on the PFM's activity and structure. Through electromyography (EMG), the contractile response of PFMs during maximal voluntary contraction was found to be diminished after RT (14). Additionally, fibrosis of the urogenital diaphragm and levator ani muscles, and a decrease in urethral length were noted following RT, with more significant changes associated with BT (15). More research needs to be conducted to evaluate if the damage to the PFMs has an effect on the efficacy of PFMT in patients who received RT treatment.

Penile clamps

Penile clamps can be an adequate option for patients with SUI within the first 6–12 months after an RP. They are also beneficial for patients who do not want or are not able to have another surgery. The compression device, which externally goes around the penis to mechanically compress the urethra, can be purchased anonymously and has been shown to increase a patient's confidence and physical activity (16). However, certain devices can cause reduced systolic velocity to the penis as well as, pain, edema, and urethra erosion (17,18). As a result, patients must de-clamp

Table 2 Conservative management of SUI

Treatment modality	AUA guideline	Comments
PFPT (2,10-15)	Grade B in the immediate prostatectomy period	No studies specifically evaluate efficacy in radiated patients
	First-line therapy in SUI and UUI/OAB	Overall, mixed data on efficacy due to differing regimens of PFPT, amount of contact with caregivers, and differing definitions of SUI
		Can increase improve time to continence (improving QoL) but not overall continence at 12 months
Penile clamps (16-18)	NA	No studies specifically evaluate efficacy in radiated patients
		Can be used in 6–12 months post-operatively
		Can increase risk of urethral erosion due to external compression
		Proper patient selection is important

SUI, stress urinary incontinence; PFPT, pelvic floor physical therapy; AUA, American Urological Association; UUI, urge urinary incontinence; OAB, overactive bladder; NA, not applicable; QoL, quality of life.

the device after 4 hours of use. Due to these risks stated above, a patient's hand dexterity and genital sensation should be considered during patient selection (16,18). A study by Moore *et al.*, compared various device models and found none were able to entirely eliminate urine loss when applied at the proper pressure (17). No study was found directly evaluating the use of penile clamps in radiated patients but given the potential for urethra erosion and insufficient resolution of UI, this therapeutic mechanism seems less desirable (*Table 2*).

Surgical management

When conservative treatment options fail, surgical options can be considered. Surgical management of SUI includes urethral bulking agents (BA), male slings (MS), and an artificial urinary sphincter (AUS). Per AUA guidelines, surgery can be considered at 6 months post-prostatectomy for bothersome SUI (Grade C) and should be offered at 1-year post-prostatectomy if symptoms are still present/bothersome. The AUS is the current gold standard of treatment for SUI, following prostate cancer treatment (Grade B), and is preferred over MS or adjustable balloons in patients who have undergone radiation therapy (Grade C) (10,19). MS and urethral BA can be considered for less invasive surgical procedures. However, in men who have undergone a RP, MS should only be considered for the treatment of mild to moderate SUI (Grade B), they should not be performed routinely on patients with severe incontinence (Grade C). Adjustable balloon devices (i.e., ProACT) can also be offered to post-prostatectomy patients with mild SUI (Grade B) (10). Per AUA guidelines, it is also important to counsel patients that decide to proceed with urethral BA that the efficacy is low, and cure is rare (Grade B) (10).

One of the most important factors in determining which procedure to pursue is the severity of incontinence. Most authors suggest using a patient's 24-hour pad weight as a degree of incontinence with the generally accepted definitions: mild (<100 g/24 h), moderate (100–400 g/24 h), and severe (>400 g/24 h) (2). In a recent US national database study, out of 1,246 men, 28.7% were treated with a urethral BA, 36.4% underwent placement of a MS and 34.9% received an AUS (20) (*Table 3*).

Urethral BA

Numerous BA have been used for the management of SUI, such as collagen, macroplastique, bulkamide hydrogel, and dextranomer/hyaluronic acid copolymer. For the treatment of PPI, the agents are injected into the submucosa of the anastomosis to help with the coaptation of the urethra. Usually, multiple injections are required for improvement and they tend to have small and short-term effects (21). The data available is scarce and contradictory. The European Association of Urology recommends only using BA in men with mild PPI seeking only short-term relief from their incontinence (21). Studies by Kuznetsov, Onur, and Imamgolu provide evidence to indicate the superiority of other surgical techniques compared to urethral BA: AUS *vs.* collagen BA (75% *vs.* 20%), InVance bone-anchored MS *vs.* collagen BA (76% *vs.* 30%) and AUS *vs.* macroplastique BA (82% *vs.* 47%) (3,21,22,40-42). No studies were found that discussed

Table 3 Surgical management of SUI

Treatment modality	Efficacy on radiated patients	Efficacy overall	Comments	AUA guideline statement
Urethral BA (3,10,21-23)	No studies found that evaluated efficacy in radiated patients	Inferior efficacy compared to AUS and sling (3,21,22) European Association of Urology recommends only using BA in men with mild incontinence seeking only short-term relief (21)	Poor outcomes, contradictory cure/improvement rate, inconsistent longevity, and ultimate lack of research in nonradiated and radiated patients make it poor long-term treatment option	Patients should be counseled that the efficacy of urethral BA is low and cure is rare (Grade B) (10)
MS				MS should be considered for mild to moderate SUI after prostate treatment (Grade B) (10); MS should not be routinely preformed for severe stress incontinence (Grade C) (10)
Adjustable				
Argus	Hübner *et al.* 77.3% dry rate in radiated patient *vs.* 79.2% dry overall (24)	Per Hübner *et al.* 79.2% dry rate overall, no statistical difference between nonradiated patients and radiated patients (24)	Few studies published, further data/research needed	
ReMeex	Limited studies Sousa-Escandón *et al.* reported lower patient satisfaction in radiated *vs.* nonradiated patients, 60% *vs.* 90.2% (26)	Success rates up to 85% reported (65% dry, 20% improved) (25)	High rate of readjustments, which require reintervention with anesthesia	
ATOMS	Irradiated patients: worst dry rates, 59% *vs.* 76%. No difference in improvement rates, 89% *vs.* 92% (27)	Overall mean dryness rate of 67%, mean improvement rate of 90% (after final adjustments) Mean satisfaction rate of 87% (27)	Explantation rate of 5.75%, complication rate of 16% (3% major) and a mean system fillings of 2.4 per patient (27) Difference in success rates possibly linked with severity of incontinence pre-procedure (28) Adjustments can be done in clinic	

Table 3 *(continued)*

Table 3 *(continued)*

Treatment modality	Efficacy on radiated patients	Efficacy overall	Comments	AUA guideline statement
Non-adjustable				
Advance	No consensus, large amount of confounding data Numerically less successful outcomes compared to the non-radiated groups, but the differences were not statistically significant (29,31-33) Bauer *et al.* and Zuckerman *et al.* studied the outcomes of only irradiated men and found a success rate of 50% and 70% (34,35) Torrey *et al.* indicated worse outcomes compared to pre-procedure (36)	Success rates up to 74% (cure rate of 58%, improvement rate of 16%) with many indicating a gradual decline in efficacy over time (29-31)	Severe pre-operative incontinence and DO have been linked to worse post-operative outcomes (30,32)	
Virtue	Limited studies Higher failure rates in patients with history of radiation (38)	At 1 year, success of 79.2% with median pad weight reduction of 88.3% regardless of baseline incontinence (3,37)	Few studies published, further data/ research needed	
ProACT	Gregori *et al.* cure rate of 66%, improvement rate of 26% and failure rate of 8% for all radiated patients (39)	Non-irradiated patients had increased cure rates compared to irradiated patients, 75% *vs.* 35.5%, respectively (39)	High initial cure rates, with poor long-term outcomes (25)	ProACTs may be offered to patients post-prostate treatment with mild SUI (Grade B) (10)
AUS	Refer to *Table 4*	Refer to *Table 4*	Refer to *Table 4*	The AUS is the current gold standard of treatment for SUI, following prostate cancer treatment (Grade B), and is preferred over MS or adjustable balloons in patients who have undergone radiation therapy (Grade C) (10,19)

SUI, stress urinary incontinence; BA, bulking agents; MS, male slings; ATOMS, adjustable transobturator male system; AUS, artificial urinary sphincter; DO, detrusor overactivity; AUA, American Urological Association.

urethral BA in radiated patients. However, Martins *et al.* reviewed 46 patients with severe incontinence and discovered that prior radiation and detrusor overactivity (DO) resulted in worse outcomes (23). In consideration of the poor outcomes, contradictory cure/improvement rate, inconsistent longevity, and ultimate lack of research in nonradiated and radiated patients, BA are not an efficacious long-term treatment modality for incontinence post-prostate cancer treatment. Additionally, per AUA guidelines, patients with SUI post-prostate cancer therapy should be counseled that the efficacy of urethral BA is low and cure is rare (Grade B) (10).

MS

While the AUS remains the gold standard for PPI, MS are popular due to their low cost, decreased invasiveness, and avoidance of mechanical manipulation to void (2). A study by Kumar *et al.*, found that when an AUS was recommended for severe incontinence, 25% of men were willing to go against the surgeon's advice in favor of a sling to avoid the mechanical element of an AUS. In contrast, all of the men who were recommended for a MS proceeded with the operation. Additionally, when given a choice, 92% of patients chose a MS over the AUS. Patients also preferred the immediate effects of the MS, when compared to the AUS, which requires post-operation healing before activation (43).

MS can be divided into adjustable and non-adjustable types, which are either positioned through a transobturator or retropubic approach. Adjustable MS include the Argus, ReMeex, and adjustable transobturator male system (ATOMS). Nonadjustable MS include AdVance and Virtue slings. Although there is no significant difference in patient satisfaction or clinical outcomes, adjustable MS have a theoretical advantage over the nonadjustable slings, as they can be easily revised to increase urethral compression in the case of persistent and/or recurrent UI, without the need for another surgery (2,25).

While various studies report conflicting data on the risk factors associated with poor outcomes, most experts report that the proper selection of a patient is principal to the procedure's success. The ideal candidate for a MS should have proper sphincter function, mild to moderate SUI, and an adequate detrusor contraction required to overcome the fixed resistance of the sling that is necessary to void (25,44).

Adjustable slings: Argus, ReMeex, ATOMS

(I) Argus

Originally, the Argus system was implanted via a retropubic approach. However, the new Argus-T model allows for transobturator placement (25). The sling can be tightened on the first days post-op through a small incision with silicone washers (21,25). A study by Hübner *et al.*, found that with a mean follow-up of 2.1 (0.1–4.5) years, the Argus system has a dry rate of 79.2%; adjustments were made in 38.6% of cases. All of the men presented with moderate-to-severe SUI, and 21.8% had undergone prior radiation therapy for prostate cancer. The study found no significant impact on the outcome, or complication rate, based on radiation history; 77.3% of the radiated patients were dry at the last follow-up. Based on this study, the Argus sling appears to be a viable option for patients with moderate-to-severe PP-SUI and irradiated patients. However, not many studies are published on the Argus sling in radiated patients and more data is required (24,25).

(II) ReMeex—suburethral sling

The ReMeex sling was introduced in 2004. It can be adjusted via an external manipulator in coordination with the subcutaneous suprapubic mechanical regulator. The reported success rates of the sling in patients with mild to severe SUI are up to 85% (up to 65% dry, 20% improved). Readjustment of the ReMeex sling is common, with up to 90% of patients requiring at least two adjustments (25). Not many studies have been published on the ReMeex sling for men with PPI, especially those with a history of radiation therapy. However, one study found a lower level of satisfaction (60%) among irradiated patients compared to non-radiated patients (90.2%) after placement of a ReMeex sling (26).

(III) ATOMS

The ATOMS sling works on a similar principle to the AUS. However, it does not circumferentially compress the urethra, and it can be adjusted postoperatively. The ATOMS sling is implanted around the bulbar urethra, taking care to preserve the bulbospongiosus, which acts as a protective layer between the urethra and implant. Tubing then connects the implant to a titanium port, which is located within the scrotum. This element allows for adjustment of the system's pressure, by modifying the volume of the cushion (25,27).

A meta-analysis by Esquina *et al.*, demonstrated a mean dryness rate of 67%, a mean improvement rate of 90% (after final adjustments), a satisfaction rate of 87%, an explantation rate of 5.75%, a complication rate of 16% (3% major) and a mean system fillings of 2.4 per patient (mean follow up 20.9 months). Studies were additionally stratified based on the proportion of radiated patients treated. Those

with >25% of irradiated patients had worst dry rates, 59% *vs.* 76% (P=0.014) but no difference in improvement rates, 89% *vs.* 92% (P=0.56). For series with a higher proportion of radiated patients, a significant difference was appreciated in pad count change, –4.43 *vs.* –3.43 pads-per-day (PPD) (P=0.026) but not for pad test change, –498 *vs.* –427 cc (P=0.48). Additionally, the complication rate was not dependent on a history of radiation, 17.8% for series with >25% irradiated patients *vs.* 15.6% with <25% irradiated patients (P=0.68) (27).

Two of the studies included in the above mentioned meta-analysis include, Hoda *et al.* (31.7% irradiated) and Seweryn *et al.* (44.7% irradiated), which reported success rates in radiated patients of 87% (58% dry, 29% improved) and 82.3% (58.8% dry, 23.5% improved), with a mean follow-up of 17.8 and 16.9 months, respectively (45,46).

Of note a long-term study by Mühlstädt *et al.*, which also reported that irradiated patients had a tendency for worse outcomes (without statistical significance) attributed the differences in success to an increase in preoperative severity of UI with which the irradiated patients presented. In the study, 82.4% of the patients with previous radiation were classified as severely incontinent, compared to 55.6% in the non-radiated cohort (28).

Overall, the ATOMS procedure is beneficial in that it requires no manipulation by the patient, there is minimal risk of mechanical failure of the device, and postoperative adjustments can be made in clinic. Furthermore, due to the design of the device (non-circumferential compression of the urethra) and mechanism of implantation (bulbospongious muscle is preserved without dissection), many series publish a lack of urethral erosion that can be seen with other devices, and low explantation rates. Therefore, this can possibly be a consideration for patients with fragile urethra mucosa (i.e., after explantation of other devices, or possibly radiation) (27). Further studies, such as randomized control trials should be considered comparing the current gold standard of the AUS (Grade B per AUA) *vs.* the ATOM sling.

Non-adjustable slings: AdVance, Virtue

(I) AdVance

Unlike the other MS, the AdVance sling is not compressive in nature. It works by repositioning the bulbomembranous urethra, the loose supporting structures of the posterior urethra, and the sphincter into the former pre-prostatectomy position (towards the bladder neck) (24,25). Critical success factors for the AdVance sling are good mobility of the urethra and adequate sphincter function. As a result, certain pre-operative tests are important to determine the candidacy of a patient for the procedure. Most experts advise that patients undergo a urodynamic study to evaluate for DO and to confirm the diagnosis of SUI. A cystoscopy should also be performed pre-operatively with a "repositioning test" (i.e., perineal pressure) to evaluate residual sphincter function during urethral repositioning, and the motility of the bladder neck and proximal urethra. Additionally, the urethral can be visually inspected for any radiation-associated alterations (i.e., scars, atrophy, poor vascularity) (34). Videofluoroscopy can be used as an alternative to the re-positioning test to demonstrate the bladder neck and proximal urethral descent (44). Finally, a 24-hour pad test is recommended to determine the incontinence severity (29,30). Most studies report that a higher preoperative pad count/weight (i.e., more severe SUI) is a risk factor for sling failure (29,33,34). As a result, Cornu *et al.* recommend a cutoff for nonadjustable slings of 200 mL on a preoperative 24-hour pad test (32). DO has also been associated with poor outcomes in relation to AdVance sling placement (30).

Published data shows AdVance sling success rates up to 74% (cure rate of 58%, improvement rate of 16%) with many indicating a gradual decline in efficacy over time (29-31). Li *et al.* reported a decrease in success from 87.3% to 62.5% after 2 years (29,47). The complications associated with the AdVance sling include transient urinary retention that usually requires a temporary catheter (14–23%), transient perineal pain (50%), wound infection, and a relatively low risk of sling removal (25,33,34).

The success of the AdVance sling in patients with a history of RT remains a highly debated topic. Published studies contradict each other with no clear resolution. Bauer *et al.*, proposed that the variance in literature outcomes could be attributable to the differences in patient selection, exclusion criteria, and differing definitions of success and continence amongst the studies (34). Many studies reported irradiated patients had numerically less successful outcomes compared to the non-radiated groups, but the differences were not statistically significant (29,31-33). Wright *et al.*, noted that the volume of leakage within the irradiated patient cohort contributed to the patients' success, stating irradiated patients with low volume leakage did well post-operatively, while radiated patients with high volume leakage did poorly (31). Bauer *et al.* and Zuckerman *et al.* studied the outcomes of only irradiated men and found a success rate of 50% and 70%, with follow-up rates of 18.8 and 15.8 months, respectively (34,35). In the study by Zuckerman, 33% of the

patients reported a decreased efficacy over time (35).

While many studies failed to show a statistically significant outcome between AdVance sling failure and a history of radiation therapy, some studies did (30,32,36). A study by Torrey *et al.*, not only showed a statistical significance between success outcomes in radiated *vs.* nonradiated cohorts, but they also reported that 42.9% of irradiated patients actually had worse incontinence following the placement of the AdVance sling, compared to 3.3% in the non-radiated group. The study indicated a failure rate of 71.4% in irradiated patients, compared to 10% in nonradiated patients. An odds ratio (OR) of 22.5 was demonstrated for no pads/reduced pads post-op when comparing patients with and without RT (36). Cornu *et al.*, also reported a significantly reduced chance of success for patients with a history of RT *vs.* non-RT men (59% *vs.* 85%, P=0.039) (32). Habashy *et al.*, used PPD as their measurement of incontinence. Overall PPD went from 2.60 (pre-operation), to 0.40 (3–6 months post-op), to 1.02 (mid-term follow-up.) However, RT was an independent predictor of poor mid-term outcome. At mid-term follow-up, men without RT history were using –1.98 PPD compared to pre-op, whereas men with a history of RT were using –0.73 PPD compared to pre-op usage. Nonradiated patients also reported a higher level of satisfaction/QoL following sling placement (30,36).

(II) Virtue quadratic sling

The Virtue sling was first introduced in 2009 and the proposed mechanism of action included distal urethral compression from two prepubic arms and ventral urethral elevation from two transobturator arms. However, the sling works via direct urethral compression against the pubic bone, similar to the InVance sling (25). Initial studies of the sling showed high rates of failure (68%) and complication (chronic pain 7%; explanation 7%, urinary retention 44%), with even higher failure rates in patients with EBRT (P=0.02) (38). Following low success rates, a new fixation technique was developed which improved outcomes. As a result of the new fixation technique, success at 12 months improved to an objective success of 79.2% with median pad weight reduction of 88.3% regardless of baseline incontinence (3,37). Few studies are published which evaluate the efficacy of the Virtue sling in irradiated patients, further studies are required for proper assessment.

Adjustable balloon device

Adjustable continence therapy (ProACT)

ProACT includes two silicone balloons that are transperineally placed under fluoroscopy, or TRUS, to the urethra-vesical junction, bilaterally. The balloons can be inflated or deflated to deliver non-circumferential pressure on the urethral lumen and provide outlet resistance, with a titratable volume that is injected into the titanium port (21,25). Literature shows high initial cure rates, with poor long-term outcomes. One study reported that after a median follow-up of 57 months, only 4.5% of patients remained dry, indicating that the ProACT is not an ideal device for long-term continence. The same study also described high complication rates, such as revision (73%), device infection, and explantation (55%) (48). Although, some studies indicate that the device can be safe and beneficial for short term relief in select patients with moderate SUI (25). Gregori *et al.*, reported a cure rate of 66%, an improvement rate of 26% and failure rate of 8% (all of which were radiated patients) (39). Non-irradiated patients had increased cure rates compared to irradiated patients, 75% *vs.* 35.5%, respectively. Ultimately, worse outcomes and an increased risk of perioperative complications were found in patients with severe UI and/or RT history (39). Per AUA guidelines, ProACTs may be offered to patients post-prostate cancer treatment with mild SUI (Grade B) (10).

AUS

While there are a variety of surgical options for patients with PPI, the AUS remains the gold standard for treatment. Per the AUA guidelines, the AUS should be considered in patients with bothersome SUI following prostate cancer treatment (Grade B), and it is preferred over MS or adjustable balloons in patients who have undergone radiation therapy (Grade C) (10). Studies have reported continence rates that can range from 55–86% following AUS placement, with high rates of patient satisfaction (2,19,49). It is currently debated if adjuvant RT adversely affects the functional outcome of an AUS prosthesis. Various studies have analyzed urinary continence outcomes following an AUS procedure, along with the infection, erosion and revision rates of irradiated *vs.* non-irradiated patients (*Table 4*). As shown in *Table 4*, the majority of recent studies indicate no significant difference of incontinence rates or complication rates (i.e., erosion, infection, revision, removal). However, due to the destructive effects of radiation therapy, Sathianathen *et al.* reported a significant difference in the presence of a complicating urethral stricture in the radiated group (62.1%) *vs.* the non-radiated group (10.4%). Radiation-induced strictures commonly affect the membranous urethra, as opposed to

Table 4 Studies evaluating the outcomes of an AUS in non-radiated *vs.* radiated males

Reference [year]	Total subjects (N)	Group	Number of men	Mean age [range] (years)	Follow up [range] (months)	Social continence rate (%)	Revision rate (%)	Erosion rate/ infection rate (%)	Comment
Wang *et al.* [1992] (50)	16	RT	16	NR	NR	87%	NR	NR/12.5%	–
Manunta *et al.* [2000] (51)	72	No RT	57	61.5 [11–87]	34.8 [6–104]	89%	16%	2%	AUS inserted within 6 months of radiation
		RT	15	68 [40–82]	39 [6–93]	53%	53%	20%	
Walsh *et al.* [2002] (52)	98	No RT	73	69	44 [5–118]	20.50%	24%	1%	Improvement: 70% non-radiated 72% radiated
		RT	18	67	47 [5–118]	11%	36%	23% (3/5 due to inappropriate urethral catheter)	
Gomha *et al.* [2002] (53)	86	No RT	58	68.3	31 [8–54]	60%	22.4%	7%	–
		RT	28	69.7	36 [15–57]	64%	25%	0%	
Lai *et al.* [2007] (54)	218	No RT	116	68.7	38.6	91%	30.20%	5.2%/6.9%	–
		RT	60	70	40.5	85%	20%	5%/3.3%	
Sathianathen *et al.* [2014] (55)	77	No RT	48	73	20 [3–65]	86.50%	12.50%	2.0%/0%	All with moderate-severe SUI; urethral stricture rate significant: 10.4% in nonradiated group, 62.1% in radiated group
		RT	29	70.9	23.3 [3–69]	86.20%	10.30%	3.4%/3.4%	
Ravier *et al.* [2015] (56)	122	No RT	61	67 [53–80]	37.3 [1–126]	75.40%	32.80%	4.9%/3.2%	–
		RT	61	70 [56–81]	NR	63.90%	29.50%	13.1%/16.3%	
Jhavar *et al.* [2017] (57)	94	No RT	63	69.6 [55–74]	75 [2–205]	73%	20%	13%/7%	–
		RT	31	NR	NR	55%	26%	20%/7%	
Guillaumier *et al.* [2017] (58)	58	No RT	35	NR	NR	80%	20%	NR	–
		RT	21	NR	NR	52%	14%	NR	
		HIFU	2	NR	NR	0%	0%	NR	

RT, radiotherapy; HIFU, high-intensity focused ultrasound; NR, not reported; AUS, artificial urinary sphincter; SUI, stress urinary incontinence.

the anastomotic contracture as seen in surgery (55). It is also important to note, that patients undergoing the AUS procedure must have the dexterity required to operate the pump.

UUI/OAB symptoms

UUI is the involuntary leakage of urine associated with a sudden uncontrollable urge to urinate. The etiology of UUI is generally related to the detrusor muscle's hyperactivity or poor compliance. Generally, radiation therapy contributes to UUI by causing poor detrusor muscle compliance, causing high intravascular filling pressures and discomfort (59). Per AUA guidelines, first-line therapy includes conservative management as stated below. Second-line therapy includes medications (i.e., antimuscarinic medications, beta-3 agonists), and third-line therapy includes intramuscular Botox injections or sacral neuromodulation (SNM) (59). Of note, some studies such as Oyama *et al.*, discuss the utility of alpha-blockers in the treatment of LUTS post-radiation (discussed below) (60).

Conservative management of UUI/OAB

Conservative management of UUI can include PFMT and pharmacotherapy. For the efficacy of PFPT, please see the

section "PFMT".

Pharmacotherapy

Impaired compliance of the bladder and DO may also contribute to the LUTS symptoms, commonly seen in patients treated for prostate cancer. Per AUA guidelines, medications (i.e., antimuscarinic medications, beta-3 agonists), are considered second-line therapy (59). Of note, some studies such as Oyama *et al.*, discuss the utility of alpha-blockers in the treatment of LUTS post-radiation (discussed below) (60). Overall, there are few published studies that have evaluated the efficacy of such drugs in irradiated patients.

Anticholinergics

Antimuscarinic drugs have been shown to reduce urgency, frequency, and UI in the general population. They work by relaxing the bladder muscles and preventing bladder spasms that signal the urge to urinate, they can also increase bladder capacity (59). Four studies were found in the literature evaluating the use of Solifenacin in PPI, with one specifically addressing the outcomes in irradiated patients. It should be noted that while solifenacin is regularly prescribed in patients with UUI, the elderly have been known to have a high risk of cognitive impairment as a side effect. These adverse effects in the elderly should be considered in patients with PPI, as they are usually older. Liss *et al.*, found that 65% of their patients reported side effects to solifenacin, with 15% stopping the medication altogether. Only 2 of the patients from this study achieved continence (21,61,62). Bianco *et al.*, randomized 640 patients in a controlled trial to evaluate the time to continence, continence rates, and the adverse side effects between the solifenacin and placebo group (63). No difference in time to continence (P=0.17) was found. However, a significant difference between the solifenacin and placebo groups was reported in relation to continence achievement by the end of the study and PPD, 29% *vs.* 21% (P=0.04), and –3.2 *vs.* –2.9 PPD (P=0.03), respectively. Furthermore, a study by Shim *et al.* reported that solifenacin significantly reduced the amount of leakage in PPI patients when they compared the pad weight between patients on solifenacin with midodrine *vs.* midodrine alone (21,64). Jaszczyński *et al.* also reported that the use of solifenacin in irradiated patients can significantly decrease the frequency of urination (–36%), nocturia (–50%), urgency episodes (–41%), and episodes of incontinence (–43%). Solifenacin was also found to increase cystometric capacity and reduce detrusor activity (61).

Bittner *et al.*, studied the use of trospium chloride in the treatment of OAB for patients having undergone BT for prostate cancer. They found that 80% of patients noted an improvement in their International Prostate Symptom Score (IPSS) score, especially urgency, following trospium chloride initiation (65).

Beta-3 agonist—mirabegron

Mirabegron, a beta-3 agonist, has been studied in the short-term relief of symptoms related to BT. At 3 months, the combination of tamsulosin and mirabegron helped improve symptoms (frequency and OAB symptoms) related to BT over tamsulosin alone (66). No other literature was found regarding beta-3 agonists and radiation therapy.

Alpha blockers—tamsulosin (flomax), alfuzosin (uroxatral) and silodosin (rapaflo)

Alpha blockers are used in the treatment of UI or OAB as they relax smooth muscles and improve urine flow. Tsumura *et al.*, compared the efficacy of silodosin, tamsulosin and naftopidil in the treatment of LUTS after BT. In this study, patients received one of the three alpha antagonists for 1 year after BT. The study reported silodosin to have greater improvements in IPSS scores compared to naftopidil at 1 month, and improved PVR, compared to tamsulosin at 6 months (67). Oyama *et al.*, demonstrated similar results, indicating better improvements in IPSS scores with silodosin compared to tamsulosin and naftopodil, up to 9 months after BT (60). However, Shimizu *et al.*, in a 12-month follow-up study, determined that the effects of silodosin are temporary. They did report silodosin significantly increased the bladder capacity when the first non-voiding contraction was seen but had no improvements in urinary flow or the BOO index (68). Ultimately, silodosin and tamsulosin have been shown to be effective in the treatment of LUTS in the first 6 months after BT, but their impact declines over time. Faithfull *et al.*, proposes that LUTS, following BT, are usually secondary to temporary swelling/obstruction caused by the implant, which is why alpha-blockers can help. It is important to note that alpha-blockers can exacerbate stress incontinence and therefore are generally not recommended following RP (69).

Surgical management of UUI/OAB

No study was found evaluating the efficacy of Botox A or SNM for UUI or OAB symptoms in irradiated patients, or PPI patients. However, in the general population, intravesical Botox has been reported to have an efficacy rate of 30–86% in treating UUI/OAB. Nevertheless, it has been shown to have limited benefits and multiple treatments are often required. Botox also carries a risk of urinary

retention (up to 5%) and clean intermittent catheterization (CIC) is required in select patients. Furthermore, repeated cystoscopy or CIC may further damage the irradiated urethra and increase the risk of cuff erosion, if AUS is planned (70). SNM is an alternative to Botox therapy. In the general population, SNM has success rates of 53% to 80%. It has not been shown to cause urinary retention and has been found to be effective in treating other forms of bladder dysfunction, such as DU with success rates of 67% to 87% (70). However, the efficacy has not been studied in irradiated patients.

Overflow incontinence/obstructive incontinence

Overflow UI in men usually occurs secondary to obstruction of the urethra via benign prostatic hyperplasia (BPH), bladder neck contracture (BNC) or urethral stricture(s). This can lead to incomplete emptying of the bladder and/or leaking of urine. Urethral strictures can be caused secondary to radiation exposure resulting in overflow incontinence and/or BOO. BOO is one of the most common adverse effects of RT treatment, with an increased risk when combined with RP; BOO usually presents with urinary retention (4). However, the lag time from radiation exposure to clinically significant urethral stricture can be many years after RT (6). At 10 years follow-up, the propensity-weighted cumulative incidence of urethral strictures and BNCs was highest among the prostatectomy with EBRT group (26%). BT with EBRT, and prostatectomy alone both had a risk of 19%, BT alone had a risk of 12%, EBRT alone carried a 10% risk and the control patients had a 7% risk (4). Overall, studies have found the incidence of urethral strictures to be 1.7% after EBRT, 1.8% after BT, and 5.2% after combined therapy (71).

The long-term incubation of urethral strictures following RT can also be demonstrated by Fridriksson *et al.* Their study demonstrated that the incidence of obstructive LUTS, in irradiated men, occurred later and incidence remained elevated to 12 years after treatment (6). A large retrospective study of 2,495 men found that 3% of patients required a channel transurethral resection of the prostate (TURP) for refractory BOO or urinary retention following BT ± EBRT. These patients had incontinence rates of 25% compared to the 3% in men with just BT (72).

High dose radiation and the dosage of radiation delivered to the apex of the prostate are independent risk factors for the development of urethral strictures. The amount of radiation delivered per treatment also appears to impact urethral stricture formation; higher intensity dosages delivered in fewer treatments have an increased risk of stricture formation (73). Other factors that are associated with an increased risk of urinary retention/obstructive incontinence after RT include prostate size, the severity of pre-operative IPSS, and the addition of neoadjuvant androgen-deprivation therapy (74).

The role of TURP prior to BT to reduce the risk of urinary retention or BOO has been a controversial topic. In recent studies, it has been reported that men undergoing TURP prior to BT initially had worse IPSS scores at 6 months, with no difference in pre-op *vs.* post-op scores at 12 months, and improved scores at long-term follow-up (2–5 years) (75).

Urethroplasty/vesicourethral anastomotic stenoses

Excision and primary anastomosis (EPA) is the most commonly performed surgical technique for radiation-induced strictures (71). Formal urethroplasties are associated with success rates of 70–86% (74). However, due to the poor vascularity of the irradiated tissue and poor wound healing, the recurrence rates of urethral strictures are as high as 30% in irradiated men, compared to the 16% recurrence rate in urethral strictures overall. Additionally, most radiation-induced urethral strictures are located in the bulbomembranous urethra, which increases the risk of *de novo* UI due to its proximity to the sphincter (5,71). New UI rates are reported in 7–50% of patients after urethroplasty. Some patients in these studies underwent AUS placement for management of their UI postoperatively (71,73). This topic is also extensively discussed in other papers in this special series.

Conclusions

UI remains a significant side effect of prostate cancer treatment. A variety of modalities can be utilized in the treatment of incontinence following a RP and/or radiation therapy. However, the efficacy of these modalities in radiated patients have not been extensively studied. The AUS and the MS are among the most studied surgical interventions for SUI in radiated populations. Given the significant and comparable positive outcomes between radiated and nonradiatied patients, the AUS remains the gold standard of treatment for SUI in both populations. Although, in certain patients, the MS may remain a viable option. Radiation has also been shown to cause symptoms of

urge incontinence. Studies have found that anticholinergics, beta-3 agonist and alpha-blockers may help to reduce these symptoms in radiated patients. Pharmacologic therapy should be considered in patients wishing to avoid surgical intervention. However, it is important to be aware of the medication side effect profile, in relation to the patient's age. Finally, patients who have undergone radiation also have a higher incidence of urethral strictures causing overflow incontinence or BOO. Patients may undergo a urethroplasty but should be aware that there is a higher risk of recurrent strictures given their history of radiation.

Ultimately, prostate cancer treatment can cause a multitude of etiologies for UI, each with different treatment interventions. Further research is required to more effectively evaluate the efficacy of these modalities on radiated patients.

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