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3rd Annual Jefferson Urology Symposium: *Men's Health Forum*

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INTRODUCTION

Recently, there hass been a strong trend for men to get their medical care services for their health issues at Men's Health Centers (MHC) in the United States. Urologists are an integral part of the comprehensive team and often head these MHCs. The care delivered at MHCs are variable and can range from a comprehensive multi-disciplinary approach in men's healthcare to a simple focus on men's common urologic issues. At many comprehensive MHCs, diagnostic testing as well as therapeutic agents may be available to rapidly resolve complex issues and help patients develop a therapeutic plan for management of their issues. In 2018 Jefferson established a comprehensive Mens Health Center at our Navy Yard facility in South Philadelphia. In our 3rd Annual Urology Symposium, ***Men's Health Forum***, we review the common urologic issues affecting men to seek specialty care at a MHC.

Historically, the most common reason men seek specialty services at the MHCs is for sexual dysfunction often associated with erectile dysfunction, Peyronie's disease, and low testosterone levels. Additionally, many men will seek care at an MHC for screening for prostate cancer, lower urinary tract symptoms associated benign prostatic hyperplasia (BPH), and urinary incontinence often associated after their treatment for prostate cancer. In our 3rd Annual Jefferson Urology Symposium, nationally recognized experts in their subspecialties discussed the topics mentioned above. The lectures included *Controversies in Testosterone Replacement*, *Innovative Strategies in Managing Peyronie's Disease*, *Surgical and Medical Management of Erectile Dysfunction*, *New Technologies for the treatment of BPH* and *Current Techniques in the Management of Post-Prostatectomy Incontinence*. In addition, there was a lecture and discussion on *Strategies in Developing a MHC*. Unfortunately, this may have been the last in person conference attended by many of the participants since it occurred just prior to the shutdown due to ongoing COVID-19 pandemic.

This supplement summarizes the data presented at the meeting with a current literature review. We hope that you find this information helpful and useful as a quick reference guide to incorporate these new technologies and techniques into your practice.

I want to thank the visiting faculty, our Jefferson Urology faculty and urology residents who contributed to the meeting. A special acknowledgement to our outstanding the Jefferson Urology Scholar senior research students who helped put this supplement together. Lastly thanks to our corporate sponsors for their support of Men's Health initiatives.

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Benign prostatic hyperplasia: an update on minimally invasive therapy including Aquablation

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Introduction: *Lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) is a common condition affecting older men. New interventional treatments have emerged and evolved over the years, each with their own distinct efficacy and safety profiles. While some have fallen out of favor, new options continue to be explored.*

Materials and methods: *We provide a review and update on minimally invasive treatment modalities for BPH, including prostatic artery embolization (PAE), Aquablation, convective water vapor thermal therapy (Rezum), and prostatic urethral lift (Urolift).*

Results: *While current urologic guidelines recommend against PAE outside of the context of clinical trials, Aquablation, Rezum, and Urolift have demonstrated excellent efficacy and durability in relieving LUTS in the BPH patient. When compared to the gold standard, transurethral resection of the prostate (TURP), these novel therapies yield equivalent or superior objective outcomes, with the additional benefit of significantly reduced sexual side effects. Additionally, Rezum and Urolift may be performed as outpatient procedures under local anesthesia, allowing for decreased hospitalizations, operative times, catheterization duration, and financial burden on the health care system.*

Conclusions: *Aquablation, Rezum and Urolift are minimally invasive surgical treatment options capable of providing rapid, significant, and durable relief of LUTS secondary to BPH. Each technique demonstrates comparable efficacy to TURP with the added advantages of preserving sexual function, decreasing patient morbidity, and limiting healthcare costs.*

Key Words: prostatic arterial embolization (PAE), Urolift, Rezum, Aquablation, benign prostatic hyperplasia (BPH), lower urinary tract symptoms (LUTS), minimally invasive therapy

Introduction

Patients with benign prostatic hyperplasia (BPH) frequently experience significant lower urinary tract symptoms (LUTS), a common myriad of urinary symptoms including urinary frequency, urgency, nocturia, incomplete bladder emptying, or weakened stream that often results in presentation to an urologist's office. While multiple medical therapies exist as first line treatment options, men who continue to have obstructive voiding symptoms, urinary tract infections, kidney injury, persistent prostatic bleeding or bladder stones may require surgical evaluation. Transurethral resection of prostate (TURP) is generally considered the standard of care for surgical management of BPH, but has been associated with both sexual and urinary comorbidities. In an effort to maximize symptom relief and patient satisfaction while minimizing negative side effects such as incontinence and sexual dysfunction (i.e. erectile dysfunction, retrograde ejaculation), multiple novel therapies have been reported. Despite the development and evolution of various treatment

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modalities, only a handful have gained popularity and stood the test of time.[1] We aim to provide a review and update on the current landscape of minimally invasive therapy for BPH, with specific focus on prostatic artery embolization, Aquablation, water vapor thermal therapy (Rezum), and prostatic urethral lift (Urolift).

Prostatic artery embolization (PAE)

PAE is a minimally invasive interventional radiological technique that can be performed under local anesthesia usually with intravenous (IV) conscious sedation. Vascular access through the femoral or radial arteries and small embolization particles are injected directly into the prostatic arteries bilaterally in order to devascularize adenomatous tissue. There is a slight advantage since it does not require any transurethral manipulation. However, the procedure requires experienced radiologists to perform as it is technically challenging with a large variation in prostatic arterial anatomy seen across patients.

In the UK Register of Prostate Embolization (UK-ROPE) study, Ray et al investigated the efficacy and safety of PAE for LUTS secondary to BPH in an indirect comparative study between PAE and TURP.[2] The prospective multicenter matched cohort study recruited 305 total patients (216 PAE, 89 TURP) across 17 UK urological/interventional radiology centers. While the results showed that PAE may provide clinically and statistically significant improvement in symptoms and quality of life (QoL), TURP demonstrated superior improvements in median International Prostate Symptom Score (IPSS) (-15.0 versus -10.0 [PAE]) and QoL (-4.0 versus -3.0 [PAE]) scores with lower overall reoperation rates (5.6% versus 19.9% [PAE]) at 12 months post-procedure. To further assess the role of PAE in BPH treatment, Zumstein et al performed a systematic review and meta-analysis with results suggesting that PAE is not as effective as established surgical therapies (TURP, open prostatectomy). However, PAE may result in fewer adverse events and side effects including patient-reported erectile function (International Index of Erectile Function 5 [IIEF5]).[3]

Although prostatic embolization may be limited or inferior compared to gold standard surgical therapies for BPH, PAE has still been shown to provide symptomatic benefit in patients with significant LUTS. Pisco et al performed a randomized, single blind, sham-controlled superiority clinical trial showing this treatment effect.[4] Patients in the PAE arm demonstrated significantly greater improvement in IPSS ($p < 0.0001$) and QoL scores ($p < 0.0001$) at 6 months post-procedure compared to the sham arm. Nevertheless, despite Food and Drug Administration (FDA) approval in 2017, PAE is considered by current AUA guidelines to be purely experimental with recommendations against its use outside of clinical and experimental trials.[5] Therefore, large-scale randomized controlled trials with longer follow up periods are necessary before PAE is considered as an alternative therapy for BPH-LUTS management to TURP.

Aquablation

Aquablation is performed using the AQUABEAM Robotic System (PROCEPT BioRobotics Inc., Redwood City, CA, USA) and was approved by the FDA in 2017. The technique involves an ultrasound-guided, robot-assisted waterjet that can precisely ablate prostatic tissue. Faber et al first described the procedure in 2015[6] with multiple updated techniques published by others.[7,8] Current AUA guidelines recommend Aquablation in symptomatic BPH patients with prostate sizes 30-80 grams.[5] Surgery requires a robotic handpiece, console, and conformal planning unit (CPU) and is performed under general or spinal anesthesia. The patient is positioned in dorsal lithotomy and the bi-planar transrectal ultrasound (TRUS) probe is positioned. TRUS is utilized before treatment to map out specific prostatic tissue to be ablated. This is performed using the mapping software, allowing for changes in depth up to 25 millimeters (mm) and angle of resection up to 225 degrees. Using the software, the desired area of ablation is outlined on a screen, with special care to avoid ablation in the area of the verumontanum. TRUS is then also used to monitor tissue resection in real-time during treatment as a targeted high velocity saline stream from the transurethrally placed robotic handpiece ablates tissue in a "windshield wiper" motion, with the computer system automatically adjusting the flow rate in each direction to alter the depth of penetration. Importantly, this procedure does not generate thermal energy, with safety mechanisms built in place to ensure that only the outlined tissue is ablated with the external sphincter protected. After completion of ablation, further hemostasis maybe needed by electrocautery via a standard cystoscope/resectoscope or light traction with a Foley catheter balloon. Post-procedure, a three-way catheter is required for continuous bladder irrigation.

Aquablation is a newer technology, lacking robust data and published literature. To our knowledge, the WATER trial represents the first randomized controlled trial studying Aquablation. This was a double-blind,

multicenter, prospective noninferiority trial comparing the safety and efficacy of Aquablation to TURP in 181 men ranging 45-80 years old with prostate sizes 30-80 grams (TRUS), moderate to severe baseline LUTS (IPSS ≥ 12), and Qmax < 15 mL/sec.[9] End points included efficacy (reduction in IPSS at 6 months) and safety (development of Clavien-Dindo persistent grade 1, or 2 or higher operative complications). Results demonstrated that Aquablation was noninferior to TURP in efficacy (mean difference in the change IPSS score at 6 months was 1.8 points greater for men undergoing Aquablation [noninferiority $p < 0.0001$]) and superior to TURP in safety (26% of men in the Aquablation group versus 42% of men undergoing TURP experienced a primary safety end point [$p = 0.0149$]). Of note, there were significantly lower rates of anejaculation in sexually active men treated with Aquablation (10% versus 36% TURP, $p = 0.0003$). This is likely due to the unique ability to carefully define the target area of prostate ablation, thereby avoiding damage near the verumontanum. Additionally, Aquablation demonstrated faster resection times (4 versus 27 minutes [TURP], $p < 0.0001$) despite similar mean total operative times (33 versus 36 minutes [TURP], $p = 0.2752$). Subgroup analysis of the WATER trial looking at men with 50-80 g prostates demonstrated significantly superior IPSS score improvement and superior safety profile with significantly lower rates of postoperative anejaculation in men undergoing Aquablation.[10] Furthermore, recently published 3-year outcome data of the WATER trial, summarized in Table 1, demonstrated similar improvements in patient symptom scores, quality of life, and uroflow parameters in the Aquablation and TURP groups, but with significantly marked reduction in postoperative anejaculation after Aquablation ($p = 0.0039$).[11]

Expanding on the results of the WATER trial, Desai et al conducted the WATER II trial to assess safety and efficacy of Aquablation in larger prostates (80-150 mL).[12] The WATER II trial defined the same efficacy and safety primary end points as the original WATER I trial, however lacked a direct comparative control arm (TURP). The initial data included 101 enrolled men and demonstrated adequate adenoma resection with a single pass in 34 patients, and with additional passes in 67 patients (mean 1.8 treatment passes). The primary safety endpoint of Clavien-Dindo grade ≥ 2 event rate at 1 month was 29.7% with bleeding complications recorded in 10 patients (9.9%), including 6 (5.9%) peri-operative transfusions. Nonetheless, the published 6-month follow up data showed that the

TABLE 1. **Three-year outcome data from the Aquablation WATER trial**

	Clinical outcomes - Mean (SD)		
Measure	**Aquablation**	**TURP**	**p value**
IPSS reduction	14.4 (6.8)	13.9 (8.6)	0.6848
IPSS reduction (Larger prostates ≥ 50 cc)	3.5 points larger reduction with Aquablation		0.0125
IPSS QoL improvement	3.2 (1.8)	3.2 (1.7)	0.7845
Changes in MSHQ-EjD	2.8 points lower with TURP		0.0008
MSHQ bother score	0.6 points higher in TURP		0.0411
IIEF-15	no statistically significant changes		not significant
Qmax improvement	11.6 (14) cc/sec	8.2 (8) cc/sec	0.0848
PVR reduction	52 (163) cc	53 (224) cc	0.9801
PSA reduction	0.9 ng/dL	1.1 ng/dL	0.5983
Anejaculation rate	11%	29%	0.0039
Urethral stricture rate	0.9%	6.2%	0.0567
Meatal/submeatal stenosis rate	2.5%	0.0%	0.5539
Retreatment rate	4.3%	1.5%	0.4219

IPSS = International Prostate Symptom Score; QoL = quality of life; MSHQ-EjD = Male Sexual Health Questionnaire-Ejaculatory Dysfunction; IIEF-15 = International Index of Erectile Function-15; Qmax = maximum urinary flow rate; PVR = post-void residual urine; PSA = prostate-specific antigen

WATER II trial met the study design goals for both safety (45.5% at 3 months, $p < 0.001$) and efficacy (mean IPSS improvement of 16.5 points at 3 months, $p < 0.001$) with significant improvements at 6 months in Qmax (10.1 mL/s increase, $p < 0.001$) and post-void residual urine (PVR) (84 mL decrease, $p < 0.0001$).[13] At 12-months follow up, effective and durable results were demonstrated with mean IPSS improvement of 17.0 points ($p < 0.0001$), mean IPSS QoL improvement of 3.3 points ($p < 0.0001$), Qmax improvement of 12.5 mL/s, and decrease in PVR of 171 mL in those with PVR > 100 at baseline.[14] Additionally, anterograde ejaculation was maintained in 81% of sexually active men. Notably, prostate-specific antigen (PSA) levels were still elevated at 12 months with mean of 4.4 ng/mL, improved from baseline mean of 7.1 ng/mL. When these 12-month results were compared to those of the WATER I trial, similar benefits were observed in both 30-80 mL and 80-150 mL prostate sizes.[15] This suggests that Aquablation may be an effective therapy independent of prostate size. However, there may be an increase in complication risk with patients with larger prostates.

Like other surgical BPH treatments, Aquablation carries the risk of blood loss and need for transfusion. In an effort to optimize benefits and minimize blood loss and transfusion rates, refined techniques have been published. Elterman et al compared athermal methods of hemostasis in preventing blood transfusions to the use of cautery across various prostate volumes following Aquablation.[16] Out of 801 patients analyzed in the study, 31 transfusions (3.9%) were reported with prostate size and method of traction contributing most to transfusion risk. In prostates ranging from 20-280 mL, an increased risk of transfusion of 0.8%-7.8% was observed when robust traction using a catheter-tensioning device (CTD) without cautery was used, whereas risk of transfusion was 1.4%-2.5% in men who underwent selective bladder neck cauterization with standard traction (catheter taped to the leg, gauze knot synched to the meatus, or no traction). This suggests an important role for transurethral cautery in hemostasis and reduction in transfusion risk.

Water vapor thermal therapy (Rezum)

The Rezum system (Boston Scientific, Marlborough, MA, USA) is a minimally invasive transurethral water vapor therapy used to treat LUTS secondary to BPH. Current AUA guidelines suggest it may be offered to patients with prostate volume less than 80 grams, especially as an effective option for preservation of erectile and ejaculatory function.[5] Another major advantage of Rezum is its ability to be performed safely as an outpatient procedure under local anesthesia.[17] The procedure is suitable for treating men over the age of 50 with evidence of efficacy in treating enlarged median lobes. However, it is contraindicated in patients with concurrent artificial urinary sphincter or implantable penile prothesis.

The Rezum system, approved by the FDA in 2015, creates water vapor (steam) thermal energy through the application of radiofrequency (RF) current against an inductive coil heater in the device's handle. This steam (103°C) can then be injected into the prostatic transitional zone. Upon contact with prostatic tissue, the steam phase shifts or condenses from vapor to liquid, releasing and convectively delivering large amounts of thermal energy (540 calories/gram). This results in disruption of prostatic cell membranes leading to immediate cell death and necrosis. Mynderse et al demonstrated that the ablative tissue was reduced in volume by 91.5% at 3 months and 95.1% at 6 months after treatment as shown on magnetic resonance imaging (MRI).[18] There was a mean reduction in whole prostate volume of about 28.9% and transition zone volume reduction of 38% on MRI at 6 months compared to baseline 1-week images. The ablative lesions were confined within the targeted treatment zone without compromising the integrity of surrounding structures. This is consistent with the thermodynamic principles of convective heating and allows for minimization of postoperative complication rates by reducing risk of injury to the bladder, rectum, or striated urinary sphincter.[19]

To our knowledge, McVary et al performed the only double-blind trial investigating Rezum in a multicenter, prospective, randomized controlled study with reported 5-year outcome data. Their data demonstrated subjective and objective improvements in LUTS observed as early as 2 weeks post-procedure with durable results through 5 years.[20-24] Previously published improvements of IPSS, IPSS-QoL, BPH Impact Index, and Qmax were sustained to 5 years with improvements of 48%, 46%, 49% and 49%, respectively ($p < 0.0001$).[24] In addition, their published 4-year data reported clinically meaningful improvements of Qmax and IPSS scores for patients who underwent treatment of enlarged median lobes when compared to those who had untreated median lobes.[23] Moreover, urinary incontinence scores (International Continence Society Male Incontinence Scale questionnaire-Short Form [ICS male IS-SF]) significantly decreased by 15% with no reported cases of sexual dysfunction at 4 years (IIEF and MSHQ-EjD scores stable and maintained).[25] Paired analysis of outcomes was also performed as part of

a crossover study to negate potential placebo effect, which revealed significantly greater improvements of IPSS, QoL, and Qmax after crossover treatments compared to that of the control period.[21] In a separate pilot study investigating safety and efficacy of Rezum, Dixon et al also demonstrated positive and evident responses as early as 1-month post-procedure with durable results at 2 years.[26,27]

In terms of safety, Rezum resulted in very few adverse events, all of which were transient and only mild-to-moderate severity. Most procedure-related adverse events occurred in the first 3 months and resolved spontaneously within 3 weeks. The most common events included dysuria (16.9%), hematuria (11.8%), hematospermia (7.4%), urinary frequency and urgency (5.9%), acute urinary retention (3.7%), and suspected urinary tract infection (3.7%).[20] Serious procedure-related adverse events were rare and included one case of bladder neck contracture and bladder calculi reported 6 months post-procedure and a second case of urosepsis after follow up cystoscopy. At 4 years follow up, there were no late occurring related adverse events, or de novo erectile dysfunction reported.[23] Mean catheterization time was reported as 3.4+/-3.2 days in a total of 90.4% (122/135) of patients in the initial study.[20] However, of these, only 32% (39/122) truly required catheterization due to unsuccessful voiding trials before discharge, whereas the remaining 68% (83/122) were at the surgeon's discretion of when to remove the catheter. As such, these results may not reflect true catherization rates in real-world practice.

In assessing Rezum's durability, it is important to consider retreatment rates. The 5-year surgical retreatment rates were reported to be 4.4%.[24] This demonstrates Rezum's advantage over other conductive thermal ablative devices such as the transurethral needle ablation (TUNA) and transurethral microwave therapy (TUMT), with reported 5-year retreatment rates of 14%-51% and 9%-21%, respectively.[28-33] Additionally, Rezum demonstrates similar, or favorable, durability compared to TURP (retreatment rates 3%-14.5% after 5 years).[34] Evidence for Rezum validates the procedure as a safe, effective, and durable BPH treatment option that can be performed under local anesthesia in an office-based setting with minimal sexual dysfunction.

Prostatic urethral lift (PUL, Urolift)

PUL using the Urolift system (NeoTract/Teleflex Inc., Pleasanton, CA, USA) is a minimally invasive technique that mechanically retracts the obstructing prostatic lobes to create a wider prostatic urethral lumen from bladder neck to the verumontanum. Urolift, approved by the FDA in 2013, is a tissue-sparing procedure using permanent nitinol and stainless steel implants to anchor luminal tissue to prostatic capsule. Implants are placed under direct cystoscopic vision in an ambulatory setting and are sized in situ to the prostatic lobe after deployment with the Urolift delivery device. While the mechanism of action is primarily mechanical, pre-clinical research on canine and cadaveric models suggests that tissue compression causes acute ischemia and focal atrophy with subsequent tissue remodeling.[35] When performing the PUL, it is recommended to start working from the bladder neck towards the verumontanum distally. Special care should be taken to avoid injury and disruption to the neurovascular bundle by deploying the Urolift implants in the anterior chamber. After implants are deployed, the procedure is considered complete when there is a continuous open channel observed on cystoscopy. Current AUA guidelines recommend its use for men with prostates less than 80 grams with a non-obstructing median lobe.[5] Men undergoing PUL report minimal sexual side affects, an additional attractive advantage over procedures designed to remove tissue. Preservation of sexual function is known to have a significant impact on quality of life, making this procedure a well-suited option for men with this priority.[36]

Another advantage of PUL is that it can be performed in an office setting under local anesthesia, including the use of topical anesthetics (lidocaine), oral sedation (benzodiazepines), and/or analgesics (acetaminophen, opioids).[37] Chilled topical lidocaine gel should be applied into the urethra for sufficient anesthetic coverage, with adequate time allowed for preoperative anesthetics to take effect.[38] If additional anesthetic is necessary, a prostatic block using 1% lidocaine injection can be performed, similar to that of a transrectal ultrasound guided prostate biopsy.

With PUL gaining popularity and use among clinicians, there is increasing scientific evidence demonstrating its safety, efficacy, and durability in treating BPH. Chin et al performed the first safety and feasibility study for PUL and demonstrated significant improvements in IPSS, QoL, BPHII and Qmax as early as 2 weeks with durable effects at 2 years follow up.[35,39] Adverse events were rare, transient, and consistent with those expected for any minimally invasive transurethral treatments. The most common device-related events were hematuria (12 patients), dysuria (11), and irritative symptoms (9), which typically resolved within 1 month. Preservation of sexual function following PUL has also been demonstrated

with improvements in MSHQ-EjD bother parameters, IIEF-5, and MSHQ-EjD function scores up to 2 years.[39]

To date, the largest, multinational, prospective randomized controlled trial investigating PUL is the L.I.F.T. study comparing PUL to a sham control with reported outcomes of up to 5 years.[40,41] At 5 years, improvements were durable in IPSS (36%), QoL (50%), BPHII (52%), and Qmax (44%), with no difference seen between Intent to Treat and Per Protocol populations. Furthermore, sexual function was stable over 5 years with no de novo, sustained erectile, or ejaculatory dysfunction.

In another randomized prospective controlled trial known as the BPH6 study, PUL was compared to the gold standard TURP with 2 year published outcomes data.[42] This study demonstrated that while significant improvements in IPSS, IPSS QoL, BPHII, and QMax were observed in both groups through 2 years, PUL was superior to TURP in quality of recovery, ejaculatory function preservation, and performance on the composite BPH6 index. However, TURP demonstrated superior change in IPSS and Qmax. There were no statistically significant differences between the study arms in IPSS QoL, and BPHII score and no significant change in ejaculatory function bother scores in either arm. Interestingly, PUL resulted in a statistically significant improvement in sleep.

Intending to simulate PUL in a day-to-day clinical setting without the rigid exclusion criteria of clinical studies, Sievert et al investigated PUL outcomes in patients with confirmed moderate-to-severe BPH-related LUTS, who were unresponsive to oral therapy, and were surgical candidates for TURP.[43] Patients were included regardless of prostate size, PVR, or history of retention, with the only exclusion criteria being presence of an obstructive median lobe. Out of 212 men, 86 chose PUL with a mean of 3.8 (2-7) implants placed in patients 38-85 years old with prostate sizes ranging 17-111 mL. Even with these looser exclusion criteria, within 1 month of surgery, 86% (74/86) of patients reported substantial symptom relief with significant improvements in Qmax, PVR, IPSS, and QoL ($p < 0.001$) that was maintained at 2 year follow up. Notably, sexual function was unchanged or improved and no Clavien-Dindo Grade ≥ 2 adverse events were reported postoperatively. However, 12.8% (11/86) of patients were retreated over the 2 year follow up period, compared to 2 year retreatment rates reported in the L.I.F.T. study (7.5%).[44] Nonetheless, the study demonstrated that PUL is an effective and promising surgical technique, with potential benefits in men with larger prostates than currently recommended in guidelines.

To better explore PUL efficacy, Eure et al retrospectively analyzed 1413 consecutive patients who received PUL with reported comparisons to the L.I.F.T. study in baseline demographics and symptom outcomes.[45] Patients in the real-world retrospective (RWR) study were modestly older ($p < 0.001$) and less symptomatic (IPSS [$p < 0.0001$], QoL [$p < 0.0001$], Qmax [$p < 0.0001$], PVR [< 0.001]) compared to those in the L.I.F.T. study. Thirty-eight patients with prostates ≥ 80 cc experienced similar absolute symptom scores throughout 6 months of follow up compared to those with smaller prostates less than 80 cc (IPSS baseline: 19.4 versus 17.6, $p = 0.1$; 1 month: 10.6 versus 9.0, $p = 0.3$; 6 months: 10.0 versus 9.6, $p = 0.8$). These results suggest that patients with prostates larger than 80 grams may still benefit from PUL. In fact, the FDA recently granted NeoTract/Teleflex Inc. an expanded indication for the use of Urolift to treat prostates up to 100 grams. However, further investigation should be performed before widespread use in larger prostates, with current AUA guidelines for surgical management of BPH still recommends an upper limit of 80 grams.[5]

In addition to prostate size, patient anatomy must be considered for men who desire PUL. Current guidelines recommend against using Urolift in men with large median lobes. This guideline has recently been challenged in the literature. Urolift is currently indicated for treating lateral lobe hyperplasia, with implants deployed at the 2 and 10 o'clock positions when viewing the transverse plane of the urethra. However, for treating median lobes, the implants are intended to affix the obstructing portion laterally to the prostatic urethra and should be deployed anterior to the 4 or 8 o'clock positions to avoid damage to the neurovascular bundles. This method opens the bladder neck and reduces the "ball-valve" effect caused by enlarged median lobes. MedLift examined the safety and efficacy of PUL in treating obstructing median lobes. Twelve-month results were recently published, demonstrating significant improvements in mean IPSS from baseline (-13.5; $p < 0.0001$), QoL (> 60%; $p < 0.0001$), BPHII (> 70%; $p < 0.0001$), and Qmax (range 90%-129% improvement; $p < 0.0001$).[46] From a safety standpoint, there was a 0% observed rate of post-procedure device-related serious complications, meeting the safety primary endpoint. Furthermore, there were no reported cases of de novo ejaculatory or erectile dysfunction. When results were compared to and combined with the original L.I.F.T. study, similar effectiveness and improvement of LUTS was found for treatment of lateral and median lobes. Further studies may help to continue expanding the indication and utility of PUL for treating median lobes in BPH.

TABLE 2. **Comparison between Rezum and Urolift**

	Water vapor thermal therapy Rezum	**Prostatic urethral lift Urolift**
Mechanism of action	• Heat • Necrosis of prostatic lobes using water vapor/steam injections • Long term: volume reduction	• Mechanical • Obstructing prostatic lobes held apart by small implants • Long term: tissue atrophy
Procedure type*	• Novel, minimally invasive surgical procedure for the treatment of BPH via a transurethral approach	
Indications*	• Moderate, to severe LUTS secondary to benign prostatic enlargement/ obstruction with underlying BPH • Failed medical management / Non-surgical candidates • Desires preservation of sexual function	
Anesthesia requirements*	• Local anesthesia (sufficient), transrectal prostatic block (if required)	
Treatment setting/location*	• Office, ambulatory surgical center, operating room (if required)	
Treated lobes*	• Lateral or Median	
Procedure time*	• Less than 1 hour	
Onset of action*	• < 1 month	
Prostate size*	• < 80 grams	
Post-procedural catheterization	• ~100% for an average of 3.4 days	• ~20% for an average of 1 day
Longest reported trial data	• 5 years	• 5 years
Randomized data	• **3** months against sham control	• 3 months against sham control • 24 months against TURP
Improvement of symptoms	• IPSS: mean 10.4 point decrease • Qmax: 4.3 mL/sec increase	• IPSS: 8-12 point decrease • Qmax: 2-5 mL/sec increase
Impact on sexual function	• No impact on erectile function • 3%-6% risk of developing ejaculatory dysfunction	• No impact on erectile function • No impact on ejaculatory dysfunction
Safety and adverse events*	• Transient, self-resolving within weeks • Mild to moderate symptoms, most commonly hematuria, dysuria, irritative symptoms	
Cost/reimbursements	• Covered by some of Medicare and most commercial plans	• Covered by all of Medicare and most commercial plans

*refers to both Rezum and Urolift

PUL offers a safe and effective office-based treatment option that can be performed using local anesthetic with minimal sexual side effects. Future studies continue to explore and expand the indications for PUL. The PULSAR (Prostatic Urethral Lift Subject With Acute Urinary Retention) clinical trial (NCT03194737) seeks to assess the feasibility and safety for using the PUL procedure in patients with acute urinary retention secondary to BPH. Additionally, the procedure is durable with a reported retreatment rate of 13.6% at 5 years.[41] Interestingly, this is a higher rate than the 5-year retreatment rate reported with Rezum (4.4%),[24] another office-based minimally invasive therapy for BPH. Further comparisons are listed in Table 2.

Conclusions

Minimally invasive surgical therapy is becoming a popular alternative to TURP or other more definitive prostate reducing procedures. Aquablation, Rezum, and Urolift are procedures that are currently approved by the AUA guidelines for the surgical management of BPH for patients with prostate sizes less than 80 grams. While PAE may be effective in treating LUTS by reducing prostate size, it is considered investigational by the current AUA guidelines. Aquablation, Rezum, and Urolift are surgical treatment options capable of providing rapid, significant, and durable relief of LUTS secondary to BPH. Rezum and Urolift procedures offer a distinct advantage over Aquablation since it can be performed in an office or an outpatient setting. Current AUA guidelines recommend each therapy for use in select patient populations. When performed in the appropriate patient, each therapy has been shown to have comparable or superior efficacy to TURP with the added advantage of preserving sexual function and decreasing patient morbidity and healthcare costs. It is important to counsel patients on all interventional options, considering prostate size and anatomy, sexual function, symptom severity, and patient expectations in order to provide successful individualized care. As urologists continue to investigate established and novel BPH treatments, the landscape for surgical BPH management will continue to evolve, providing unique opportunities for enhanced patient care. □

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Peyronie's disease: what do we know and how do we treat it?

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CHUNG PH, HAN TM, RUDNIK B, DAS AK. Peyronie's disease: what do we know and how do we treat it? *Can J Urol* 2020;27(Suppl 3):11-19.

Introduction: *Peyronie's disease is a common, benign condition characterized by an acquired penile abnormality due to fibrosis of the tunica albuginea. This may lead to penile curvature, deformity, discomfort, pain, and erectile dysfunction, resulting in emotional and psychosocial effects on patients. Therefore, it is important for urologists to thoroughly evaluate the extent of the patient's bother and discuss treatment goals, therapeutic options, and expectations.*

Materials and methods: *We provide a review of the current landscape for the diagnosis, management, and treatment of Peyronie's disease, including oral, topical, intralesional, external energy, and surgical therapies.*

Results: *The hallmark of managing Peyronie's disease is attentive patient counseling. Patients may be hesitant to discuss their symptoms unless inquired directly and may not be aware that treatments exist. It is not uncommon for Peyronie's disease to be diagnosed incidentally during a routine or unrelated healthcare visit, with reported rates of incidental diagnosis as high as 16%. Treatment options are stratified by disease phase which is defined by whether symptoms (e.g. penile deformity and discomfort) are actively changing or have stabilized. Conservative therapy is the most common recommendation during the active phase with more invasive treatments reserved for the passive phase. Conservative therapy may include oral or topical medication, intralesional injection, and external energy therapy. These treatments may also have a role in improving symptoms during the passive phase prior to undergoing more definitive surgical treatment. Surgical interventions include tunical plication, plaque incision or excision with or without grafting, and penile prosthesis implantation. Despite the variety of treatment options available to patients, each has a distinct efficacy and adverse effect profile, warranting thorough discussion to meet patients' goals and manage expectations.*

Conclusion: *Peyronie's disease is a common condition that is underdiagnosed and undertreated. Patients with Peyronie's disease will benefit from a comprehensive evaluation and in-depth counseling so that they may become familiar with the natural disease course and have appropriate expectations of each treatment option.*

Key Words: Peyronie's disease, penile deformity, penile curvature, collagenase histolyticum, penile plication, plaque excision

Introduction

Peyronie's disease (PD) is a benign condition characterized by an acquired penile abnormality due to fibrosis of the tunica albuginea. It is a common condition with an estimated prevalence reported to range from 0.5% to 20.3% within specific populations.[1,2] However, given that many patients may be reluctant or embarrassed to seek professional help from their doctors, PD is likely underdiagnosed and consequently undertreated. Often, PD is diagnosed incidentally during healthcare visits for other primary concerns, such as prostate cancer screening (reported 8.9% prevalence) or erectile dysfunction (reported 16% prevalence).[3,4] The most common inciting event is thought to be sexual activity, during which patients may experience penile buckling in the erect or semi-erect state resulting in microvascular trauma to the penile shaft.[5,6] This repetitive minor penile trauma initiates a collagen deposition cascade which results in plaque formation within the penile tunica albuginea. The plaques may be palpable or non-palpable and many patients do not recall a specific incident that preceded symptom onset.

The plaque may restrict tunica lengthening on the affected side during erection leading to curvature with possible deformity, discomfort, pain, and/or erectile dysfunction (ED). These changes in penile appearance and function often take an emotional and psychosocial toll on patients resulting in bother, depression, and relationship difficulties. Therefore, it is important for urologists to thoroughly discuss the extent of bother,

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treatment goals, therapeutic options, and expectations with the patient. In this review, we discuss the current landscape for the diagnosis, management, and treatment of PD, including medical (oral, topical, intralesional, external energy) and surgical (penile plication, plaque incision or excision, penile implant) treatments.

Diagnosis

The diagnosis of PD starts with a thorough history evaluating the presentation, duration and evolution of penile deformity and concomitant symptoms such as pain or discomfort. Bother or distress may also exist and manifest as interference with intercourse, changes in confidence, and changes in interpersonal relationships. Urologists may find utility in using the Peyronie's Disease Questionnaire (PDQ) or other PD questionnaires, which have been shown to demonstrate valuable subjective data in conjunction with objective measurements.[7,8] Past medical history and family history are important to identify known risk factors and comorbidities associated with PD, including penile fracture or trauma, Dupuytren's contracture, plantar fibromatosis, diabetes, cardiovascular disease, ED, and low testosterone; however, most patients do not report an exact inciting event.

Physical exam should focus on the genitalia to assess for penile deformity, presence of palpable abnormalities, and location of pain or discomfort. Evaluation of the penis should be performed in both flaccid and erect states with baseline measurement of penile curvature documented based on visual estimate, home photography, and/or more objective measurements performed such as utilizing a protractor or goniometer.[9] While careful history and physical examination may be sufficient to diagnose PD and move towards medical management, current American Urological Association (AUA) guidelines recommend an intracavernosal injection test with or without duplex Doppler ultrasound prior to any invasive treatment (e.g., intralesional treatments, penile prosthesis placement, or surgery).[10] The intracavernosal injection test enables urologists to better assess the extent of penile deformity, plaque(s), and pain in the erect state, while the addition of duplex ultrasound can better characterize plaque size and/or density, differentiate between calcified and non-calcified plaques, and obtain information on the vascular integrity of the penis.

It is also important to clinically identify and categorize whether the patient presents during the active or passive phase of PD as this will guide subsequent management. The active phase is characterized by dynamic and changing symptoms with patients presenting with penile and/or glanular pain or discomfort with or without erection. Penile deformity and plaque may not be fully developed, distress may be present, and erectile function may be compromised. Importantly, some patients may experience painless deformity as well as intact erectile function. While invasive treatment is not advised during this phase, urologists should carefully plan with patients to educate them on their treatment options, expectations, and goals, as well as PD natural history and timeline. The following phase is the passive phase, during which symptoms have been clinically quiescent or unchanged for ≥ 3 months based on either patient report or clinician documentation. Pain with or without erection may still be present but is less common. Also, penile deformity is now stable and no longer progressive.

Understanding the natural history of PD enables urologists to better guide patients regarding disease progression and timeline, and patient expectations. Mulhall et al performed a study that followed 246 men with newly diagnosed PD who had no medical treatment.[11] The mean duration of PD at follow up was 18 months. Their results showed that all patients who initially reported penile pain had improvement; 89% of whom reported complete resolution at follow up. However, of the men who reported penile curvature, only 12% improved (mean change 15°), 40% remained stable, and 48% worsened (mean change 22°) at follow up. These results combined with more recent studies suggest that many or most patients will have resolution or improvement of penile pain over time without intervention, while curvature and/or other deformities are much less likely to improve naturally.[12,13] Therefore, patients should be counselled accordingly, and treatment options should be discussed to target patient goals. Treatments should not be offered in patients whose PD does not cause them bother, as the risks may outweigh the benefits.

Medical treatments

Oral and topical therapies

During the active phase of PD, the only medication class recommended by current AUA guidelines are oral non-steroidal anti-inflammatory drugs (NSAIDs), which can be offered to patients in need of pain management.[10] However, it can prove difficult to anticipatorily take NSAIDs before sexual activity, due to its often-spontaneous nature. Pentoxifylline (PTX), a nonspecific phosphodiesterase inhibitor, is another oral medication with limited but promising scientific data. Smith et al reported in a retrospective cohort study

that 92% of the PTX treatment group demonstrated plaque improvement/stabilization compared to 44% in the no treatment group.[14] Coenzyme Q10 (CoQ10) has also had newer data suggesting its efficacy and safety for PD treatment. Safarinejad performed a double-blind, placebo-controlled randomized study and found significantly reduced curvature and plaque size, and increased International Index of Erectile Function (IIEF) scores in the CoQ10 group compared to placebo, with no significant effects on pain.[15] Colchicine and potassium aminobenzoate have also been studied in the literature; however, data are limited with varying results, requiring further investigation with larger randomized controlled trials. As for other oral therapies, AUA guidelines recommend against the use of vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, and combination vitamin E with L-carnitine due to the lack of compelling evidence suggesting their efficacies.[10] With any oral medication, patient compliance may prove to be an issue, thereby warranting appropriate patient counseling while determining the best treatment plan for these patients.

Limited studies have been performed evaluating topical therapies for PD. Fitch et al performed a randomized placebo-controlled pilot study which found that topical verapamil hydrochloride 15% gel improved curvature and reduced plaque compared to placebo at 9 months follow up.[16] Topical liposomal recombinant human superoxide dismutase has also been shown to improve pain, curvature, and plaque size.[17,18] Future studies with larger patient cohorts need to be performed to further investigate these potentially promising topical therapy options. Current guidelines do not suggest their use as a treatment for PD.[10]

Injection therapies

Intralesional injection therapy has been widely studied in the literature and include collagenase clostridium histolyticum (CCh), interferon-α2b, and verapamil. CCh targets collagen within plaques and works to break them down to improve curvature and deformities. Current AUA guidelines recommend CCh to be performed with clinician/patient modeling in PD patients during the passive phase with curvature 30°-90° in the dorsal, lateral, or dorsal/lateral planes with intact erectile function (with or without the use of medications).[10] These recommendations are based largely on the results of the double-blind, randomized, placebo-controlled IMPRESS (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) I and II trials which facilitated approval by the Food and Drug Administration.[19] The IMPRESS trials found significant improvement in penile curvature deformity with similar results when stratified by degree of baseline deformity (30°-60° or 61°-90°). Post hoc meta-analysis of the two trials revealed a mean 34% improvement in penile curvature in the CCh group compared to a mean improvement of 18.2% in the placebo treated men ($p < 0.0001$). Additionally, PDQ-bother score was significantly improved in the treatment group compared to placebo (-2.8 +/- 3.8 versus -1.8 +/- 3.5; $p = 0.0037$). These results strongly demonstrated the safety and efficacy of CCh for the treatment of passive phase PD, at least within the inclusion criteria specified.

Patients should be appropriately counseled on expectations, as CCh does not guarantee complete straightening of the penis. Additionally, due to the costs, side effects, and rigorous protocol, patients may elect to drop out early from treatment. Important adverse events identified included penile ecchymosis (80%), swelling (55%), pain (45%), hematoma (< 1%), and corporal rupture (< 1%). Therefore, patient reassurance and regular follow up with patients is crucial as patients are often scared after adverse events. Regarding the more serious adverse event of corporal rupture following CCh, there is ongoing discussion on whether to manage these patients similar to that of traumatic penile facture or with more conservative measures including observation and medical management.

Recent studies have further explored the utility of CCh. To investigate its safety and efficacy during the active phase, Nguyen et al performed a retrospective study and found no statistically significant differences in final change in curvature between active and passive phase patients (16.7° versus 15.6°; $p = 0.654$) and in treatment-related adverse events (11% versus 10%; $p = 0.778$).[20] These results suggest that CCh may produce similarly safe and effective outcomes in treating PD in both active and passive phases. Another study targeted shortening the treatment protocol to assess safety and efficacy. Abdel Raheem et al published their results from a prospective study of 53 PD patients who received 3 CCh injections 4 weeks apart with daily combination home modeling, stretching, and a vacuum device to mechanically stretch the plaque.[21] Their study showed significant improvements in IIEF (20.9 to 23.8; $p < 0.001$), PDQ-bother score (8.9 to 6.1; $p < 0.01$) and mean penile curvature (31.4% improvement; $p < 0.01$) after only 3 injections. These results suggest the treatment protocol may be shortened and refined with similarly effective results.

Interferon-α2b may also be a potential option and works by inhibiting fibroblast proliferation and increasing collagenase production, but may cause

adverse events including sinusitis, flu-like symptoms, and minor penile swelling. These adverse events tend to be short in duration (< 48 hours) and may be managed effectively with over-the-counter NSAIDs. Interferon-α2b has been studied for use in both active and passive phases. In a randomized prospective study, Inal et al showed in 30 men (early stage PD) that penile pain resolved after 6 months in more patients who were administered interferon-α2b alone (71%) or interferon-α2b + vitamin E (83.3%) compared to vitamin E alone (50%).[22] However, the study showed no statistically significant changes in both objective and subjective parameters. Furthermore, the study's sample size was small (10 per group) and there was no true placebo group. Current data is limited for use in treating PD during the active phase and more studies are required.

To assess the safety and efficacy of interferon-α2b during the passive phase, Hellstrom et al performed a single-blind, multicenter, placebo controlled, parallel study in a total of 117 consecutive PD patients.[23] Injections were administered biweekly for 12 weeks with the control group receiving 10 mL of saline and the treatment arm receiving $5x10^6$ U interferon-α2b. Interferon-α2b demonstrated significantly greater improvements compared to placebo in mean penile curvature (-13.5° versus -4.5°; $p < 0.01$), mean plaque size (-2.6 cm^2 versus -0.9 cm^2; $p < 0.001$), and mean plaque density assessed from questionnaires graded between 0 to 3 (-0.77 versus -0.23; $p < 0.05$). Interestingly, both the control group of this study as well as the IMPRESS trials demonstrated improvements at follow up, suggesting that the mechanical disruption performed by the needle upon injection may in and of itself assist plaque breakdown. In a separate study, Trost et al retrospectively analyzed 127 men (median history of PD of 2.0 years) treated with interferon-α2b and found that 54% responded to therapy with an overall mean improvement of 9.0° ($p < 0.001$).[24] These studies suggest that interferon-α2b may be administered to PD patients, with stronger data demonstrating its utility during the passive phase which is reflected in the current AUA guidelines.[10]

Verapamil works as a calcium channel blocker and increases collagenase activity. Adverse events may include hypotension, headache, penile bruising, dizziness, nausea, and pain at the injection site. The first published study exploring its use as an intralesional injection was performed by Levine et al in 1994 and later updated in 2002.[25,26] The authors published their experience with verapamil in 156 men during the passive phase (mean disease duration 17.7 months) with 140 patients completing treatment (10 mg biweekly injections over 6 months). Of the 140 patients, 60% had an objectively measured decrease in curvature (mean reduction 30°) with 62% reporting subjective improvement during follow up (mean 30.4 months). Positive results have also been demonstrated for use during the active phase. Arena et al showed in a study of 39 patients that 50% of those treated during the active phase experienced curvature improvement, compared to only 10.2% in the passive phase patient group.[27] These results suggest that verapamil may be more effective as an active phase treatment. Nevertheless, there have been no published studies of verapamil with placebo-controlled trials. Therefore, there is weak evidence demonstrating its efficacy and use. Due to this reason, it remains a conditional recommendation in treatment guidelines.[10]

External therapies

External energy therapies include penile low-intensity shockwave therapy (LiSWT), electromotive drug administration (EMDA) or iontophoresis, and penile traction therapy (PTT). AUA guidelines suggest that LiSWT may play a role during the active phase for pain management.[10] Palmieri et al performed a prospective, double-blind, placebo-controlled clinical trial which randomized PD patients (≤ 12 months) to receive either LiSWT (n = 50) or placebo (n = 50).[28] The study showed that at 24 weeks follow up, mean pain scores on a visual analog scale decreased more from baseline in the LiSWT group (5.5 to 0.46) than in the placebo/sham group (5.2 to 2.7). In a separate study, Palmieri et al conducted a prospective, randomized, controlled clinical trial comparing LiSWT alone to combination LiSWT + tadalafil 5 mg for management of patients with PD (< 12 months) and ED.[29] At 12 weeks follow up, mean visual analog scale score, mean IIEF, and mean quality of life score were significantly improved in both groups while mean plaque size and mean curvature were unchanged. Importantly, at 24 weeks there was a significantly higher mean IIEF and mean quality of life score in patients that received LiSWT + tadalafil, suggesting its potential use in the conservative management of patients with PD and ED during the active phase. Hatzichristodoulou et al replicated these findings of pain relief during passive phase treatment in a placebo-controlled, prospective, randomized, single-blind study.[30] Their study demonstrated a greater decrease in mean pain scores on a VAS in the LiSWT group (4 to 1.5) compared to placebo/sham (4 to 3). Additionally, a subgroup analysis of the 45 patients who experienced pain at baseline showed that 85% (17/20) of patients in the LiSWT group reported pain decrease compared to only

48% (12/25) in the placebo group (p = 0.013, RR=0.29, 95% CI 0.09-0.87). However, while these studies have demonstrated positive findings in terms of pain relief, none reported significant improvements in penile curvature or plaque size. Furthermore, Chitale et al reported no significant changes in IIEF, pain reduction, curvature, and plaque size in their prospective randomized controlled double-blind trial comparing limited shock wave therapy to sham treatment in 36 PD men (stable disease > 6 months).[31] Given its limited utility in treating only pain symptoms, which often spontaneously resolve in the natural history of PD, along with the associated risks and adverse events (i.e. localized petechial bleeding/bruising, urethral bleeding or transient hematuria, minor ecchymosis, increased pain), providers ought to thoroughly discuss the risks, benefits, and cost of LiSWT. Further investigation is needed, with current AUA guidelines giving a conditional recommendation for its use to improve penile pain while recommending against its use for reduction of penile curvature or plaque size.[10]

EMDA is an external energy therapy that involves using iontophoresis as a mechanism to transdermally deliver drug therapy to target tissues with minimal side effects. Greenfield et al performed a randomized, double-blind, placebo-controlled trial of 42 passive phase PD patients which compared EMDA verapamil to saline and found that there was no statistically significant difference between the two treatment groups at 3 months follow up.[32] Given poor evidence of efficacy, the AUA guidelines do not recommend EMDA with verapamil for treatment of PD.[10] However, scientific studies continue to explore various combination therapies with EMDA. In a prospective, randomized controlled study, Di Stasi et al looked at EMDA combination therapy with verapamil + dexamethasone.[33] After 6 weeks, the EMDA verapamil + dexamethasone study group demonstrated significant decreases in median plaque volume (824 mm to 348 mm) and in penile curvature (43° to 21°), whereas the control group demonstrated no significant changes. Additionally, the treatment group experienced significant permanent pain relief compared to transient pain relief in the control group. However, with only a single study and a small sample size, further randomized controlled studies with larger sample sizes are required before determining meaningful benefit.

PTT is a therapy that works through a mechanical means and has been studied for use in both active and passive phases. Levine et al performed the first study which used the FastSize Penile Extender (Aliso Viejo, CA, USA) in 11 men (mean PD duration 29 months), 8 of whom previously failed non-surgical treatments.[34] The traction therapy involved using the device 2-8 hours per day for 6 months. After 6 months, all men experienced reduced curvature (mean reduction 22°) and increased stretched penile length (up to 2.5 cm). Additionally, mean IIEF increased from 44.6 to 55 and there was no change in penile sensation or new ED in the treatment group. In another study, Gontero et al investigated PTT using the Andropenis (Andromedical, Madrid, Spain) penile extender in 15 patients with PD for over 12 months, curvature < 50°, and fibrous plaque diagnosed on physical exam or ultrasound.[35] Traction was performed for 5-9 hours per day for a total of 6 months. While the study reported an increase in mean stretched and flaccid penis length after 6 months (1.3 cm and 0.83 cm respectively), only 6/15 patients experienced improvement in penile curvature with nonsignificant decrease from mean baseline of 31° to 27° after 6 months (p = 0.059).

To explore the efficacy of PTT in the active phase, Martínez-Salamanca et al performed a nonrandomized prospective controlled trial comparing 55 active phase men who underwent PTT for 6 months to 41 active phase men who received no intervention.[36] Their results showed that PTT during the active phase significantly decreased mean curvature at 9 months (mean decrease 20°; p < 0.05), decreased pain (VAS score decrease from 5.5 to 2.5; p < 0.05), and improved erectile function, hardness, and ability to achieve penetration. Importantly, PTT was associated with sonographic plaque disappearance in 48% of patients and reduced the need for surgery in 40% of patients who would otherwise have been surgical candidates. While these studies demonstrated some positive results, the previously described regimens presented significant limitations. Patients may be reluctant to consider PTT due to the strict regimen with frequent and lengthy treatment times for 6 months, discomfort, and the presence of an apparatus on the penis.

As a result, the novel RestoreX (PathRight Medical Inc., Plymouth, MN, USA) PTT device was developed and studied to determine whether this therapy regimen could be made more accessible and attractive for patients.[37] In their study, Ziegelmann et al performed a randomized, controlled, single-blind, intent to treat trial in men with PD, with a total of 110 men randomized 3:1 to the PTT group (30-90 minutes per day for 3 months) or control group (no therapy for 3 months). At 3 months, PTT using RestoreX demonstrated significant improvements over the control in penile length (1.5 versus 0 cm; p < 0.001), curvature (-11.7° versus 1.3°; p < 0.01), and erectile function (IIEF-Erectile Function domain 4.3 versus -0.7; p = 0.01) among those with ED. This study demonstrated safe and effective PTT using a novel

device with a shorter treatment regimen. Additionally, Wymer et al reported in a separate study that RestoreX PTT may offer a more cost-effective method for achieving ≥ 20% curvature improvement compared with surgery or CCh.[38] While PTT has shown positive results in the scientific literature with promising developments on the horizon, current AUA guidelines do not include its use in their recommendations.[10] Further studies should be performed exploring PTT on a larger scale.

Surgical treatments

Penile plication

Historically, surgery has been considered the gold-standard treatment for PD with relatively high success rates (65%-96% achieving penile straightening).[38] Tunical plication surgery involves the placement of sutures on the side opposite of the plaque to "pull" the penis into a straighter shape. The surgery may be offered to patients who have adequate penile rigidity for coitus (with or without pharmacotherapy and/or vacuum device therapy). Several studies have been performed demonstrating its safety and efficacy as a simple and straightforward surgery with minimal chance of inducing ED or decreased sensation. Surgical technique may vary depending on plaque location and may involve midline incision, circumcision incision, or penile degloving. Furthermore, surgical plication options include corporoplasty techniques (i.e. Nesbit, Yachia) and nonincisional techniques. Various modifications have been made over the years to improve outcomes and avoid adverse events. Gholami and Lue published their results using a 16-dot plication technique in 132 consecutive patients, which demonstrated excellent and durable results with 93% of patients reporting straight erections at 6 months postoperatively.[39] Other studies have also pushed the limits in plication techniques and understanding. Once reserved only for noncomplex small degrees of penile deformity, newer studies have demonstrated the efficacy of penile plication in more complex deformities as well as those of different curvature types (dorsal, ventral, lateral). Adibi et al published their results in 43 patients with complex penile deformity (11 biplanar curvature, 32 severe curvature ≥ 60°) treated with plication surgery.[40] Their study utilized a 2 cm penoscrotal incision mobilized distally along the penile shaft without degloving. In the 11 men with biplanar curvature, median angle in the primary plane of curvature improved from 45° to 10°, with the secondary plane corrected from 35° to 5° using an average of 7 sutures. Among the 35 patients with severe curvature, plication was able to correct the median angle from 70° to 15° using an average of 11 sutures. In a separate study comparing the safety and efficacy of patients undergoing penile plication for different types of curvature, Chung et al performed a retrospective review with outcome data in patients with dorsal, ventral, and lateral curvature.[41] The study demonstrated that penile plication was safe and effective for correcting all directions of PD curvature with patient-completed satisfaction surveys at a mean of 15 months demonstrating equally high rates of satisfaction for penile curvature, penile rigidity, strength of erection, and overall satisfaction. Data revealed a similar number of sutures required for each group (8-9) to achieve similar curvature correction (37°-45°). Decreased penile length was reported subjectively, however objective length loss was small (mean length loss for all groups, 0.3 cm-0.8 cm). These studies demonstrate that plication can be a safe and effective surgical treatment option for PD in dorsal, ventral, lateral, biplanar, and severe curvatures.

Plaque incision or excision with or without grafting

Plaque incision or excision with or without grafting is an alternative surgical technique which can be offered to patients with adequate rigidity for coitus (with or without pharmacotherapy and/or vacuum device therapy). This surgery may be most applicable to patients with severe deformities, significant hourglass deformities, or plaque burden. Plaque incision or excision comes with increased risks, with studies reporting complication rates as high as 67% for postoperative ED and 20% for decreased sensitivity.[42,43] Interestingly, while these surgeries often preserve penile length, rates of penile shortening have been reported to range from 18% to 43%.[43,44] Nevertheless, the surgery has demonstrated durable and effective results with Wimpissinger et al reporting a 73% patient satisfaction rate with plaque incision and vein grafting at mean follow up of 156 months.[43] Sansalone et al also demonstrated high patient satisfaction rates of 97% at mean follow up of 20 months following plaque incision and grafting with bovine pericardium in 157 men.[45]

Grafting materials vary and include autografts, synthetic inert substances (e.g. Dacron, Gortex, silicone with silastic borders), allografts, xenografts, and collagen fleece. In a study comparing patient-perceived outcomes of plaque incision with saphenous vein grafting to corporeal plication, Kim et al reviewed the records of 67 patients at 1 year follow up.[46] Study results showed no differences between the two techniques regarding satisfactory straightness ($p = 0.13$), satisfaction with surgery ($p = 0.71$),

new use of erectile aids (p = 0.06), pain on erection (p = 0.12), or subjective penile shortening (p = 0.41). However, patients who underwent plaque incision with grafting had longer operative times (p = 0.0001) and were more likely to experience loss of rigidity (p = 0.03), inability to have intercourse (p = 0.05), and sensation loss (p = 0.0045). On the other hand, patients in the plication group were more likely to experience palpable nodules (p = 0.03). These results suggest that plication may yield similar results while maintaining fewer side effects. Nevertheless, plaque incision or excision with or without grafting provides an effective surgical option for patients with extensive plaque, severe or complex deformities, and/or for those who desire preservation of penile length.

Penile prosthesis

Penile prosthesis (PP) surgery may be offered to patients with concomitant PD with ED and/or penile deformity sufficient to impair sexual intercourse despite pharmacotherapy and/or vacuum device therapy. This surgery may offer patients a solution to both issues in one surgery as the insertion of PP may correct deformity without the need for other surgical interventions. Importantly, results from the PROPPER (Prospective Registry of Outcomes with Penile Prosthesis for Erectile Restoration) study demonstrated that inflatable PP (IPP) patients can produce high rates of patient satisfaction (> 80%) and device usage (> 88%), with decreased rates of depression (baseline 19.3% to 10.5% at 1 year [p = 0.02] and 10.9% at 2 years [p = 0.07]).[47]

Surgeons need to be prepared for adjunctive maneuvers since Levine et al determined in their single-center study that satisfactory straightening was accomplished in 4% (4/90) of patients with IPP alone while the remaining 79% (71/90) required IPP + modeling.[48] Manual modeling with the device inflation may correct deformities as the penis is bent in the direction opposite the curvature to help disrupt the plaque. Wilson and Delk published their results in a study of 138 patients treated with IPP insertion and manual modeling of the erect penis.[49] Their technique achieved successful straight, rigid erections in 86% (118/138) of patients with 90% (124/138) actually using their IPP without penile shortening or impaired sensation at mean follow up of 32 months. The most worrisome complication during modeling is urethral perforation, which occurred in their study in 4 patients (3%).

Combining IPP with penile plication or graft excision/incision have also been reported in the scientific literature, demonstrating safe, efficacious, and durable results in addressing severe curvatures and ED during the same case. Rahman et al reported complete correction in all 5 patients who received combined plication with IPP placement with no recurrence at mean follow up of 22 months.[50] Cormio et al reported their successful outcome in a patient 8 years after combined plication + IPP surgery (normal voiding function, successful intercourse, straight penis, IIEF-5 score 24).[51] In a retrospective review, Chung et al demonstrated high patient satisfaction and effective curvature correction following synchronous IPP placement and plication down from a mean of 39° to a mean < 5° in PD patients presenting with dorsal (n = 11), lateral (n = 2), and biplanar curvatures (n = 5).[52] In a study that evaluated IPP placement with tunica albuginea-relaxing incisions without grafting, Djordjevic and Kojovic reported complete penile straightening in 95% (59/62) of patients at median follow up of 35 months.[53]

Some patients who undergo IPP placement for ED have undiagnosed concomitant PD that is only identified intraoperatively due to prior history of incomplete assessment secondary to poor erection quality. Tausch et al demonstrated in a retrospective study that regardless of whether PD was identified preoperatively, synchronous plication/IPP or Yachia corporoplasty can be safely and effectively performed with satisfactory results.[54] These studies show that IPP alone, with modeling, or combined with other surgical techniques synchronously yield beneficial results.

Other potential treatments

Vacuum therapy

Vacuum therapy has been explored in the scientific literature and aims to treat PD through mechanical straightening of penile curvature. Raheem et al performed a study of 31 PD patients with mean disease duration of 9.9 months.[55] The treatment regimen involved using the vacuum device (Osbon ErecAid, MediPlus, High Wycombe, UK) for 10 minutes twice daily over a 12-week period. After 12 weeks, there was a clinically and statistically significant improvement in penile length, curvature, and pain. Notably, 21 patients demonstrated improved curvature (5°-25°), 7 had no change, and 3 had worsened curvature. Of the 31 patients, 51% (16/31) were satisfied with the outcome of therapy, with 15 undergoing subsequent surgical correction. These results suggest that vacuum therapy may be safe to use in both active and passive disease phase, may improve or stabilize PD curvature, and may reduce the number of patients requiring surgery. Nevertheless, larger studies need to be performed and current guidelines do not recommend its use as a stand-alone treatment option.[10]

Autologous platelet rich plasma

Autologous platelet rich plasma (PRP) injection have been used in other medical therapies and may be effective for use in PD by improving angiogenesis and wound healing. However, one concern with PRP is early washout, which may be avoided by using platelet rich fibrin matrix. In a preliminary study to assess safety and feasibility of platelet rich fibrin matrix injections for treatment of urologic conditions including PD, Matz et al reviewed data in 17 patients with a mean receipt of 2.1 injections per patient.[56] Of the 17 patients, 11 had PD with PRP injected with ultrasound into the plaque. While sample sizes were very small, 80% (4/5) PD patients with subsequent follow up (overall mean 15.5 months) reported subjective improvement in curvature. Adverse events in all 17 patients included mild pain (23.5%) and bruising (5.9%). To date, there exists only this one study exploring this therapy. As for stem cell therapy in treatment of PD, there have been promising published results, but only involving rat models.[57,58]

Conclusion

PD is a common condition that can potentially result in physical, emotional, and/or psychological distress. Patients may be embarrassed to seek professional help or may be unaware of their available treatment options. As a result, patients may not discuss their signs or symptoms unless directly asked. For these reasons, PD is likely underdiagnosed and therefore undertreated. Urologists should become comfortable with discussing and managing these issues with patients in order to properly diagnose patients, educate them on disease progression and timeline, target treatment goals, reach a shared decision regarding possible treatment, and manage expectations. Treatment options offered may vary based on practice resources and surgeon experience. In fact, due to the complex nature of managing and treating PD, the role may be best suited for experts with appropriate and specific experience, tools, and surgical skillset. As new medical and surgical treatments are being studied, the landscape of PD management may continue to evolve and should target the maximizing of patient satisfaction while minimizing adverse events. □

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Controversies with testosterone therapy

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KHERA M. Controversies with testosterone therapy. *Can J Urol* 2020;27(Suppl 3):20-23.

Introduction: *Over the past decade, there have been concerns with safety of testosterone therapy (TTh) in hypogonadal men. Several concerns have centered on the use of TTh and its potential link to cardiovascular (CV) events, prostate cancer, and benign prostatic hyperplasia (BPH). There has also been controversy in determining which patients are appropriate candidates for TTh and if lifestyle modification has any role in improving serum testosterone values in hypogonadal men.*

Materials and methods: *A literature review of all articles assessing testosterone and the use of TTh and the association with CV events, prostate cancer, BPH and lifestyle modification was conducted.*

Results: *Majority of patients treated with TTh today are treated off-label. Low serum testosterone levels have been associated with increased CV events. Currently, there is inconclusive evidence to support that TTh increases the risk of CV events. There is an absence of evidence linking TTh to the development of prostate cancer or worsening of BPH symptoms. Finally, lifestyle modification, such as decreasing weight and improving sleep, can improve serum testosterone levels in hypogonadal men.*

Conclusions: *Clinicians prescribing testosterone should be aware of the current controversies associated with TTh. The current literature does not suggest that there is a significant risk with TTh and prostate cancer, worsening of BPH symptoms or CV events. However, more studies, including randomized placebo-controlled trials, are needed. Finally, patients should be counseled appropriately regarding the indications for TTh and the benefits of lifestyle modification prior to initiating TTh.*

Key Words: testosterone therapy, safety, hypogonadal men

Indications for testosterone therapy

In 1981, the FDA issued a class labeling change regarding the indications to treat hypogonadal patients. The label at that time stated "Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone." The label then went on to list certain medical conditions associated with primary and secondary hypogonadism, such as orchitis or pituitary tumor, respectively. Nowhere in the label did it list symptoms, such as erectile dysfunction, low libido, or fatigue, as indications for treatment. However, the label at that time did list "idiopathic" as a one of the potential causes for hypogonadism. Therefore, if a hypogonadal patient did not have a listed medical condition, one could assume that the cause was idiopathic and the patient could be treated on-label. In 2015, the FDA issued a safety announcement stating "The U.S. Food and Drug Administration (FDA) cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone." As a result of this announcement, the FDA required that the testosterone label remove the word "idiopathic" under the listed conditions indicated for testosterone therapy (TTh). Thus, hypogonadal patients not having a medical condition known to result in hypogonadism were considered to be treated off-label at this point. Maseroli et al found that roughly 85% of patients being treated with TTh did not have a known medical condition associated with hypogonadism and thus they were being treated off-label.[1] Another concern with the indications for TTh is the use of T as monotherapy to treat erectile dysfunction. Current T guidelines recommend the use of TTh in hypogonadal men who

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have symptoms such as erectile dysfunction. In fact, Wu et al found that sexual symptoms, such as decreased morning erections, erectile dysfunction and decreased frequency of sexual thoughts, were the most sensitive and specific symptoms for identifying hypogonadal men.[2] However, the American Urological Association (AUA) Erectile Dysfunction (ED) Guidelines do not recommend the use of TTh solely for the treatment of erectile dysfunction.[3] These guidelines recommend that men with ED and testosterone deficiency who are considering ED treatment with a PDE5i should be informed that PDE5i may be more effective if combined with testosterone therapy. The AUA ED Guidelines further state "Men should be advised that testosterone therapy is not an effective mono-therapy for ED. If the man's goal is amelioration of ED symptoms, then he should be counseled regarding the need for ED therapies in addition to testosterone therapy."

Testosterone therapy and cardiovascular risk

For many years it was believed that low serum T levels increased the risk for cardiovascular (CV) events. Numerous prospective studies demonstrated that men with lower serum T levels were more likely to die at an earlier age, mainly due to increased CV events. On the contrary, there have been many published studies demonstrating that TTh may improve the risk factors for cardiovascular disease (CVD), such as obesity and metabolic syndrome. A review article by Morgentaler et al found that of the over 200 articles assessing CV risk with TTh, only four studies suggested that TTh may increase the risk of CV events.[4] Several dozen studies demonstrated beneficial effects of normal T on CV risk and mortality. Low levels of T were associated with increased risk of mortality and CVD. Finally, many studies suggested that severity of CAD was inversely correlated with serum T levels.

Based on the four studies suggesting that TTh may increase CV risk, the FDA issued a warning in the testosterone label in 2015 stating "Long term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiological studies and randomized controlled trials have been inconclusive for determining the risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, with the use of testosterone compared to non-use. Some studies, but not all, have reported an increase risk of MACE in association with the use of testosterone replacement therapy in men." It is important to note that the European Medicines Agency (EMA), which is the equivalent to the FDA in Europe, performed its own review of CV and TTh literature and declined to add any new CV warnings. In 2018, Miner et al conducted a review of all articles since the FDA label change assessing the CV risk associated with TTh.[5] These authors identified 23 studies of which none reported an increase in MACE with TTh. In fact, they found that men whose T normalized with TTh had a reduced risk of MI and death compared with men whose T levels failed to normalize.

The 2018 AUA T Guidelines offered recommendations on counseling hypogonadal patients regarding potential CV risk.[6] These guidelines recommended that clinicians should inform T deficient patients that low T is a risk factor for CV disease. The AUA T Guidelines also recommend prior to initiating treatment, clinicians should counsel patients that at this time, it cannot be stated definitively whether TTh increases or decreases the risk of CV events (e.g., myocardial infarction, stroke, cardiovascular-related death, all-cause mortality). Finally, the AUA T Guideline recommend "Testosterone therapy should not be commenced for a period of 3 to 6 months in patients with a history of CV events. Other testosterone guidelines, such as the Endocrine Guidelines, suggest waiting a minimum of 6 months before initiating TTh after a CV event. The AUA T Guidelines also recommend that prior to initiating TTh, patients at high risk for CV events should be referred for further evaluation.

Currently underway is the largest randomized placebo-controlled trial assessing the use of TTh on MACE, which includes nonfatal MI and nonfatal stroke or death due to CV causes. This study, also known as the TRAVERSE trial, is expected to enroll 6000 participants and is anticipated to be completed by June of 2022.

Testosterone and the prostate

The effects of the TTh on the prostate have been a concern to most clinicians and patients for decades. However, over the past 15 years, this paradigm has shifted. Whereas 15 years ago most clinicians believed that TTh was unsafe to give to men due to the risk of developing prostate cancer,[7] now there are clinical trials using TTh to treat men on active surveillance as well as those with metastatic prostate cancer. In 2003, Rhoden and Morgentaler evaluated the use of TTh in hypogonadal men with a history of high grade prostatic intraepithelial neoplasia (HGPIN).[8] In this study, 20 men had HGPIN and were considered high risk for developing prostate cancer. These authors found that after 1 year of TTh, men with HGPIN did not have a

greater increase in PSA or a significantly increased risk of cancer than men without HGPIN. In 2003, this article was considered controversial as there were concerns of giving TTh to men with HGPIN. Over the next 15 years, there were many studies assessing the use of TTh in men following radical prostatectomy and radiation therapy for prostate cancer.[9-11] While these studies were predominately retrospective in nature and selected for low risk patients, they did not demonstrate an increased risk of prostate cancer recurrence with TTh in these men. Further studies during this time also assessed the use of TTh in men on active surveillance with no increased risk of cancer progression.[11,12]

More recently, there have been studies assessing the use of TTh to treat men with castrate resistant prostate cancer or with low metastatic prostate cancer burden or biochemical PSA recurrence. In 2015, Schweizer et al published a series of 14 men with castrate resistant prostate cancer who were treated with high doses of TTh.[13] These patients received testosterone enanthate 400 mg IM every month for 3 months. Androgen deprivation therapy (ADT) was also continued at this time to suppress endogenous testosterone production, allowing for rapid cycling from supraphysiologic serum T levels to near castrate serum T levels. This rapid cycling was termed bipolar androgen therapy (BAT). The investigators found that BAT was well tolerated and that 50% of patients had a reduction in their PSA, and 50% of patients also had improved radiographic responses. All patients (10 of 10) demonstrated a reduction in PSA after receiving BAT, suggesting that BAT may also restore androgen receptor sensitivity. In a subsequent study by Schweizer et al, the effects of BAT in 29 men with androgen ablation naïve prostate cancer was evaluated.[14] These 29 asymptomatic hormone sensitive prostate cancer patients had either low metastatic prostate cancer burden or non-metastatic disease with a biochemical PSA recurrence. These men received 6 moths of ADT followed by 400 mg of testosterone cypionate IM every 4 weeks for 3 months. The investigators found that 59% of men had a PSA < 4 ng/dl after 18 months (primary endpoint) and that many of these men had significant improvements in quality of life and erectile function.

In light of these new publications over the past 15 years, it is not surprising that many clinicians are not as concerned with giving TTh to men with a history of prostate cancer. A study by Millar et al in 2016 sent a survey to urologists regarding their opinion and prescribing patterns on TTh in men on active surveillance for low risk prostate cancer.[15] This survey found that 96% and 84% of urologists believed that it was safe to give TTh to men with a history of a radical prostatectomy and radiation therapy, respectively. In fact, 63% of urologists believed it was safe to give TTh to men on active surveillance. It is important to note that the AUA T guidelines recommend that patients with testosterone deficiency and a history of prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of testosterone therapy.[6] However, the AUA T Guidelines do recommend that clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer.

Many urologists are still concerned that TTh will worsen lower urinary symptoms (LUTS). This concern is also fueled by the fact that current package inserts of testosterone products state "Patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH." However, currently there is no convincing data to support this claim. In fact, a review article by Delay and Kohler found that long term TTh either had no effect on LUTS or actually improved LUTS over time.[16] Other studies have also found improvements in voided volumes and post-void residuals in men taking TTh.[16] Thus, patients should be counseled appropriately regarding the use of TTh in men with BPH and LUTS.

Testosterone and lifestyle modification

Initial treatment options for many medical conditions include lifestyle modifications. For example, patients presenting with hypertension, hyperlipidemia, or obesity are first encouraged to try lifestyle modification before considering medical therapy. Lifestyle modification as well as varicocelectomy have also been shown to improve serum T levels in hypogonadal men. Camacho et al conducted a longitudinal study of 2736 men assessing changes in weight and testosterone levels.[17] These investigators demonstrated that there is a bi-directional relationship between weight and serum T levels. In this study, men who lost ≥ 15% of their body weight demonstrated a significant increase in free testosterone (FT) (51.8; 95% CI 1.7, 101.9 pmol/l). In addition, those men whose weight increased by ≥ 15% demonstrated a greater decline in FT (-47.1; 95% CI -136.9, 42.7 pmol). In a meta-analysis of 22 studies assessing the effects of weight loss (diet or surgery) on T levels, weight loss through both diet and bariatric surgery were both effective in significantly increasing serum total and free testosterone.[18] A low calorie diet resulted in a 9.8% weight loss with a 83 ng/dL increase in serum T levels. However, bariatric surgery resulted in a 32% weight loss with a 250 ng/dL increase in serum T values. Thus, weight loss seems to be an effective strategy to increasing serum T levels especially if the weight loss can be sustained.

Sleep plays an important role in maintaining normal serum T levels. Greater degrees of nocturnal hypoxia, such as seen with conditions like obstructive sleep apnea (OSA), can result in lower serum T levels due to blunting of LH levels. Improving sleep apnea, either with the use of a CPAP machine, or surgically through uvulopalatopharyngoplasty, has been shown to improve serum T levels.[19] Finally, Leproult et al demonstrated that restricting sleep to 5 hours a night for 8 nights can decrease T levels by 10% to 15%.[20]

Varicocele repair has also been shown to improve serum T values. Sathya et al conducted a prospective study of 200 men who received varicocelectomy or observation.[21] Serum T levels increased on average 80 mg/dL after varicocelectomy. Seventy-eight percent of the patients in the varicocelectomy group normalized their serum T levels compared to 16% in the control group. A meta-analysis by Li et al evaluated 814 patients undergoing varicocele repair.[22] They found that serum T levels increased approximately 100 ng/dL after varicocelectomy. While varicocele repair may increase serum T levels, it appears that this increase is modest, and currently hypogonadism is not an established indication for vaicocelectomy.

Conclusion

Clinicians prescribing testosterone should be aware of the current controversies associated with TTh. Controversies associated with TTh include potential risk of developing prostate cancer and worsening of LUTS. In addition, there are concerns of TTh potentially increasing CV risk. The current literature does not suggest that there is a significant risk with TTh and prostate cancer, LUTS, and CV events. However, more studies, including randomized placebo- controlled trials, are needed. Clinicians prescribing TTh should also be aware that the majority of hypogonadal patients currently being treated with TTh are being treated off-label. Finally, lifestyle modification, such as weight loss and improvement in sleep, as well as varicocelectomy, can improve serum T values. Patients should be counseled appropriately regarding the indications for T therapy and the benefits of lifestyle modification prior to initiating TTh. □

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An overview of biomarkers in the diagnosis and management of prostate cancer

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UHR A, GLICK L, GOMELLA LG. An overview of biomarkers in the diagnosis and management of prostate cancer. *Can J Urol* 2020;27(Suppl 3):24-27.

Introduction: *Prostate cancer is a common malignancy with highly variable clinical presentation and outcomes. Diagnosis and management remain a challenge and at times become highly controversial. Novel biomarker assays have shown promise as an adjunctive tool to aid in patient shared decision-making, risk stratification, and disease management. This presentation at the 2020 Jefferson Urology Symposium provided a review of current commonly used biomarkers for prostate cancer.*
Materials and methods: *We reviewed the current literature on the use of biomarkers in the diagnosis and treatment decisions in localized prostate cancer.*
Results: *Biomarker assays were reviewed and presented according to clinical application of each test. In the consideration of initial prostate biopsy the blood tests for PHI, and 4K Score, and urine tests PCA3, Select MDx and ExoDx are available. In the consideration of treatment versus active surveillance in the biopsy positive setting OncotypeDx, Prolaris and Decipher are available. In patients with an initial negative biopsy, 4K score, PCA3, ExoDx and the tissue biopsy based Confirm MDx assay can help guide the decision to perform repeat biopsy. In the consideration for adjuvant radiation following radical prostatectomy the most extensive literature available supports the use of Prolaris or Decipher tissue assays.*
Conclusions: *With the significant burden of men being diagnosed with prostate cancer, it is desirable to appropriately risk stratify patients to avoid unnecessary biopsies and over-treatment in low risk patients and guide appropriate treatment strategies in high risk patients. Selected biomarkers presented are useful adjunctive precision medicine tools to aid in shared decision making and to direct treatment decisions.*

Key Words: prostate cancer, biomarkers, genomics, precision medicine, active surveillance

Introduction

Prostate cancer is the second most common solid tumor cancer and the most frequent urologic malignancy in men worldwide. In 2020 it is estimated that in the United States 191,000 men will be diagnosed and approximately 33,000 men will die from the disease. It accounted for 26% of all new cancer cases in men in the United Kingdom in 2017.[1,2] The application of prostate-specific antigen (PSA) based screening has led to an increase in men undergoing prostate biopsy and has provided the opportunity for early cancer diagnoses with the risk of unnecessary biopsy resulting in over diagnosis of clinically unimportant disease.[3,4] With the widespread prevalence of prostate cancer, it is important to distinguish between patients with clinically significant cancers that require treatment and those who may be candidates for less aggressive active surveillance and avoid unnecessary treatment. While men with higher Gleason scores have been shown to have higher mortality rates, men with low risk disease have about a 3% mortality rate at 15 years after diagnosis. In patients with low risk disease who have a non-aggressive cancer, there is potential for over-treatment, often with significant, life altering side effects.[5,6] In patients who underwent radical prostatectomy, it has been reported in the literature that up to 90% of patients experienced some degree of erectile dysfunction and more than 50% reported incontinence.[7] Because of the heterogenous nature of prostate cancer, correctly identifying patients through precision medicine strategies who may be at risk for aggressive disease as well as those with indolent disease in order to guide the best management is essential.

Current clinical tools used to manage prostate cancer typically includes PSA levels, digital rectal exam (DRE) abnormalities, imaging data, age coupled with

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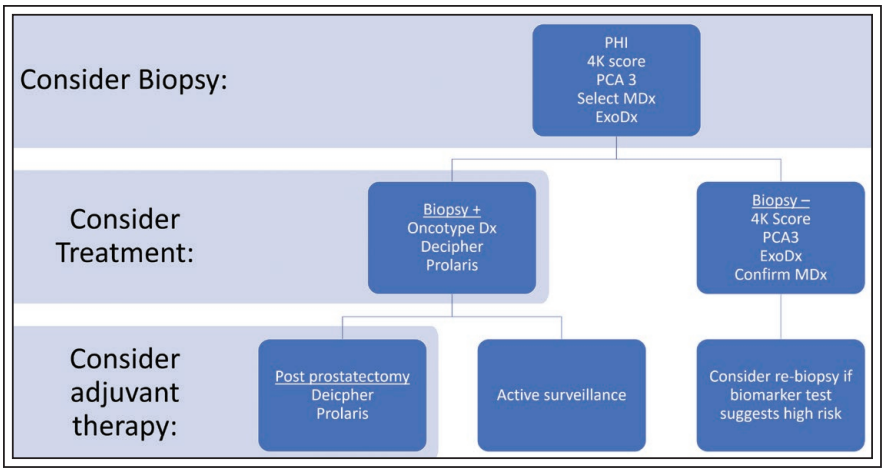

Figure 1. Clinical applications of some commonly used biomarkers in prostate cancer.

overall health and life expectancy, ethnicity, genetic predisposition and pathologic tumor characteristics. In men with elevated PSA > 4 ng/mL, up to 75% will have a negative prostate biopsy. Over the last few years biomarker testing has become popular as supplemental tools to aid in decision-making. The use of prostate cancer molecular biomarker analysis of the tumor is now included in guidelines such as in the National Comprehensive Cancer Network (NCCN) for risk stratification and staging of localized disease. A variety of molecular based tests are commercially available that may provide useful adjunctive information at various stages in the prostate cancer pathway including diagnosis, primary treatment or adjuvant therapy. The presentation, summarized here, provided a basic overview of the biomarker tests that are currently available, stratified by indication for each specific test, Figure 1.

For patients with clinical suspicion of prostate cancer who are considering biopsy

Prostate Health Index (PHI) (Beckman Coulter, Brea, California, USA) score is an FDA approved blood test that takes into account multiple proteins including PSA, free PSA and pro2PSA in a single formulated value that is more specific for prostate cancer than PSA alone. It is indicated for men with no prior biopsy who have a PSA between 4-10 ng/mL and non-suspicious DRE. It has been associated with both the presence of prostate cancer on biopsy, and a Gleason score of 4+3 or greater. It also reduces the rate of negative biopsy. PHI is reported in one of four categories correlating with increased probability of cancer.[8,9]

4K score (OPKO Health, Elmwood Park, New Jersey, USA) is a blood based test that considers 4 kallikreins (total PSA, free PSA, intact PSA, hK2) as well as clinical information (age, DRE, prior biopsy results) in an algorithm to predict aggressive prostate cancer. It is reported as a percentage of having Gleason ≥ 7 disease. It also stratifies the 20 year risk of developing metastatic disease and prostate cancer mortality. It is indicated in men considering initial biopsy or those with prior negative biopsy with ongoing clinical suspicion of cancer.[10]

Progensa Prostate cancer gene 3 (PCA3) (Hologic, Marlborough, Massachusetts, USA) is a urine based biomarker collected after DRE for use in men with suspected prostate cancer before initial biopsy or after prior negative biopsy. PCA3 is a prostate specific protein not expressed in other tissues or cancers, and is overexpressed by prostate cancer cells. Unlike PSA, it is unrelated to overall prostate size, and unchanged by 5 alpha-reductase inhibitor status. It has been suggested that for biopsy naïve patients, PCA3 > 60 increases likelihood that cancer will be detected, and a value < 20 has a high negative predictive value for cancer presence.[11-15]

Select MDx (MDxHealth, Irvine, California, USA) is a non-invasive urine methylation assay for biopsy naïve men with an elevated PSA and/or DRE that produces a likelihood of detecting prostate cancer on biopsy (illustrated by a percentage). It measures urinary mRNA levels of HOXC6 and DLX1 proteins; higher levels are associated with increased probability of having aggressive cancer. This test predicts Gleason ≥ 7 disease with 98% negative predictive value (NPV) and Gleason ≥ 8 disease with 99% NPV and has been shown to reduce the number of unnecessary biopsies by up to 53%.[3]

ExoDx IntelliScore (Exosome Diagnostics, Cambridge, Massachusetts, USA) is a validated urine test in men over 50 years old who are scheduled for initial prostate biopsy with PSA levels 2-10 ng/mL to predict the likelihood of harboring grade group 2 or greater cancer. It is a standalone result calculated solely from exosome gene expression with exclusion of clinical parameters to produce a low or high risk score. Using a validated pre-determined cut off point of 15.6, the test has a negative predictive value > 90%, and a sensitivity of 92%.[16]

Confirm MDx (MDxHealth, Irvine, California, USA) is a non-invasive test that relies on archival on prior negative prostate biopsy specimens collected within the past 30 months in patients with persistent abnormal PSA who are considering a repeat biopsy. It uses a three-gene (*GSTP1*, *APC*, and *RASSF*) PCR assay to identify an epigenetic field surrounding cancer cells and map DNA methylation which may help guide future biopsy targets. A positive result provides risk prediction for Gleason ≥ 7 disease. A negative result with no areas of DNA methylation corresponds with a 96% NPV for Gleason ≥ 7 disease and 90% NPV for all prostate cancer.[17,18]

For patients with biopsy proven prostate cancer considering active surveillance or treatment, or post prostatectomy patients considering adjuvant therapy

Oncotype DX - Genomic Prostate Score (GPS) (Genomic Health Inc., Redwood City, California, USA) is a non-invasive test on biopsy tissue used to identify the aggressiveness of disease and provide a personalized risk assessment in NCCN-defined very low risk, low risk, and intermediate risk cancer patients. The assay predicts tumor aggressiveness based on 17 gene panel (12 prostate cancer related genes and 5 housekeeping controls) within cellular communication pathways including androgen signaling, stromal response, and cellular organization and proliferation stages. Results are reported as a GPS score from 0-100 where higher scores correlate with higher risk of aggressive disease. Risk of adverse pathology (Gleason > 4+3 and/or pT3+), metastatic disease and prostate cancer death at 10 years is also predicted.[19]

Decipher (GenomeDx Biosciences, Vancouver, BC, Canada) is a genome wide test reflecting multiple biological pathways in patients with NCCN-categorized very low, low, or favorable intermediate risk cancer after a positive biopsy. It is reported as a continuum risk score from 0-1 and is independent of clinical or pathological features. It predicts the likelihood of high grade disease, 5 year metastasis, and 10 year cancer specific mortality. It has also been shown to be an independent predictor of adverse pathology and metastasis. Decipher can be performed on post radical prostatectomy specimens and is useful in patients who have adverse pathology (pT3 disease, positive surgical margins) or biochemical persistence/recurrence to help identify patients likely to benefit from adjuvant or salvage radiation. In patients with a risk score ≥ 0.4, there was a 6% versus 23% incidence of metastatic disease at 5 years after adjuvant versus salvage radiation.[20,21,22]

Prolaris (Myriad Genetics, Salt Lake City, Utah, USA) is also a tissue biopsy based test that combines RNA expression of 46 genes (31 cell cycle progression genes and 15 housekeeping controls) with clinical and pathologic features to stratify 10 year risk of metastasis after definitive treatment and disease specific mortality if managed conservatively. This test can also be useful in post prostatectomy specimens to predict 10 year risk of biochemical recurrence to help identify patients who may benefit most from adjuvant therapy.[23]

For patients with advanced disease and in the decision for systemic therapies**

AR-V7 (Genomic Health Inc., Redwood City, California, USA) is a blood-based test useful in patients with metastatic castrate-resistant prostate cancer who have previously or are currently on androgen-receptor (AR) targeted medications to help determine appropriate future systemic therapy. AR-V7 is a truncated AR circulating tumor cells that is activated independent of androgen binding, and may be present in men with previous or current AR targeted therapy. AR-V7 positive patients have poor response to AR blockade, and therefor may benefit more from chemotherapy or other non-androgen pathway therapies. In contrast, AR-V7 negative patients may respond to all therapeutic agents.[24,25]

Conclusion

Prostate cancer can be a highly variable and heterogeneous disease, making diagnosis, prognosis and treatment a challenging task. Historically, management decisions have been based on clinico-pathologic features and PSA trends. With an increasing number of aging men in the population at risk for this disease, there are significant implications of these biopsy and subsequent treatment decisions. Risk stratification will help avoid unnecessary biopsies and over-treatment in low risk patients, and guide treatment strategies in high risk patients who will derive the most benefit. Biomarkers are becoming useful adjunctive tools to help risk stratify patients and ultimately guide individual management, either at the decision for initial biopsy or in determining between active surveillance or active treatment with radiation or surgery for localized disease.[4]

Each of the biomarkers presented have unique performance characteristics and are subject to proprietary considerations. Since multiple biomarker tests currently exist with many more in development, it may be difficult for clinicians to decide on which test to use. Large scale prospective studies may help validate biomarker usage

and define clinical applicability but are not being widely adopted. One example of comparative prostate cancer biomarker testing is the recently completed Canary Prostate Active Surveillance Study (PASS).[26] This study examined the association of urinary biomarkers PCA3 and TMPRSS2:ERG (T2:ERG) with biopsy-based reclassification of men on active surveillance. Other factors to consider when deciding to use a specific biomarker are cost and insurance coverage.

The field of precision medicine is rapidly evolving, and our symposium presentation focused on some of the more commonly used FDA approved markers. There are many other biomarkers under study in areas such as liquid biopsies for circulating DNA and the use of genetic testing for prostate cancer risk assessment and management of all stages of disease.[27,28] The future of these precision oncology initiatives will rely on the identification of more patient specific biomarkers. These new markers will exploit the unique inherited and somatic genomic characteristics of the patient and his prostate cancer to further guide diagnosis and treatment in all stages of disease.

** Editors note

In May, 2020 two PARP inhibitors, rucaparib and olaparib, were approved for metastatic castrate resistant prostate cancer with a deleterious BRCA or homologous recombination repair (HRR) gene mutation. □

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The medical and surgical treatment of erectile dysfunction: a review and update

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KARAKUS S, BURNETT AL. The medical and surgical treatment of erectile dysfunction: a review and update. *Can J Urol* 2020;27(Suppl 3):28-35.

Introduction: *Erectile dysfunction (ED) is a common condition affecting more than 3 million men in the United States every year. Given the prevalence of severe co-morbidities associated with ED, the clinician must take a thorough history and conduct a diagnostic exam accordingly. The clinician should consider that every man who presents with ED is unique with regards to his symptoms, degree of stress, associated health conditions, sexual relationship quality, and sociocultural context. The clinician determines an appropriate treatment plan that is aligned with the patient's and his partner's priorities and values, adopting a shared decision-making process. The clinician must possess sufficient knowledge of all available treatment modalities and be able to offer to all treatment options that are not contraindicated, regardless of invasiveness or irreversibility, as potential first-line treatments.*

Materials and methods: *Current medical and surgical treatment options in ED, including novel and innovative therapeutic options, were reviewed.*

Results: *There are a variety of treatment options for the management of ED, both medical and surgical. The most commonly considered medical treatment option is phosphodiesterase type 5 inhibitors (PDE5i), which has been proven successful in up to 65% of men with ED. Other treatment options, such as vacuum erection device or intracavernosal injection therapy using vasodilator medications, should be considered in men who have contraindications or are non-responders to PDE5i. Surgical treatment of ED using penile implants has undergone multiple improvements over the years with low device failure and infection risks providing an effective and satisfying treatment alternative. Other therapies, such as penile vascular surgery, extracorporeal shock wave therapy, and intracavernosal stem cell therapies, are novel and should be considered investigational due to lack of evidence supporting their long term safety and efficacy.*

Conclusions: *The management of ED requires considerations of all aspects of the patient's health and involvement of the patient and his partner in the decision-making process. Patients should be informed of all available treatment options and be able to choose the option that is most aligned with their condition, goals, and risk tolerance. There are medical and surgical therapeutic options available in the management of ED, all supported with the best level of evidence. Novel therapeutic options are promising; however, randomized controlled trials with long term follow up periods and larger sample sizes are needed to support their safety and efficacy.*

Key Words: sexual dysfunction, phosphodiesterase 5 inhibitors, vacuum erection device, intracavernosal injection, penile prosthesis

Introduction

Erectile dysfunction (ED) is not an uncommon condition that has a significant impact on the quality of life of men and their partners worldwide. Over 150 million men globally were affected by ED based on estimations in 1995, and this number is predicted to reach approximately 322 million by 2025.[1] The reason for the increase in the global prevalence of ED is believed to be due to the increased prevalence of associated risk factors such as the global aging population, obesity, sedentary lifestyle, cardiovascular diseases, diabetes, depression, and BPH.[2-4] ED prevalence is usually underestimated in many developing countries because help-seeking is rare among men with ED due to its associated stigma, and it is a non-life-threatening condition. However, previous research indicated that the presence of ED is a predictor of cardiovascular disease (CVD), dementia, and all-cause mortality.[5,6] The most common underlying mechanism of ED is vascular, and symptoms of ED may precede a CVD event by up to 5 years, and the degree of ED correlates with the severity of CVD.[7]

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Given the high prevalence of ED and the high number of severe co-morbidities associated with it, the clinician must be able to conduct a valid diagnostic exam and offer available treatment options to patients. A guideline has been published by the American Urological Association (AUA) last updated in 2018 to provide a clinical strategy for the clinicians in the diagnosis and management of ED.[8] Based on the AUA guideline for ED, men presenting with symptoms of ED should undergo a complete history and physical examination. Validated questionnaires such as the International Index of Erectile Function (IIEF), Erection Hardness Scale (EHS), and Sexual Health Inventory for Men (SHIM) are recommended to assess the severity of ED, to measure treatment effectiveness, and to guide future management. However, none of these questionnaires is valid for sexually inactive men. Laboratory tests such as fasting blood glucose, lipid profile, urinalysis, complete blood count, TSH, and serum testosterone can be done at the initial visit if the patient has an underlying condition.

Using the shared decision-making process as a cornerstone for care, all patients along with their partners, if possible, should be informed of all treatment modalities that are not contraindicated, regardless of invasiveness or irreversibility, as potential first-line treatments. For each treatment option, the clinician should ensure that the man and his partner have a full understanding of the benefits and risks/burdens associated with that choice. Additionally, the clinician needs to be aware of the health literacy of the patient, as well as social, cultural, religious factors.

Every man who presents with ED is unique based on his symptoms, degree of stress, associated health conditions, relationship quality, and sociocultural context. All treatment options that are not medically contraindicated should be considered; however, the clinician evaluating all these issues should determine an appropriate treatment that is aligned with the man and his partner's priorities and values. Additionally, ED occurs in a complex psychosocial context related to masculinity and sexuality. The patient should be strongly advised to receive psychotherapy or psychosexual counseling to promote treatment adherence, reduce performance anxiety, and integrate treatments into a sexual relationship.

This current article aims to conduct a review of current medical and surgical treatment options, as well as novel and innovative therapeutic options in ED.

Current treatment modalities for ED

ED has been significantly associated with general health status. Lifestyle modifications such as weight loss, physical exercise, a healthy diet, smoking cessation, and reducing alcohol intake should be discussed with any man with ED. Lifestyle modifications show their effect via amelioration of endothelial dysfunction by inducing NO production, decrease in oxidative stress, reduced insulin resistance and lowering inflammatory state associated with metabolic diseases.[9]

In addition to lifestyle modifications, the AUA guideline acknowledges noninvasive and invasive treatment options, including oral phosphodiesterase type 5 inhibitors (PDE5i), vacuum erection devices (VED), intracavernosal injections (ICI), intraurethral suppositories, and penile prostheses for ED. PDE5i are usually suggested by clinicians as first-line therapy due to their clinical efficacies and safety profiles. However, any of these treatment options can be chosen as first-line therapy by patients.

Additional testing and specialist referral are typically options reserved for cases where initial treatments failed. Other indications for specialist referral include: (1) younger patients with a history of pelvic or perineal trauma, (2) patients with significant penile deformity, (3) complicated endocrinopathies, (4) complicated psychiatric or psychosexual disorders, (5) need for vascular or neurosurgical intervention, and (6) medicolegal reasons.

Novel approaches to treat ED, including but not limited to extracorporeal shock wave therapy (ESWT), penile vascular surgeries, stem cell therapies (SCT), and platelet-rich plasma (PRP), have shown promising initial results and may become more commonly suggested by clinicians for ED treatment.

Oral PDE5i

Oral PDE5i, including sildenafil, tadalafil, vardenafil, and avanafil, have been preferred as first-line therapy by clinicians due to their clinical efficacies and safety profiles. Up to 65 % of men who are taking PDE5i show a good response after initial treatment.[10,11] However, the underlying pathophysiology of ED, such as post radical prostatectomy or radiation, and co-morbidities such as diabetes can decrease the success rate of PDE5i.[12-15]

Nitric oxide (NO) increases the cGMP levels in corpus cavernosum smooth muscle cells following reflexogenic or psychogenic stimulation resulting in penile erection by smooth muscle relaxation. PDE5i prevent cGMP degradation by inhibiting the PDE5 enzyme and keeping cGMP levels high.[16] It is important to highlight that PDE5i are not effective without the induction of penile erection via NO release. PDE5i do not work sufficiently in diabetic neuropathy or cavernous nerve damage from pelvic surgeries, such

as radical prostatectomy or other pelvic surgeries, due to lack of neuronal NO release.

PDE5i are contraindicated in patients who are using nitrates due to leading potentially serious fall in systemic blood pressure. There is a possible drug-drug interaction between PDE5i and anti-hypertensive agents such as alpha-blockers or potent CYP3A inhibitors such as azole antifungals, antiretroviral protease inhibitors, macrolide antibiotics, and anti-depressants.[17] The lowest possible starting dose should be prescribed, and the dosage should be titrated by close monitoring.[18]

Although PDE5i possess different biochemical and pharmacologic properties, all have similar efficacy in the general ED population. Sildenafil and vardenafil are similar with regards to the duration of action being up to 10-12 hours, with a peak absorption of 30-60 minutes. A high-fat meal decreases their efficacies, and the medication should be taken 1 hour before eating or 2 hours after eating to maximize absorption. Avanafil is absorbed in 15-30 minutes with a duration of action for up to 6 hours. The half-life of tadalafil is longer (17 hours), and its duration of action is up to about 24-36 hours with a longer onset of action of 60-120 minutes. Additionally, both avanafil and tadalafil are not affected by food intake. Tadalafil is the only oral medication approved by the U.S. Food and Drug Administration (FDA) to be used daily to treat ED, as well as to treat lower urinary tract symptoms in benign prostatic hyperplasia.

Dose titration of PDE5i is a key step to providing optimal efficacy while minimizing adverse effects. The man and his partner should be counseled with administration of an initial treatment dose, which may need to be decreased to alleviate unacceptable adverse effects or increased due to inadequate response. The variations in dose-response effects across PDE5i medications are small, non-linear, and generally not clinically significant. However, a clinical trial comparing dose-response effects of sildenafil 10, 25, and 50 mg reported variations on hardness, frequency and duration of erections, and frequency of sexual intercourse. Still, none of these alternative dosages altered the number of attempts at intercourse.[19]

When initiating treatment with PDE5i, the dosage can be chosen at mid-range; however, clinicians may consider initiating therapy at a higher dose for more severe ED when it is due to diabetes, radiation, or prostatectomy. On another note, penile rehabilitation with PDE5i remains unproven, and the early use of PDE5i following radical prostatectomy may not improve spontaneous unassisted erectile function.

If the patient shows symptoms and signs of testosterone deficiency with low total testosterone levels (< 300 ng/dL), PDE5i treatment for ED may require combination therapy with testosterone to improve its effectiveness.[20,21] Testosterone therapy is not sufficient for ED as a monotherapy; however, the restoration of testosterone levels likely supports the maximum efficacy of other ED treatment options.[22] Most adverse effects associated with the use of PDE5i are mild to moderate, including dyspepsia, headache, flushing, back pain, nasal congestion, myalgia, visual disturbance, and dizziness.

Vacuum erection device

The VED is a mechanical device that is placed over the penis to generate a negative pressure to pull blood into the penis and cause an erection. A rubberized band is then placed around the base of the penis to maintain the erection during sexual intercourse. The device cost is low, and it is effective in men with ED associated with diabetes, spinal cord injury, post-prostatectomy, and other conditions. The satisfaction rate was reported up to 90%. However, the discontinuation rate was up to 30% due to pain and temporary changes to penile sensation due to the rubberized band, ejaculation problems, and bruising if the device is over pressurized.[23-26] Additionally, its use may be difficult for patients with insufficient dexterity or a large amount of lower abdominal fat and buried penis.

Intraurethral alprostadil

Alprostadil is an exogenous form of prostaglandin E1 (PGE1). Alprostadil, in the form of a urethral suppository, is delivered into the corpus cavernosum by direct diffusion or via collateral vessels. As a result, intracellular levels of cyclic AMP increase in corpus cavernosum smooth muscle cells, leading to penile erection. This route of administration is less invasive but less effective than ICI. However, it may be a good option for patients who do not prefer injection methods or cannot use oral medication due to contraindications.[27] A test dose of medication should be administered in the clinic with patient to monitoring for hypotension and other possible adverse events such as penile pain and urethral burning. Additionally, instructions on the use of the urethral suppository can be given to the patient while titrating medication dose in the office.

Intracavernosal injection

A medication can directly be injected into the corpus cavernosum from the lateral base of the penis. Other injection sites are not preferable to avoid injecting the urethra in the ventral side and neurovascular bundle at the dorsal side. Papaverine, PGE1, and phentolamine are

commonly used injectable agents administered either as monotherapy or combination therapy in clinical practice. ICI is an alternative treatment for oral ED therapy with better satisfaction rates up to 94% and minimal systemic side effects.[27,28] However, ICI therapy presents some barriers for patients or partners. Its administration is more challenging compared to other options. Also, it causes more anxiety due to the fear of injecting the penis. The first dose should be administrated in the clinic to determine the optimal dosage to achieve a good erection that does not last longer than 1 hour. Additionally, a man and his partner may feel more confident with the method and facilitate adherence to the treatment after a self-injection training session.

The most commonly used medication for ICI is PGE1, also known as alprostadil, which is the only FDA approved medication to be used for ICI. The overall satisfaction rate of alprostadil monotherapy for ICI approximates 80% with dose titration from 1.25 to 20 μg.[29] Combination therapies are also recommended by clinical guidelines as an alternative to monotherapy to achieve higher efficacy and a more favorable side-effect profile by using lower dosages of each agent. Alprostadil can be combined with papaverine and phentolamine and called "tri-mix." When two medications are combined, it is called "bi-mix." A combination of papaverine and phentolamine is widely used as a bi-mix for injection even though it is not FDA approved for ICI in ED treatment. Papaverine is a nonspecific phosphodiesterase inhibitor and increases intracellular levels of both cAMP and cGMP. Phentolamine is an alpha-adrenergic receptor blocker and reduces sympathetic tone in the penis, thereby opposing vasoconstriction. Papaverine was the first medication discovered to be used for ICI. However, it is rarely used as monotherapy due to lower overall efficacy and higher AEs such as corporal fibrosis, high potential of priapism, and liver toxicity. Phentolamine also shows limited efficacy as a monotherapy. It is usually combined either with alprostadil or papaverine. Bi-mix utilizes the synergistic actions of cAMP elevation by alprostadil (20 μg/mL) with phosphodiesterase inhibition by papaverine (30 mg/mL) or alpha-adrenergic blockage by phentolamine (0.5 mg/mL), resulting in a response rate of 68.5%.[30] In combination with three mediations called tri-mix, and its overall success rate reported 72.6%.[31] Concentrations of each component vary widely in the literature, but ratios of 12-30 mg papaverine: 10-20 μg alprostadil:1 mg phentolamine are common.[8]

Patients should be counseled regarding the potential AEs of ICI therapy. The most serious AE is priapism. Several studies reported a mean rate of 6.3% for prolonged or painful erections and 1.8% for priapism using alprostadil, 8.9% for prolonged or painful erections and 5.5% for priapism using bi-mix (papaverine and phentolamine), and 2.8% for prolonged or painful erections and 3.1% for priapism using tri-mix.[8] Penile and genital pain is one of the common AEs with bruising. The highest rates of pain have been reported in patients who were using either alprostadil or papaverine as a monotherapy. Additionally, penile fibrosis, plaques, and penile deformities have been reported with the use of ICI. Clinical guidelines suggested that clinicians should document the preexistence of any of these conditions before initiating ICI. Regular patient follow ups are essential for assessing the progression or onset of these conditions.

The contraindications of the use of ICIs include Peyronie's disease, a history of recurrent priapism, and bleeding disorders.

Penile prosthesis implantation

The penile prosthesis is a surgically implanted device that has been used for ED treatment over the last 40 years. The device has undergone multiple improvements over the years to minimize device failure and infection risk and optimize device function to maximize the patient's and his partner's satisfaction. There are a variety of forms of penile prostheses, including malleable and inflatable devices. The malleable device contains two semi-rigid cylinders that are implanted into the penile corpora. It is an ideal option for patients who are physically handicapped with poor hand dexterity. While malleable device has poor concealment, it has lower mechanical failure rates due to its minimal components.[32] There are two types of implantable penile prosthesis (IPP) that consist of either two or three pieces. The two-piece IPP can provide full rigidity. However, the cylinders prefill with fluid due obviating the need for a reservoir, which achieves some degree of tumescence. It can be a good option for patients with the hostile pelvis. The three-piece inflatable penile prosthesis device consists of two fluid-filled cylinders that are implanted into the penile corpora, along with a pump that is placed in the scrotum and a fluid reservoir that is situated in the abdomen. It is considered a better option than the malleable prosthesis producing better penile rigidity and more flaccidity that closely replicates normal erection. The patient satisfaction rates of IPP are 86% that is higher than oral medication or ICI [guideline]. The 5 and 10 year overall survivals of modern prosthetics are estimated to be 90.4% and 86.6%, respectively.[33]

Short term complications related to IPP implantation include bleeding, bruising, hematoma, wound separation, and severe pain, while long-term complications include erosion or cylinder extrusion, mechanical failure, and changes in penis length. Infection is the most serious AE, which may occur typically within the first 3 months or maybe as a late complication. It usually requires the removal of the prosthesis. However, infection rates have been reduced to 1%-2% after the development of antibiotic and hydrophilic coatings, as well as improvement in surgical techniques.[34] Penile prosthetic surgery should not be performed in the presence of systemic, cutaneous, or urinary tract infections.

The penile prosthesis may be considered as a first-line therapy; however, it is typically reserved for patients who have not responded to less-invasive ED treatments. Other ED treatments after prosthesis explantation generally are not successful. Given the invasive and essentially irreversible nature of penile prosthesis implantation surgery, thorough counseling regarding short and long term postoperative expectations (including possible penile length loss associated with ED) is essential.

Penile vascular surgery

Penile arterial reconstruction surgery may be considered for young patients who do not have any veno-occlusive dysfunction, evidence of generalized vascular disease, or other co-morbidities that could compromise vascular integrity.[8] There have been numerous controversies due to the absence of large prospective and well-controlled studies. Also, the long term success of the procedure is not well-established.

Penile arterial reconstruction surgery would potentially be beneficial to an otherwise healthy patient aged < 55 years with arteriogenic ED. Occlusion of common penile or cavernosal arteries should be documented by penile duplex Doppler ultrasound or cavernosography and selective internal pudendal arteriography.

The surgical principle of penile arterial reconstruction surgery includes an anastomosis of the inferior epigastric artery to dorsal penile arteries in an end-to-side fashion or to the deep dorsal vein with additional proximal and/or distal vein ligation.[35]

Penile venous ligation surgery is proposed to correct veno-occlusive ED; however, long term success is unlikely achievable for the management of ED.[8] It is currently considered investigational due to inaccurate or deficient methods for diagnosing and correcting the relevant defect.

Extracorporeal shock wave therapy

Extracorporeal shock wave therapy (ESWT) on penile tissue is thought to be effective. due to microtrauma that upregulates the angiogenic growth factors and activates some factors for tissue restoration and repair. In addition to angiogenesis and tissue restoration, previous animal studies reported that ESWT improves erectile function in a rat model of cavernous nerve injury by inducing nerve generation via increasing brain-derived neurotrophic factor (BDNF) expression and neuronal nitric oxide synthase (nNOS)-positive nerves and activating Schwann cells.[36,37]

ESWT has not been approved by the FDA and is still considered investigational. Several studies had reported its efficacy and safety in mild to moderate vasculogenic ED when PDE5i treatment failed.[38-40] However, well-designed prospective randomized clinical trials are limited in the literature. The duration of treatment efficacy, optimal treatment parameters, such as dosing frequency, energy flux density settings, and the number of shocks, and the selection of device types (linear versus focused shock wave) are not well-established.

Randomized controlled studies with larger sample sizes are needed to determine its long term efficacy and side effects using a validated and standardized protocol.

Intracavernosal stem cell therapy

In recent years, there has been an increase in the use of SCT for ED treatment. Currently, mesenchymal stem cells isolated from adipose tissue are the most frequently used cells in studies. These stem cells are capable of differentiating into a variety of cells, such as cavernosal smooth muscle cells, endothelial cells, or neuron cells, that can promote cell growth and survival, angiogenesis, and immunomodulation via a variety of growth factors.[41-44] Previous animal studies using SCT have shown improvement in erectile function in diabetic ED, cavernosal nerve injury, and prostate radiation models.[42,45,46]

There are several clinical trials in small study groups that have shown promising results using SCT without significant adverse effects in diabetic and post-prostatectomy ED.[47,48] However, stem cells' differentiation capability as a progenitor cell presents safety concerns for the risk of malignant proliferation as well as potential immune response. In addition to these concerns, the long term efficacy of SCT is uncertain, as are the optimized source and dose of stem cells. Further randomized controlled studies are warranted with long-term follow up periods, standardized protocols, and larger study groups.

Platelet-rich plasma and other therapies

Platelet-rich plasma (PRP) is an autologous blood product that contains a high amount of platelets with various growth factors, including platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF). These growth factors have been shown to induce angiogenesis, cell regeneration, proliferation, and differentiation with stem cell migration in preclinical and clinical studies.[49-53] Intracavernosal injection of PRP promotes nerve regeneration and the recovery of erectile function in rodent cavernous nerve injury models.[54-56] However, there has been a lack of understanding of the underlying mechanism of PRP on neuroregeneration in studies using animal models of cavernous nerve injury.[50,57,58]

A phase 1 human trial of intracavernosal PRP in 17 patients with ED and Peyronie's disease reported no major adverse effect. In the same study, ED symptoms were assessed in 7 men using IIEF-5 questionnaire, and IIEF scores were found to improve by an average of 4 points while there was no decline in erectile function.[50] However, PRP is considered an experimental treatment, and higher-quality randomized controlled studies with larger patient samples with long term follow up are needed.

Conclusion

In clinical practice, the majority of patients with ED are placed on oral treatment with PDE5i as initial therapy. However, improving overall health with lifestyle modification and treatment of underlying comorbidities may alone enhance erectile function. The clinician should discuss all possible choices during the initial visit, regardless of its invasiveness, considering the patient's health literacy and sociocultural background. Shared decision making between clinician, patient, and partner plays a vital role in promoting treatment

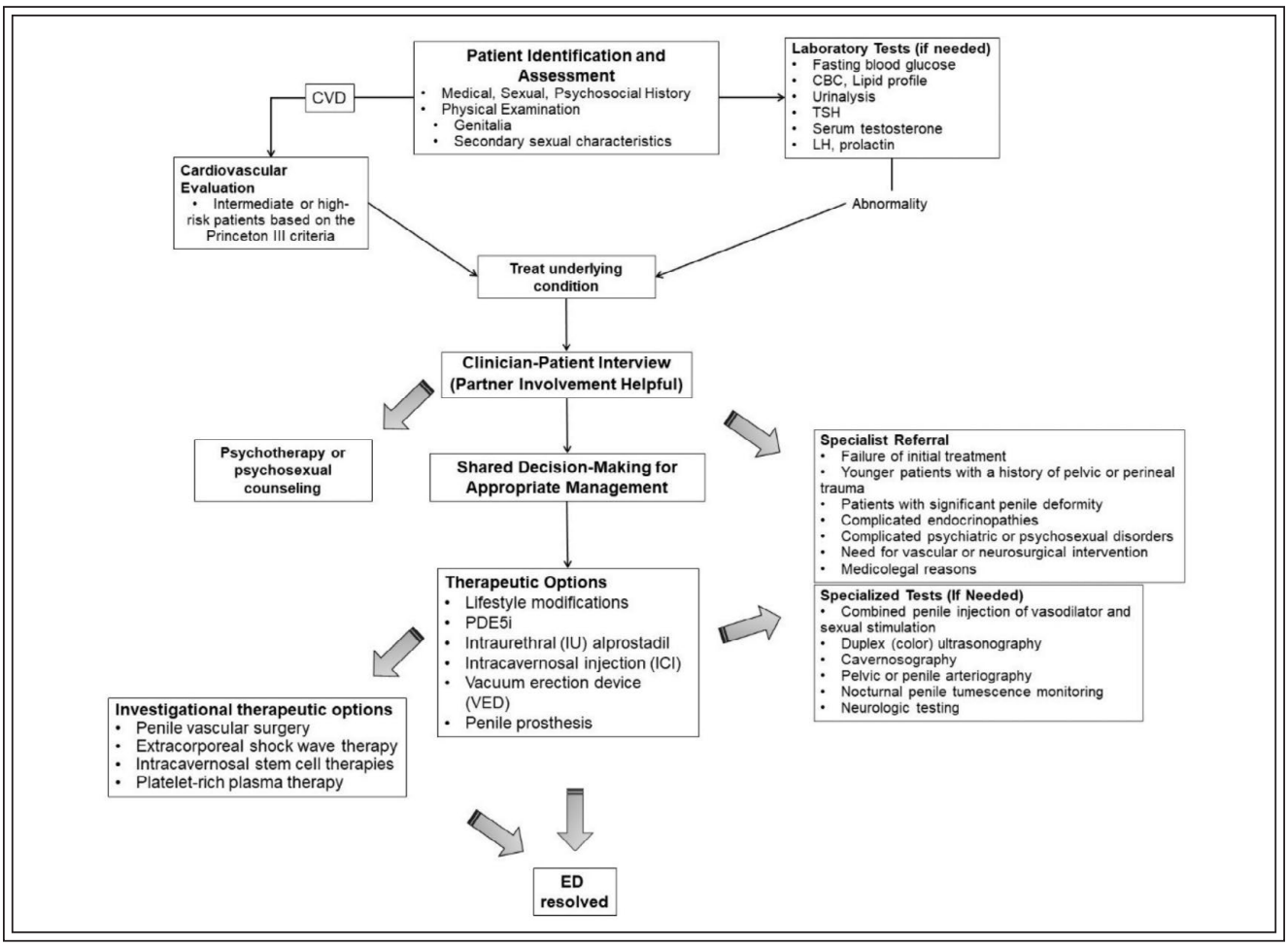

Figure 1. Algorithm for the management principles of patient presenting with erectile disfunction.

adherence. Before starting PDE5i, the clinician should provide instructions to maximize benefits and efficacy. Dose titration is essential to achieve the best efficiency with minimal adverse events. Referral to mental health professionals should not be overlooked; performance anxiety and communication between partners need to be addressed to achieve full success.

Treatments such as transurethral alprostadil, ICI, or VED should be offered in case that PDE5i fails or there are contraindications to use of such medication. In-office injection tests should be utilized before initiating therapies like transurethral alprostadil or ICI to establish an effective dose and monitor adverse effects. In-office trials also help patients gain confidence with technique and facilitate adherence. If non-surgical options fail, penile prosthesis implantation should be discussed. The clinician should review the short and long term expectations of penile prosthesis implantation with the patient and his partner in-depth due to the irreversible consequence of surgery.

There have been many emerging therapies developed for ED treatment over the last decade. Some of these innovative and novel therapies, such as SCT, gene therapy, and PRP, may indeed replace or regenerate the endothelial, neuronal, and smooth muscle cells in the penis. However, the long term implications of these therapies are unknown. Well-designed randomized controlled studies adopting standardized protocols and including larger study populations are needed. An algorithm for the management principles of patient presenting with ED is described in Figure 1.

On another note, new pharmacologic agents targeting underlying pathophysiologies such as guanylate cyclase activators, NO donors, and RhoA/Rho-kinase inhibitors are promising therapies based on preclinical studies. Improvements in novel surgical techniques using tissue transplants and new device-based treatments such as novel drug or drug delivery systems may be implemented as ED therapies in the future.

Disclosures

Dr. Serkan Karakus has no disclosures.
Dr. Arthur L. Burnett is an investigator for Boston Scientific, Coloplast, Endo Pharmaceuticals, National Institutes of Health, and Pfizer. He is a consultant for Futura Medical, Novartis Pharmaceuticals, and Urology Times Editorial Council. He is an associate editor for International Urology and Nephrology (journal) and Andrology (journal). Boston Scientific financially supports, in part, the Sexual Medicine fellowship program in The Brady Urological Institute at Johns Hopkins in Baltimore. □

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Male urinary incontinence after prostate disease treatment

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DAS AK, KUCHEROV V, GLICK L, CHUNG P. Male urinary incontinence after prostate disease treatment. *Can J Urol* 2020;27(Suppl 3):36-43.

Introduction: *Incontinence after prostate treatment (IPT) is an important and common problem for men and can lead to decreased quality of life. The proper evaluation and management of IPT requires both knowledge of the mechanisms for its development and of multiple evolving therapy types.*
Materials and methods: *An update is provided on the evaluation and management for IPT. The underlying pathophysiology of the contributing conditions is explored along with the appropriate assessment prior to therapy. Surgical techniques including the artificial urinary sphincter (AUS) and male urethral sling are detailed specifically and compared.*
Results: *IPT can result from radical prostatectomy (RP), prostate radiation, and surgery for benign prostatic hyperplasia. All of these may increase the risk for stress urinary incontinence (SUI), urge urinary incontinence (UUI), or mixed incontinence. SUI after RP remains the largest component of IPT. Perioperative pelvic floor muscle therapy and advances in surgical technique have helped to prevent and treat post-RP SUI. The AUS and male urethral sling are both excellent surgical options for SUI with the AUS being currently indicated for a broader set of patients. Predominant UUI should be treated in a stepwise manner based upon guidelines for overactive bladder.*
Conclusions: *Evaluation of men with IPT should include determining components of SUI and UUI as these will direct medical and surgical therapy. While advances in surgical technique and technology have reduced prevalence of SUI after RP, many men still require treatment. Surgical treatments with AUS and male urethral sling provide excellent outcomes in well selected patients.*

Key Words: male incontinence, artificial urinary sphincter, male urethral sling

Introduction

Urinary incontinence (UI) of all kinds increases the risk for anxiety and depression and is associated with lower healthcare related quality of life.[1] Reasons for UI are many-fold and particular attention must be paid to those that develop in the setting of treatment of other conditions. Such is the case for men who develop UI after surgical treatment for prostate cancer, from prostate radiation therapy (RT), and from surgery for benign prostatic hyperplasia (BPH). These types of incontinence as a group are termed incontinence after prostate treatment (IPT).[2]

IPT as a definition is inclusive of all types of UI including stress urinary incontinence (SUI), urge urinary incontinence (UUI), and mixed incontinence. SUI after radical prostatectomy (RP) is the most common and significant component. Men with prostate cancer are at a 4-fold increased risk for UI after RP when compared to watchful waiting.[3] Recent data suggest an average long term SUI rate after robot-assisted laparoscopic prostatectomy (RALP) of 8%-16% with variability based upon SUI definition, surgical technique, and skill level.[4,5] Pelvic floor muscle therapy (PFMT) in the perioperative setting and advances in RP surgical techniques have been shown to improve continence rates over time.[4,6] However, many men still develop symptoms bothersome-enough to seek intervention.

In this paper we provide a review and update of the evaluation and management for IPT. The underlying pathophysiology of the components of IPT is explored in addition to preventive measures (surgical and non-surgical) that have been popularized. Surgical therapy for male SUI is highlighted including the artificial urinary sphincter (AUS) and male urethral sling.

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Etiology of IPT

Radical prostatectomy

UI after RP is largely SUI however UUI may develop as well. SUI following RP is thought to result from several possible anatomic and nerve-related changes that occur from surgery. Rhabdosphincter incompetence alone has been found to be the sole cause of SUI after RP in 40%-92% of cases.[7] Given, however, that a large fraction of men recover continence by 6-12° months postop, it is thought that the insult is likely to the nerves and supporting tissue of the sphincter rather than direct sphincter damage per se. Studies have shown that preservation of membranous urethral length (MUL) > 12 mm is associated with increased continence following RP as well.[8]

UUI related to detrusor overactivity (DO) has been found to develop after RP as well. In a study by Groutz et al, post-RP DO was found in up to 34% of men. However for only about 7% of men was it the sole cause of UI.[9] A review by Thirucheivam et al of men with UI after RP who underwent urodynamic assessment found a more variable rate of overactivity between 2%-63%.[10] Overall, men with UI after RP should be evaluated for both SUI and UUI and treatment decisions based upon the relative components of each.

Radiation therapy

RT to the prostate has long been known to have deleterious effects on the bladder and rectum, potentially leading to long term tissue damage and dysfunction. Pathologically, DNA-damage induced by RT can lead to long term inflammation, endarteritis, urothelial proliferation, collagen deposition, and fibroblast infiltration.[11] In the bladder, these inflammatory changes can lead to a nociceptive response that may manifest as DO.[12] Hoffman et al found that men who received pelvic RT for prostate cancer (with or without prior RP) had a higher rate of DO that those who did not get radiation (70% versus 38%, respectively) and had lower maximum cystometric capacity (253 mL versus 307 mL, respectively).[13] UI after prostate RT in the absence of surgical prostate therapy should raise the suspicion for DO which should be the initial focus of investigation.

Surgery for BPH

Surgical removal of the obstructive prostatic adenoma in BPH can be associated with the development of other lower urinary tract symptoms including UI. Rassweiler et al found that after transurethral resection of the prostate, between 30%-40% of men can experience transient SUI, which drops down to < 0.5% over long term follow up.[14] Studies of the holmium laser enucleation of the prostate (HoLEP) have also shown postoperative UI; Cho et al reported a de novo SUI and UUI rate of ~10% each after HoLEP which fell to about 1% each at 12 months.[15] These men need careful evaluation to assess all the possible types of UI that may be present.

Prevention of IPT

Preventative measures for IPT have principally involved increased knowledge of PFMT and refinement of RP techniques. The 2019 AUA/SUFU guidelines recommend that PFMT may be offered in the pre-RP setting and should be offered after surgery. Recent data suggest a possible increased value for pre-surgical PMFT. In a randomized trial by Milios et al, men planning RP randomized to intensive PMFT (120 contractions per day) versus conventional PMFT (30 contractions per day) starting 5-weeks preop experienced a faster return to continence and less severe leakage on 24-hour pad weight test.[16] This more intensive regimen is promising and deserves future study.

Techniques in RP have advanced significantly and have led to increased continence rates postoperatively. Sridhar et al reviewed surgical factors associated with increased postoperative continence which included bladder neck preservation, neurovascular bundle preservation, athermal division of the dorsal venous complex, preservation of ancillary anatomic support to the rhabdosphincter, preservation of MUL, and anatomic anterior/posterior reconstruction.[17] A recent review by Phuken et al of the Retzius-sparing technique in RALP showed that it was associated with improved continence rates and short time to continence recovery compared to standard RALP.[18]

Patient evaluation

Office evaluation of men with IPT should begin with the relevant history and physical examination. Multiple questionnaire tools exist to help distinguish the types of UI men may experience. The International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI SF) and the Michigan Incontinence Symptom Index (M-ISI), Tables 1 and 2, respectively, are brief tools designed to assess precipitating leakage events and symptoms.[19,20] An additional quasi-objective evaluation tool is the bladder diary for tracking fluid intake and leakage/symptom timing. Pad use including type, frequency, and level of dampness should also be assessed to better roughly define the quantity of leakage experienced.

Please consider the following questions as they apply over the past four weeks

How often do you leak urine? (check one box)	never	☐ 0
	about once a week or less	☐ 1
	two or three times a week	☐ 2
	about once a day	☐ 3
	several times a day	☐ 4
	all the time	☐ 5
How much urine do you usually leak? (check one box)	none	☐ 0
	a small amount	☐ 2
	a moderate amount	☐ 4
	a large amount	☐ 6
Overall, how much does leaking interfere with everyday life?	0 1 2 3 4 5 6 7 8 9 10	
	none at all	a great deal
	ICIQ score: sum above =	☐ ☐
When does urine leak? (check all that apply)	never - urine does not leak	☐
	leaks before you can get to the toilet	☐
	leaks when you cough or sneeze	☐
	leaks when you are asleep	☐
	leaks when you are physically active/exercising	☐
	leaks when you have finished urinating and are dressed	☐
	leaks for no obvious reason	☐
	leaks all the time	☐

Table 1. International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI SF).

During the Past Month:	Never	Rarely	Occasionally	About Half the time	Most or all of the time
1. How often has urine leakage occurred in association with any physical activity (such as lifting, bending, sitting down, standing up, exercising, etc)?	0	1	2	3	4
2. How often has lifting light objects (such as a gallon of milk) caused you to leak urine?	0	1	2	3	4
3. How often has walking or light exercise cause you to leak urine?	0	1	2	3	4
	Never	Seldom	About once a week	About once a day	More than once a day
4. How often have you leaked urine because you could not wait to empty your bladder?	0	1	2	3	4
5. How often has a sudden urge to urinate caused you to leak urine?	0	1	2	3	4
6. How often have you leaked urine because you could not reach a bathroom in time?	0	1	2	3	4
	None	Thin pad or tissue	Medium/ regular pad	Large/maxi pad	Absorbent, disposable, undergarments
7. On average, what form of protection do you use to protect against wetness during the day?	0	1	2	3	4
	None	1 per day or less, or only for security	1 per day and it is usually wet	2-3 per day	4 or more per day
8. On average, how many of these (pads, tissues, disposable undergarments) would you use to protect against wetness during the day?	0	1	2	3	4
				Total Severity Score: Items 1-8	
	Never	Rarely	Sometimes	Most of the time	All of the time
9. Overall, how often have you needed to change your daily activities because of your urinary incontinence?	0	1	2	3	4
	No problem	Very small problem	Small problem	Moderate problem	Big problem
10. Overall, how big of a social problem (anxiety/embarrassment/ avoiding social activities) has your urinary incontinence been for you during the past month?	0	1	2	3	4
				Total Bother Score: Items 9-10	

Table 2. Michigan Incontinence Symptom Index (M-ISI).

Office stress testing via valsalva or cough can be done to verify urine leakage and confirm SUI. The Male Stress Incontinence Grading Scale (MSGIS) may be employed as well; Yi et al found that increased grading on the MSGIS correlated well with increased 24-hour pad weight in men with SUI seeking surgical intervention.[21]

A 24-hour pad weight testing provides the most objective measure of daily urine leakage.[22] Pad number, in contrast, can be affected by patient age and activity level and may not accurately reflect the degree of urine lost.[23] However, formal 24-hour pad testing may be burdensome to the patient and logistically difficult to perform. The ICIQ-UI SF can additionally be correlated with both pad number and 24-pad weight testing and may be useful as a long-term tracking metric.

Evaluation with cystourethroscopy is recommended by the 2019 AUA/SUFU guidelines to rule out competing bladder/urethral pathology and to better define the patient's anatomy. Urethral stricture disease or vesicourethral anastomotic stenosis in the post-RP setting may be identified and necessitate a staged treatment approach. Urodynamic testing may also be used if the underlying diagnosis is unclear or if the patient's bladder function is questionable.[2]

For any patient the degree of bother should be the driving force behind treatment in the absence of concerning features. The American Urological Association Symptoms Score (AUA-SS) is an additional excellent tool to assess this and is easy to administer in the office.

Pre-surgical management

After RP, patients should be offered PFMT as it has been shown to decrease time to continence recovery. Fernandez et al found in their meta-analysis of eight randomized trials that a regimen of three sets of 10 contractions daily led to improved short and long term continence rates compared to no therapy.[6]

Critical in pre-surgical management for post-RP patients specifically is to evaluate additional UUI. The main surgical treatments for SUI do not address UUI which may lead to worsened SUI surgical outcomes if left unmanaged. If UUI is identified it should be treated in accordance with the AUA/SUFU guidelines on Diagnosis and Treatment of Non-Neurogenic Overactive Bladder in Adults.[24] This includes a stepwise approach consisting of behavioral modifications, medical therapy, and surgical intervention as indicated.

Patients who have ongoing bothersome IPT with a significant component of SUI (which is typically the case) may be offered surgical treatment as early as 6 months postop. At that point it is important to decide if the patient's continence is continuing to improve or if it has plateaued. At 12 months patients still bothered should be offered surgical intervention if no contraindications exist.[2]

Surgical management

Artificial urinary sphincter

The artificial urinary sphincter has long been the gold standard for male SUI. The modern device consists of a pressure-regulating balloon (PRB), fluid-filled urethral cuff, and inflation pump. In AUS placement the patient is positioned in dorsal lithotomy and prepped. Flexible cystoscopy (if not done previously) is then performed to rule-out urethral stricture disease or vesicourethral anastomotic stenosis, both of which increase the risk for post-AUS failure and should ideally be treated before AUS placement.[25] After careful dissection to isolate the bulbar urethral the circumference is measured and a cuff size is selected. Men who have had prior AUS with urethral atrophy, prior urethral erosion, of pelvic radiation may require additional techniques such as double-cuff placement or transcorporal cuff placement to achieve satisfactory results.[2] Greater care should be taken in these patients especially at correct cuff sizing. After cuff placement the PRB is placed (typically into the space of Retzius) and filled with 23 mL of sterile saline or contrast corresponding to 61-70 cmH2O. The pump is placed into a subdartos pouch completing the procedure.

Excellent outcomes for the AUS have long been reported. The AMS 800 (Boston Scientific Corporation, Marlborough, MA, USA) is widely used with the most robust literature. In a large single-center series by Linder et al in 2015, 1,083 AUS placements between 1983-2011 were analyzed. For men with any degree of initial SUI, at a median follow up of 4.1 years 59% reported 0-1 pad per day and 94% reported high-satisfaction.[26] A systematic review by Van der Aa et al combined 12 AUS studies and found a general 0-1 pad per day rate of 61%-100% with "complete dryness" varying from 4%-86%.[27] Overall patients should be counseled that the effectiveness and durability of the AUS has been long tested and offers the potential for excellent results for any degree of SUI.

AUS revision does sometimes become necessary due to device failure or infection. In a recent cohort of 1,154 primary AUS implants, Boswell et al reported overall device survival of 72%, 56%, and 41% at 5, 10, and 15 years postop, respectively.[28] Historically sub-cuff atrophy was thought to be the leading cause of overall device failure. However, since the introduction of the 3.5 cm cuff, atrophy leading to failure may be less

common. Bergeson et al reviewed 177 AUS revisions between 2007-2019 of which only 8% were resultant from urethral atrophy. Notably there was only 1 case of atrophy leading to failure with a 3.5 cm cuff. In this series PRB failure was the most frequent cause of device failure (34%) followed by mechanical cuff failure (17%).[29]

Fortunately, long term satisfaction with AUS is excellent even after revision surgery. Viers et al reviewed a cohort of 467 primary AUS implants and 122 revision implants. Eight-five percent of men in his cohort had undergone RP and 26% had prior radiation therapy. At over 10 years follow up, satisfaction remained up to 75% with no difference between the primary and revision groups.[30] Patients should always be counseled on the possibility of device failure and need for revision surgery during preop office consultation.

Male urethral sling

Male urethral slings are becoming more popular for use in male SUI. First developed in the 1960s and 1970s, multiple changes in design and materials over time have decreased complication rates and increased patient satisfaction. Physiologically male slings function by compression or repositioning of the urethra to increase outflow resistance.[31] However this process must be done without creating frank urinary obstruction. Several general designs have been developed including the bone-anchored male sling (BAMS), transobturator sling, adjustable sling, and the quadratic sling.[32]

One of the most studied modern urethral slings is the transobturator AdVance model sling (Boston Scientific, Minnetonka, MN, USA). Collado et al evaluated long term outcomes of the AdVance sling and AdVance XP sling for men with mild-to-moderate SUI (defined as 24-hour pad weight < 400 mL).[33] Inclusion criteria for this study also included a positive "repositioning test" whereby coaptation of the rhabdosphincter was assessed and confirmed during active contraction. The overall cure rate (defined as no pad use) among a total of 94 patients was 77% at a median follow up of 49 months. Small bladder capacity and DO were found to be predictive of surgical failure. A review by Doudt et al in 2018 identified a similar success rate among three studies of the AdVance or AdVance XP slings at between 74%-93%.[34] Recent studies of other sling types have shown similar results.[34]

With regard to adverse events, in 2018 Ye et al performed a review of outcomes and complications in seven studies using the AdVance sling.[35] They identified an acute urinary retention rate of 0.6%-15%, perineal pain rate of 0.8%-50%, and hematoma rate of 0.7%-3.2%. Explanation was uncommon and occurred in up to 1.6% during a period of 27 month follow up. Overall the complications after male urethral sling are reversible and should not be deterrent from pursuing sling if it is otherwise appropriate.

AUS versus male urethral sling

Men who present with bothersome mild-to-moderate SUI are generally faced with a decision between pursuing AUS or male urethral sling. Both options are considered appropriate based on the 2019 AUA/SUFU guidelines, however several patient-specific factors must be taken into consideration.[2]

Raup et al found that cognitive dysfunction and decreased manual dexterity predicted overall AUS failure independent of age.[36] Men with such issues may ultimately enjoy better quality of life with male urethral sling. Bladder dynamics must be considered as well as prior studies have shown that DO increasesß the risk for worse outcomes after sling placement.[33] This is of particular importance given the risk of DO after radical prostatectomy (2%-63%) and after radiation therapy for prostate cancer (up to 85%).[10] The 2019 AUA/SFU guidelines recommend that AUS was the preferred option in the setting of pelvic RT given the lack of robust data for sling in this group.[2] Advances in sling technology may change this recommendation in the future.

Special consideration should be given to men seeking treatment for SUI after previously having an incontinence procedure. Ajay et al retrospectively reviewed 61 men who failed male urethral sling therapy and compared outcomes between revision with AUS vs revision with repeat sling.[37] Secondary treatment failure occurred in only 6% of those undergoing revision with AUS compared to 55% for repeat sling. Similarly, Lentz et al analyzed 29 men who underwent AUS placement after failing sling therapy and compared them to a control group of men undergoing primary AUS placement.[38] Men who received AUS after sling experienced similar results to primary AUS with 96% using 0-1 pads per day at 3 months. Overall, in the context of revision surgery after either AUS or male urethral sling, men should be counseled that secondary AUS placement is the preferred option and can have similar results to primary AUS.

The decision between AUS and male urethral sling must therefore be highly individualized. Poor manual dexterity/cognition and aversion to mechanical implants should direct towards male urethral sling. In contrast, a history of prior RT, the presence of DO, the need for revision surgery, or severe SUI (24-hour pad weight > 400 mL) should direct toward AUS.

Urethral bulking agents

Urethral bulking agents have been studied as a minimally invasive treatment for male SUI. While the 2019 AUA/SUFU guidelines did list urethral bulking agents as a treatment option, it noted the low efficacy, high re-treatment rate, and rare chance for cure.[2]

Conclusion

IPT remains a common and important problem for men and is associated with reduced quality of life. Evaluation of these men requires careful analysis of timing of urine leakage and associated symptoms. SUI, UUI, and mixed incontinence may manifest after RP, radiation therapy, or surgery for BPH and it is imperative for the urologist to determine the contribution of each type to men's symptoms. Surveys such as the ICIQ-UI SF and M-ISI are easy office assessment tools that should be part of the evaluation armamentarium.

SUI after RP remains the major driver for IPT. Advances in surgical technique in RP have reduced the rates of SUI, however this is still a significant problem. The benefits of PFMT in the prevention/improvement of SUI are well established and further research may refine the timing and implementation of these measures. The AUS and male urethral sling remain the most widely used and well-studied surgical interventions for male SUI. Long term data supports the AUS as the gold standard therapy which may be used regardless of SUI severity, bladder dynamics, prior radiation, or revision surgery. Men should be counseled on the risks and benefits of all available options and care should be taken to exclude competing pathology that may affect results. □

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Holmium laser enucleation of the prostate (HoLEP): size-independent gold standard for surgical management of benign prostatic hyperplasia

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DAS AK, HAN TM, HARDACKER TJ. Holmium laser enucleation of the prostate (HoLEP): size-independent gold standard for surgical management of benign prostatic hyperplasia. *Can J Urol* 2020;27(Suppl 3):44-50.

Introduction: *Holmium laser enucleation of the prostate (HoLEP) has become an increasingly common surgical management option for treatment of symptomatic benign prostatic hyperplasia (BPH). Transurethral resection of the prostate (TURP) has long been considered the gold standard, contemporary literature and newer guidelines indicate that HoLEP has become the new size-independent endoscopic gold standard for surgical BPH treatment.*
Materials and methods: *We provide a review and update on current HoLEP surgical techniques, outcomes, safety, and durability according to the growing body of literature.*
Results: *The current body of literature and guidelines indicate HoLEP as a safe and effective surgical treatment for symptomatic BPH regardless of prostate size. Durable long term subjective and objective outcomes have been demonstrated in previous studies, extending beyond 10 years.*
Conclusions: *HoLEP continues to demonstrate durable long term efficacy for treating patients suffering from lower urinary tract symptoms (LUTS) due to BPH. The American Urological Association (AUA) guidelines recommend its use as a size-independent endoscopic treatment option. HoLEP has proven itself to be the new gold standard in surgical treatment for LUTS secondary to BPH with the ability to endoscopically treat prostates independent of size, with durable long term outcomes.*

Key Words: HoLEP, BPH, LUTS

Introduction

Benign prostatic hyperplasia (BPH) represents the most common benign neoplasm in American men, with almost 3 in 4 affected by the seventh decade of life.[1] Proliferation of prostatic glandular epithelium, smooth muscle and connective tissue results in prostatic urethral compression, manifesting as bladder outlet obstruction (BOO) and lower urinary tract obstructive symptoms (LUTS).[2] Historically, surgical management of BPH has been transurethral resection of the prostate (TURP) and has served as the gold standard to which all other treatments are compared.[3] Monopolar TURP does carry the risk of TUR syndrome, which occurs between 0.78% and 1.4% of cases,[4] and results in neurologic disturbance, pulmonary edema, cardiovascular compromise, and potentially death secondary to dilutional hyponatremia.[5] TURP can also have increased bleeding risk in those on anticoagulation and can be challenging in men with larger prostates. In the current current American Urological Association (AUA) guidelines for the surgical management of BPH, TURP is one of the options for prostates less than 80 grams (g).

For larger prostates (> 80 g), open simple prostatectomy (OSP) has traditionally been the main surgical treatment option, though laser enucleation has become widely adopted as well. The holmium laser has been employed to treat BPH after its successful use in treating urinary calculi.[6] This laser enables the surgeon to enucleate the transition zone of the prostate from the surgical capsule by taking advantage of existing anatomic planes. In doing so, significantly improving total tissue removal compared to TURP and is less invasive than OSP while maintaining equivalent outcomes.

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Analysis of these treatment modalities has shown HoLEP to have improved subjective and objective outcomes, including AUA Symptom Score (AUA-SS), postoperative Q_{max} and retreatment rates, when compared to TURP and OSP.[7] Additionally, HoLEP results in reduced immediate complications, decreased length of hospital stay (LOS), shorter catherization times, and decreased blood loss when compared to TURP[8] and OSP.[9] According to current AUA guidelines, laser enucleation techniques are the only recommended size-independent endoscopic surgical option for symptomatic BPH.[3] This review will detail surgical strategies and techniques, outcomes, safety, and long term durability of the HoLEP procedure.

Equipment and technique

The standard HoLEP technique has been previously described[10] and is performed using a high-power 100-120 W holmium laser (Lumenis, Yokneam, Israel) with an end-firing 550-micron laser fiber. Newer laser systems, with two pedals, offer the ability to alternate between treatment settings – commonly 2.0 J with a frequency of 40-50 Hz and wide pulse width – and hemostasis settings – typically 1.5 J and 30 Hz. The procedure is performed using a 26-Fr continuous flow endoscope with a laser bridge. The laser fiber is delivered through the working channel within a 7 Fr laser catheter, which provides stabilization of the fiber throughout the procedure. The inflow port is connected to two separate 3 liter normal saline irrigation bags, which are left wide open, and the outflow port is left to gravity drainage.

The classic, and most commonly used, HoLEP technique is performed by enucleating the median and lateral lobes of the prostate and releasing them into the bladder. Incisions are made at the 5- and 7-o'clock location at the bladder neck and are carried down to the fibers of the prostatic capsule. These incisions are then extended distally and joined proximal to the verumontanum. Starting at this distal location, the median lobe is dissected off of the capsule until it can be released into the bladder. This process can be aided by using the end of the scope to lift the prostatic adenoma while using the laser fiber to develop the dissection plane at the level of the capsule. A similar approach is utilized for the lateral lobes, which are enucleated separately. An additional 12-o'clock incision is made at the bladder neck and again carried distally to the level of the verumontanum, with care to avoid damage to the external urethral sphincter. This incision is again carried down to the level of the prostatic capsule and using similar technique, the lobe is gradually dissected free, as the surgeon works to connect the 12-o'clock incision with the 5-o'clock incision. Once all lobes are enucleated, hemostasis can be achieved by activating the laser on bleeding tissue, but from a further distance than usual. This technique serves to "de-focus" the laser energy and results in tissue blanching and coagulation.

Once all three lobes are free-floating within the bladder, the endoscope is exchanged for an offset nephroscope with a straight working channel through which a soft tissue morcellator is placed. It is important to maintain a full bladder during this process, as decompression can lead to bleeding and decreased visualization. A second irrigation channel is placed in order to optimize visualization during morcellation, with the morcellator serving as outflow suction. Suction on the morcellator is activated, which draws the prostatic adenoma onto the blades. Once the adenoma is visualized to be safely away from bladder mucosa, the blades are activated and prostatic tissue is extracted. Under usual circumstances, the surgeon is able to completely morcellate all adenoma tissue, however, there are instances in which this cannot be completed, and remaining tissue must be extracted by other means (i.e. resectoscope or foreign body grasper). After ensuring all tissue has been removed from the bladder, a 24-Fr three-way Foley catheter is placed and continuous bladder irrigation is initiated.

The newer techniques and equipment HoLEP may help improve OR time, shorten the learning curve, and reduce the incidence of transient stress incontinence. Newer HoLEP surgical techniques include the two-lobe and complete en-bloc enucleation of the prostate.[12,13] In a randomized control trial comparing two-lobe technique to the standard three-lobe technique, Xu et al demonstrated reduced incidence of retrograde ejaculation and urinary incontinence.[11] Similarly, studies comparing efficacy and safety of traditional HoLEP and en bloc technique have shown potential advantages toward the latter technique, including decreased enucleation time and total operative time owing to faster identification of the surgical capsule,[13,14] lower risk of major complications,[15] and improvements in quality of life.[15] A study comparing traditional three-lobe, two-lobe, and en bloc techniques done by Tokatli et al, found decreased enucleation time with the two-lobe technique, and also higher rates of transient urinary incontinence in the en bloc group.[16]

Varying laser settings have also been studied with results demonstrating that low-powered HoLEP (LP-HoLEP) can be performed feasibly, safely, and effectively.[17,18] A randomized trial by Elshal et al comparing lower power (LP)-HoLEP (2 J, 25 Hz) to

standard HoLEP (2 J, 50 Hz) found no difference in enucleation efficiency, postoperative dysuria and sexual function or objective flow rates between the two techniques.[19] As low-power holmium lasers are widespread given their use in treating urinary calculi, this could aid in adoption of the HoLEP technique.

Another promising change in operative efficiency has come from novel improvements in morcellator technologies. Currently, three main prostate morcellators exist: VersaCut (Versapulse; Lumenis Inc., Santa Clara, CA, USA), Piranha (Richard Wolf Inc., Knittlingen, Germany), and DrillCut (Karl Storz Inc., Tuttlingen, Germany). VersaCut was the first morcellator used for HoLEP and utilizes reciprocating non-toothed blades controlled by a foot pedal and continuous suction. The Piranha and DrillCut morcellators use oscillating toothed blades which rotate at variable rates with intermittent suction. Studies have compared the morcellator technologies with seemingly variable conclusions. El Tayeb et al performed a prospective randomized trial comparing the Piranha to the VersaCut, which revealed that despite the Piranha having a statistically significant increased cost ($p < 0.001$) and a more complicated design (less user-friendly for operating room staff), 75% of urology faculty, fellows, and residents preferred it over the VersaCut, reporting more efficient tissue removal.[20] Rivera et al examined cost comparisons between VersaCut and Piranha and found that both morcellation efficiency ($p < 0.01$) and expense of operating room time ($p < 0.005$) significantly favored the Piranha, even when controlling for disposable costs ($p < 0.05$).[21] Another retrospective study done by McAdams et al found that the Piranha's oscillating morcellation efficiency was nearly double that of VersaCut (8.6 g/min versus 3.8 g/min, $p < 0.0001$) with no apparent learning curve.[22] In contrast, Maheshwari et al revealed in their study that while VersaCut demonstrated significantly higher morcellation efficiency, the safety profile of the Piranha was significantly better.[23] Hodhod et al demonstrated that the DrillCut morcellator had superior ex vivo morcellation power but modest aspiration speed in comparison to other morcellators.[24] In a different study, Ibrahim et al conducted a prospective, randomized controlled trial comparing the DrillCut to the VersaCut, revealing that the DrillCut was associated with significantly lower morcellation rate ($p = 0.03$) and significantly higher cost of disposables ($p < 0.01$).[25]

Lastly, the recent advancements in laser technology in the form of a larger vapor bubble per pulse have shown potential usefulness in quicker dissection of adenoma off the capsule with better hemostasis. This technology is currently being evaluated at several centers to see if there is a true reduction in enucleation time with improved coagulation compared to standard holmium lasers.

Efficacy, outcomes, and durability

HoLEP has been extensively studied and many large trials have examined efficacy and outcomes. To our knowledge, Tan et al performed the first randomized trial comparing HoLEP to TURP for the treatment of BOO secondary to BPH.[26] Their study demonstrated that HoLEP was superior to TURP with more prostate tissue removed (40.4 versus 24.7 grams), shorter mean catheter time (17.7 versus 44.9 hours), shorter hospital stay (27.6 versus 49.9 hours), and greater relief of obstruction at 6 month follow up as assessed by pressure flow studies, though at the cost of increased operative time for HoLEP (62.1 versus 33.1 minutes). Long term follow up data at 7 years showed that HoLEP was at least equivalent to TURP with no significant differences Q_{max}, AUA symptom score (AUA-SS), quality of life (QoL) score, BPH Impact Index (BPHII), International Index of Erectile Function (IIEF), International Continence Society Short Form Male questionnaire (ICSmaleSF) Voiding Score, or ICS Male Incontinence Score (IS) after 1 year.[27] No patients who underwent HoLEP required re-operation, while three (17.6%) of those who underwent TURP required further intervention.[27] Kuntz et al found in a prospectively randomized comparison of HoLEP and TURP done for BOO in patients with prostates less than 100 g that while having longer operative times, HoLEP had comparatively shorter catheter time, LOS, and blood loss.[28] Ahyai et al reported 3-year follow up data, showing AUA-SS and PVR were better in the HoLEP grouped compared to TURP.[29] Q_{max} and reoperation rates were similar between the two groups. These results strongly suggest HoLEP to be a true alternative with unique advantages over TURP. Meta-analyses of other trials comparing HoLEP to TURP also found comparable symptom improvement[30] or superior results seen in patients who underwent HoLEP, again demonstrating its advantage over TURP with regard to blood loss, catheterization time, and hospital stay.[30,31] Yin et al found in their meta-analysis that while TURP demonstrated significantly shorter operative times ($p = 0.001$) and lower incidence of postoperative dysuria ($p = 0.003$) compared to HoLEP, Q_{max} and International Prostate symptom score (IPSS) were significantly improved in the HoLEP group ($p < 0.0001$ and $p = 0.01$, respectively) at 12 months postoperatively.[31] In extensive analysis, HoLEP has been found to be at least as effective as the prior gold standard, TURP, for treatment of BPH, with unique advantages.

A multitude of data exist comparing HoLEP to more invasive procedures such as open simple prostatectomy (OSP) or robot-assisted simple prostatectomy (RSP). Kuntz et al reported 5-year follow up results on their randomized controlled trial comparing HoLEP versus OSP for prostates > 100 grams and demonstrated similar improvements in AUA-SS, Q_{max}, and PVR between the two groups.[32] Both groups also demonstrated similarly low reoperation rates (5% in HoLEP, 6.9% in OSP [p = 1.0]). A separate randomized control trial performed by Naspro et al compared HoLEP and OSP in prostates > 70 grams with 2-year follow up data.[33] Their study revealed findings favoring HoLEP, including decreased catheterization time ($p < 0.001$), shorter hospital stays ($p < 0.001$), and decreased blood loss with lower transfusion rates ($p < 0.001$).[33] The study also found similar improvements from baseline in urodynamic parameters, and comparable late complication rates between the two groups, though OSP was found to have decreased operative time. These studies suggest that HoLEP is a minimally invasive alternative to OSP with at least similar efficacy in large prostates. With regard to RSP, Zhang et al performed a study comparing perioperative outcomes between 32 RSP patients and 600 HoLEP patients at two separate academic institutions.[34] Results showed that HoLEP demonstrated reduced mean operative times ($p < 0.001$), decreased blood loss with lower transfusion rates, shorter hospital stay, and decreased catheterization time, with no difference in Clavien 3+ complication rates. This suggests that in expert hands, HoLEP appears to have a favorable perioperative profile compared to RSP, though long term follow up data are not yet available.

Ahyai et al contends that prior studies finding increased operative time for HoLEP, as compared to TURP and OSP likely had some confounding variables, including limited surgeon experience with HoLEP, unavailability of tissue morcellators, and the fact that significantly more tissue was being treated during HoLEP than with other modalities.[35] The study compared 100 TURP and 60 OSP cases from previous randomized controlled trials with a matched pair analysis of 1000 HoLEP cases. These were matched based on documented resected prostate tissue, and resection speed in grams per minute was calculated. The study revealed that resection speed and operative time for HoLEP were significantly faster than TURP ($p < 0.01$) and similar to those of simple OSP ($p \geq 0.21$).

In addition to comparative studies comparing HoLEP to other surgical BPH management options, many large-volume studies with long term data exist. Krambeck et al performed a retrospective analysis of 1065 HoLEPs at a single institution, which showed that HoLEP effectively improved both AUA-SS and Q_{max}; mean AUA-SS decreased from 20.3 preoperatively to 5.3 at 12-month follow up, while Q_{max} increased from 8.4 mL/sec preoperatively to 22.7 mL/sec at 12-month follow up.[36] Elmansy et al retrospectively analyzed 949 patients who underwent HoLEP and had durable improvement in both objective and subjective outcomes at 62-month follow up.[37] To our knowledge, the longest follow up study was performed by Ibrahim et al, and consisted of 1476 patients over an 18-year period who underwent HoLEP at a single institution with over 9 years of follow up data.[38] These patients were found to have significant improvements in mean IPSS ($p < 0.001$) and QoL ($p < 0.001$) compared to preoperative values with only 21 patients requiring reoperation (1.4%). Furthermore, in the 132 patients who could be followed more than 10 years, Q_{max} ($p < 0.001$) and PVR ($p < 0.001$) were significantly improved.

The current AUA guidelines for surgical management of BPH recommend HoLEP and ThuLEP (thulium laser enucleation of the prostate) as the only size-independent treatment options.[3] HoLEP has been more rigorously scrutinized, with more publications, trials, is performed at more institutions, and has been around longer than ThuLEP. Humphreys et al retrospectively analyzed 507 patients who underwent HoLEP and evaluated both objective and subjective measures stratified by prostate size (< 75 g, 75-125 g, > 125 g).[39] No significant differences were found between the three cohorts with regard to hospitalization, catheterization time, AUA-SS, average Q_{max}, average PSA, and complications (i.e. transient stress incontinence, transient dysuria, blood transfusion requirement, strictures). Similar studies have been performed in patients with large prostates > 175 grams[40] and ≥ 200 grams,[41] demonstrating that HoLEP is a safe and effective procedure with satisfactory outcomes and low morbidity, independent of prostate size.

Safety, complications, and adverse effects

HoLEP has demonstrated its safety advantages over TURP and OSP, including decreased blood loss and lower transfusion rates.[8,9,28,30,31,33] The unique properties of the holmium laser allow it to coagulate tissue as it cuts, significantly improving hemostasis during HoLEP. The relatively short wavelength of the holmium laser allows for rapid tissue vaporization, while a shallow depth of penetration and coagulation (0.4 and 0.3 mm, respectively) minimizes damage to surrounding tissue. Additionally, the pulsed laser energy of the holmium laser enables efficient cutting and coagulation of vessels, compared to other laser

energies. Due to these unique properties, HoLEP may be safely utilized in patients with bleeding disorders or those on anticoagulation.[42,43] El Tayeb et al performed a study which compared 116 HoLEP patients who required anticoagulation (AC) or antiplatelet (AP) therapy to 1558 HoLEP patients who were not on AC/AP therapy.[44] The study showed that other than prolonged hospitalization ($p < 0.001$) and duration of continuous bladder irrigation ($p < 0.001$), the use of intermittent or continuous AC/AP therapy did not adversely affect outcomes. With regard to antiplatelet therapy, Sun et al performed a large retrospective study of 1124 HoLEP patients comparing patients who were receiving dual antiplatelet therapy (DAPT), continuous single antiplatelet (AP) therapy, single AP therapy but intermittent during preoperative time, and no AP therapy.[45] Similar complication 30-day complication rates were found ($p = 0.678$) between all groups, with all patients demonstrating improved IPSS, QoL scores, and PVR at 12-month follow up. This literature along with current AUA guidelines recommend that HoLEP is a safe and attractive option for use in patients who are at higher risk of bleeding, such as those on anticoagulation.[3]

In addition to excellent hemostatic properties, previously described size-independent treatment efficacy, HoLEP has also shown an age-independent treatment efficacy and safety profile. Mmeje et al retrospectively analyzed and compared outcomes and morbidity in 311 HoLEP patients aged 50-59, 60-69, 70-79, and ≥ 80 years, with functional outcomes assessed using IPSS, Q_{max}, PVR, and urinary continence.[46] No significant differences were observed between groups with regard to morbidity rates, hospitalization time, 1-year functional outcomes, incidence of Clavien 3+ complications, and change in serum hemoglobin levels.

Intraoperative and postoperative complications from HoLEP are rare, with Krambeck et al describing 24 incidents (2.3%) in a study of 1065 HoLEPs described above.[36] These complications included clot retention (7 patients), significant hematuria prolonging hospitalization (5 patients), open cystotomy to remove adenoma (3 patients), myocardial infarction (3 patients), and atrial fibrillation requiring cardioversion, morcellator bladder injury, cerebral vascular accident, and sepsis (1 patient, respectively). Urethral stricture requiring office dilation ranged from up to 1.3% at short/intermediate term follow up to 0% at long term follow up, while bladder neck contracture rates ranged from 0.8 to 6% over the same follow up period. At the most recent follow up in their study, 3 patients (0.3%) were in urinary retention and significant stress and urge incontinence was noted in 9 (0.8%) and 6 (0.6%) patients, respectively. Similarly, Elmansy et al reported low complication rates, and rates of persistent stress and urge incontinence of 1 and 0.5% in their 10-year follow up data of 949 HoLEP patients.[37] Additionally, 0.8% of patients developed bladder neck contracture, and 1.6% of patients developed urethral stricture with only 0.7% of patients requiring reoperation due to residual adenoma.[37] In the 18-year follow up study described above, Ibrahim et al also reported low complication rates with perioperative blood transfusion required in 0.8% of patients, and postoperative urethral stricture and bladder neck contracture development in 21 (1.4%) and 30 patients (2.1%), respectively.[38] Notably, only 21 patients (1.4%) required repeat HoLEP. With durable long term data and multiple studies, the literature strongly indicates HoLEP as a safe procedure with low complication and treatment failure rates.

Despite its long term durable treatment efficacy and safety profile, HoLEP does carry the risk of ejaculatory dysfunction and altered orgasm perception.[47] Placer et al reported loss of antegrade ejaculation in 70.3% of 202 sexually active HoLEP patients, while 21% reported a reduction in semen quantity.[48] However, rates of sexual side effects appear comparable between HoLEP and TURP/OSP.[33,49,50] Furthermore, Klett et al reported in a retrospective study with 3-year follow up data in 393 HoLEP patients that there was a significant subjective improvement in IPSS compared to baseline ($p = 0.0001$) with no significant change from baseline in mean IIEF-5 scores at 3, 6, 12, 24, and 36 months.[51] Additionally, attempts have been made to maintain ejaculatory function with HoLEP, with Kim et al demonstrating an overall success rate of ejaculation preservation in 46.2% of their patients who received an ejaculatory hood sparing technique.[52] The results of these studies highlight the importance of proper patient counseling prior to HoLEP regarding sexual side effects, while also providing data on promising future directions with regards to optimization of surgical technique.

Patient preference and learning curve

While HoLEP has its distinct advantages and side effect profile, it can be difficult to assess patients' perspectives and satisfaction across the multiple treatment modalities for symptomatic BPH. Abdul-Muhsin et al utilized an independent third-party survey sent to all patients who underwent any surgical treatment for BPH over a 6-year period to help address this question.[53] There was a response rate of 55.6% (479 respondents), including patients who received HoLEP (n = 214), TURP (n = 210), holmium laser ablation of the prostate (n = 21), photoselective vaporization

(n = 18), transurethral incision of the prostate (n = 9), and open simple prostatectomy (n = 7). For the tested individual domains, significant differences were noted in urinary intermittency ($p < 0.001$), weak stream ($p = 0.003$), straining ($p < 0.001$), and QoL ($p = 0.001$), in favor of HoLEP. Additionally, HoLEP demonstrated a significant advantage in voiding ($p = 0.02$) and QoL domains ($p = 0.03$) using ICSmaleSF, as well as the lowest rates of patient regret.

Despite endorsement in the literature and AUA guidelines, wide adoption of HoLEP and implementation in the urology community has been somewhat limited. This is most likely secondary to the steep learning curve of the HoLEP procedure. Relatively few US urologists receive HoLEP training during residency and learning the technique afterward can be challenging. Robert et al conducted a prospective, multicenter observational study involving surgeons experienced in TURP and OSP, but with no previous HoLEP experience.[54] Nearly half of the centers ultimately chose to either abandon the HoLEP technique before the end of the study or to not continue performing HoLEP at the conclusion. In a systematic review assessing the HoLEP learning curve, Kampantais et al showed that HoLEP has an acceptable learning curve with a proposed number of 25-50 cases.[55] A structured mentorship program and the use of simulation can greatly reduce the number of cases needed. A separate systematic review focusing on the complications of the HoLEP learning curve demonstrated that complication rates are similar or lower to those reported by traditional techniques.[56]

Conclusions

Overall, HoLEP has proven to be an extremely effective, safe, and durable treatment for patients suffering from LUTS due to BPH. The AUA guidelines highlight this by recommending HoLEP as a size-independent treatment option for those who are candidates for surgical treatment. The literature shows HoLEP to be an equivalent if not superior surgical solution to TURP and OSP with a growing body of research comparing HoLEP favorably to other techniques such as RSP. While there are some limitations to this technique, including high rates of retrograde ejaculation and a steep learning curve, HoLEP has a large body of literature demonstrating its efficacy, long term durability, and favorable risk profile. HoLEP offers a surgical management option for patients who may not be optimal candidates for other procedures based on prostate size, age, or bleeding risk. Given its widespread utility and durable outcomes, HoLEP is quickly becoming the new gold standard in the treatment of surgical BPH. □

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Developing a men's health program

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Introduction: *Many healthcare disparities exist between men and women due to differences in lifestyles and health seeking behaviors. Such differences lead to higher mortality and lower life expectancy in men. The field of urology has the unique opportunity of acting as a gateway to men's overall health, where a urologist can diagnose medical diseases in patients and refer them to the appropriate specialist. In this review article we discuss the need for men's health programs and our experience with creating such program in Philadelphia.*

Methods and materials: *In this review article we outline our experience with creating a men's health program to serve the diverse Philadelphia population. We discuss the healthcare needs and demographics of our geographical area.*

Results: *We identify factors essential for the success of our men's health program such as: developing a business model, drawing support from our institution, identifying key medical specialties to include in the program, assigning patient navigators and integration of electronic medical records.*

Conclusion: *Men's health program provide tailored care for male patients that best suits their needs and healthcare seeking behaviors. The success of such programs requires commitment from physicians from many medical specialties to provide holistic care.*

Key Words: men's health, program, urology

Introduction

We recognize the healthcare needs and utilization patterns of men are dissimilar to the needs of women. Men have a higher mortality rate and worse health outcomes compared to their female counterparts. World Health Organization (WHO) data in 2012 showed that men were more likely to die younger than women in every country surveyed, with some countries showing a male death rate twice as high as females. Also, men have a lower life expectancy than women worldwide, and this life expectancy gap is projected to broaden overtime.[1] In the United States, men die 5.4 years earlier than women and have a 43% higher all-cause death rate.[2] This discrepancy in mortality is secondary to modifiable (diet, exercise, healthy behavior, occupational exposure, substance use) and unmodifiable risk factors (genetics). Research into differences between female and male behaviors found that males are more likely to engage in harmful activities such as smoking, drug and alcohol use, and medical care avoidance.[3] One driving force for such risky health behaviors is the societal construct of masculinity. Such standards promote risk-taking, avoiding healthy behaviors, and putting work ahead of all other responsibilities.[3] Encouraging positive societal peer pressure can encourage men to live healthy lives and develop healthy habits. Houle et al showed that men with positive peer pressure from family and co-workers are more conscious about their health, develop healthy habits, and improve interpersonal relationships.[4]

Men view their healthcare needs from a different perspective than our female counterparts; whereas women tend to focus on prevention, men tend to focus on repair. Though women visit the doctor 150% as often as men, men cost the healthcare system more than women because they seek care at more advanced stages of disease. Reasons for this disparity are many, including male perception of a strong, unbreakable self-image, attitudes towards financial and family responsibilities, and denial. Twenty-five per cent of men have acknowledged they would wait as long as possible before seeking care for a specific problem.[5] Men tend to have a higher mortality risk due to cardiovascular, pulmonary and infectious diseases. Additionally, men demonstrate a higher disposition towards behaviors such as smoking, alcoholism, substance abuse, unsafe sex, and other high risk behaviors leading to intentional and unintentional injuries. Avoidance is especially common in men ages 20 to 40. In this age range, men are twice as likely as women to die from any cause.

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Differences in behavior between men and women lead to discrepancies in healthcare needs and utilization. Healthcare avoidance behavior prevents men from seeking screening tests which can diagnose diseases in their early stages and reduces healthcare cost.[1] The unique healthcare seeking behavior of men requires targeted outreaching and health programs to meet their health needs. Programs which target specific groups of men have been shown to be effective if the information is perceived to be individualized and if the medical staff fosters autonomy and shared decision-making.[6] Robinson et al examined the efficacy of targeted men's health program and note that an important factor for success is the personalization of information to make it relatable to men at different stages of their health journey. This personalization can be achieved by including: resources to support men's social interactions, encouraging support from peers, promoting ownership over information, and providing support for shared decision-making.[6]

Even though many studies have examined the need for a Men's Health Program, few studies outline the process of developing one. In this article, we will discuss our experience with creating a Men's Health Program at Thomas Jefferson University Hospital to serve the diverse population of Philadelphia and the Greater Delaware Valley.

Urology as a gateway to health

Urology may be viewed as the portal into overall male health.[7] Men are more likely to see an urologist for sexual and urinary dysfunction than see their primary care physician for routine healthcare visits. A urology office visit should be seen as an opportunity to evaluate a man for risk factors such as cardiovascular disease and diabetes which can be discovered during workup of erectile dysfunction.[7] Recognizing the need for an organized approach to Men's Health, The American Urological Association (AUA) established a Committee on Male Health with the goal "to promote lifelong male health, wellness, and disease prevention through integration of expertise from urology and other healthcare specialties."[8] The committee then developed the AUA Men's Health checklist as a guide to men's health based on age. The checklist includes age based recommendations for health maintenance, health screening and cancer screening to be utilized by urologists and primary care providers.[8]

Our population

According to the 2017 US Census, the Greater Delaware Valley ranks as the eighth largest in the nation, numbering 7.2 million people. The city of Philadelphia, the region's economic center, has 1.6 million residents.[9] Data would support a city-wide incidence of erectile dysfunction of 120,000 and a regional incidence of 450,000 men.[10] The Olmstead County Survey found 17% of men age 50-59, 27% of men 60-69, and 37% of men 70- 79 years of age have symptomatic BPH which deserves diagnosis and treatment.[11] The American Heart Association estimates nearly half of Americans have heart disease. CDC data from 2015 showed that 10.8% of adults older than 20 years of age living in Pennsylvania suffer from diabetes, 28.6% suffer from obesity, and 37.9% suffer from heart disease.[12] With such prevalence of urological and non-urological conditions, it is necessary to address the healthcare needs of our population in a holistic approach that ensures patients' compliance. Prior to the creation of our health program, Philadelphia and surroundings lacked a multidisciplinary Men's Health Program.

Many different types of men's programs exist. Some are devoted entirely to the diagnosis and management of erectile dysfunction; other programs focus on research. At Thomas Jefferson University, the goal was to develop a multidisciplinary program which focuses on a comprehensive approach to Men's Health, emphasizing Urology, Cardiology, Endocrinology, Primary Care, Sports Medicine, and Sleep Medicine. Each department at our institution offers a full complement of subspecialists who are able to respond to an individual patient's needs, regardless of complexity. For example, within the Urology section of the Program, we offer care in reconstruction, erectile dysfunction, infertility, voiding dysfunction, and oncology. Using the AUA Men's Checklist as a guide, we developed baseline diagnostic studies for new patients enrolled in the program.

Birth of the men's health program

A needs assessment targeting the Greater Delaware Valley was performed with the assistance of a consulting group. The analysis included the volume of patients, established competitors, and insurance demographics. A business plan was developed in strong collaboration with University administration. Of note, our administration provided invaluable support throughout the program's creation, and continues to help insure its success.

Cooperating physicians in each of the key areas were identified who would represent the perceived areas of greatest patient need, i.e. erectile dysfunction, voiding dysfunction, cardiovascular disease, diabetes, sleep apnea, sports related injury prevention and

management, and primary care. A central location was identified which would facilitate "one-stop shopping" for patients, and facilitate physician interaction. Our facility conveniently offers outpatient surgical, radiologic and pharmacy services as well.

A Patient Navigator was determined to be essential to programmatic success. The role of this individual is manifold, including coordinating patient intake, identifying specific patient needs, scheduling same-day appointments, monitoring patient follow up, maintaining the patient database, coordinating marketing efforts, and community outreach. Internal marketing through the University Intranet introduced the program to the Jefferson community. Individual departments of medicine and surgery, including subspecialties, were supplied with patient information brochures. Referring physicians were invited to introductory lectures given by the participating physicians. These doctors also gave lectures focusing on their area of expertise in relation to Men's Health at community events in the Philadelphia region. Other modes of external marketing included newspaper articles and social media outlets. These featured physicians affiliated with the program targeting audiences to raise awareness of pertinent medical issues, highlighting the benefits of our Men's Health program.

Incorporation of electronic medical record

Integration of the University Electronic Medical Record (EMR) is an essential element for the Men's Health Program. The EMR must allow the patient to be enrolled regardless of the portal of entry. At Jefferson, patients may be scheduled directly by patients through a universal call-in number (1-800-JEFFNOW), through the patient navigator, or from individual physician offices. Additionally each physician is empowered to nominate patients electronically. The EMR is also instrumental in following patients as they move through the system. For example, a patient seen in Urology, determined to need evaluation by Endocrinology, is referred via the EMR. The patient's intake note from the initial physician is read by the consulting physician and the primary healthcare professional. In turn, the consultant's recommendations are transmitted to all involved, as well as pertinent diagnostic studies. Communication amongst providers is thereby accomplished; the patient is included as well in the information exchange. The EMR also allows patients to email directly with the treating physicians, allowing for timely and effective communication. The EMTR also enables the patient to view their diagnostic results.

Programmatic success may be calculated several different ways. The EMR enables determination of raw patient numbers managed, and their demographics. Patient satisfaction studies may be incorporated as well through after visit surveys. It also allows for collection of pertinent financial data, including downstream revenue attributable to the program. Data for academic research and publication may be captured as well.

Conclusion

The development of a successful Men's Health program mandates defining programmatic goals. It requires a robust infrastructure which includes a strong commitment from providers, marketing, informational technology and financial/investment support. The rewards to be gained include increased patient volume, greater downstream revenue, but most importantly, an increase in patient awareness ultimately yielding improved long term patient outcomes. □

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