

Is it time to offer True Minimally Invasive Treatments (TMIST) for BPH? – A review of office-based therapies and introduction of a new technology category

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Introduction: The options for treating benign prostatic hyperplasia (BPH) beyond medication and traditional transurethral surgery continue to expand. Undesirable side effects to medication and surgeries have driven interest toward minimally invasive surgical therapies (MISTs), including convective water vapor ablation (Rezum) and prostatic urethral lift (UroLift). While these treatments can be performed outside of the operating room, they do require special equipment and the use of rigid cystoscopy. A new class of treatments, which utilize no special equipment beyond a flexible cystoscope are emerging, the first of which, the temporary implantable nitinol device (iTind) is already FDA approved.

Materials and methods: A comprehensive review of the literature using PUBMED, EMBASE, Scopus focused on the two commercially available MISTs, Rezum and

UroLift, was performed. Additionally, we evaluated the existing literature for the novel iTind.

Results: UroLift and Rezum have demonstrated significant improvements in validated questionnaires such as IPSS and IPSS QoL. They generally maintain erectile function (IIEF) and ejaculatory function (MSHQ). The short term recovery seems to slightly favor UroLift, while re-treatment rates seem to favor Rezum. The iTind also appears to improve subjective and objectives outcomes, though longer term follow up is still maturing.

Conclusion: The currently available MISTs have changed the way we treat BPH, offering a middle ground for men between oral medical therapy and more invasive transurethral surgery. While these MIST treatments require specialized and costly equipment, the proposed a new category, the True Minimally Invasive Surgical Therapy, or TMIST, offers an off-the-shelf, affordable and comfortable solution for men suffering from LUTS secondary to BPH.

Key Words: benign prostatic hypertrophy (BPH), true minimally invasive surgical therapy, TMIST, office-based therapies

The ever-increasing impact of benign prostatic hyperplasia (BPH) is truly a global phenomenon. An

aging population and improved access to 21st century endoscopic care means more men will be diagnosed and treated for BPH. We are all too familiar with the dogma of watchful waiting, medical therapy and finally surgical intervention. Depending on where you live in the world, the options are various. Transurethral resection of the prostate (TURP) has been the mainstay of management for nearly a century. TURP and its laser alternative offsprings offer durable outcomes with ever

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increasing safety profiles. However, the sheer number of men requiring surgical intervention vastly outpaces our operative resources. Medical therapy has alleviated some of the demand on surgery yet many men remain dissatisfied with both long term medications and current surgical choices. Not to mention, many men managing LUTS with medical therapy may develop, silently, long term permanent damage to their bladders from chronic bladder outlet obstruction. The burden of taking pills daily for life, along with the sexual (erectile, libido and ejaculatory) side effects is off-putting to numerous men. Surgery is no better, with the need for general anesthesia, recovery off work to convalesce and the inherent risks of complications including urinary incontinence, bleeding and permanent ejaculatory dysfunction.

In light of such BPH treatment shortcomings, we have witnessed the introduction of the minimally invasive surgical therapies (MISTs) in the past 5 years. While the interest of an office-based therapy have been sought after with earlier iterations (i.e TUNA, TUMT), we currently have two commercially-available, FDA and Health Canada approved and guidelines endorsed options, UroLift (NeoTract/Teleflex Inc., Pleasanton, CA, USA) and Rezum (Boston Scientific Corp., Marlborough, MA, USA). Both technologies alleviate the burden on operating room resources as they can be performed in other settings without the need for general anesthesia.

Prostatic urethral lift (PUL) or UroLift uses intraprostatic implants to retract obstructing prostate tissue inward towards the capsule. Numerous studies have been conducted since 2011, when Woo et al, first described their initial experience.¹ In the LIFT study, a prospective, randomized, sham-controlled, double-blinded clinical trial, 140 men underwent UroLift implantation, while 66 had sham rigid cystoscopy. The most recent 5-year follow up reported improvements in IPSS from 22.3 to 14.5 and improved IPSS QoL from 4.6 to 2.5. Qmax showed modest improvement from 7.9 mL/s to 11.1 mL/s. Notably, there were no de novo cases or erectile or ejaculatory dysfunction.² The surgical retreatment rate at 5 years in this cohort was 13.6% and there were 13 patients who had implants removed from the bladder. The sham group was allowed to cross-over and their 2-year outcomes (IPSS, IPSS QoL, Qmax) were similar to the treatment group with 10% requiring retreatment.³ The BPH6 study in 2017 was a randomized clinical trial comparing UroLift to TURP. The TURP group experienced greater improvements in IPSS and Qmax, however the UroLift group had superior recovery and ejaculatory function preservation. UroLift did not improve post-void residual (PVR), whereas TURP did experience reduced PVR.⁴ The recent MedLift study examined the application of UroLift in

patients with obstructing median lobes, who would have been excluded from the original LIFT study. This modified technique to treat the median lobe resulted in durable improvements in IPSS, IPSS QoL, Qmax, and a retreatment rate of 2% at 1 year.⁵

Convective water vapor energy (WAVE) ablation or Rezum uses radiofrequency to heat water into steam which is injected transurethrally into the obstructing prostate tissue resulting in cell death and volume reduction. The first prospective study in 2016 of 65 men showed significant improvements lasting up to 2 years with no changes in ejaculatory or erectile function. Retreatment occurred in only one patient.⁶ The pivotal Rezum II prospective, multi-center, double-blinded randomized controlled trial included 135 treated men and 61 sham controls. The outcomes of the cohort, which has been followed for 4 years, was published in 2019.⁷ McVary et al showed significant improvements in IPSS (21.4 to 11.4), IPSS QoL (4.3 to 2.3), Qmax (9.5 mL/s to 13.7 mL/s), and a surgical treatment rate of 4.4%. There were no cases of de novo erectile dysfunction and transient anejaculation in 4 patients which resolved after 3 months. A subsequent series by Darson et al reported similar improvements in 131 men with a retreatment rate of 3.1% at 1 year.⁸ Mollengarden et al reported on 129 men with 6 months follow up.⁹ Again, similar consistent improvements were seen with a 2.3% retreatment rate. Ejaculatory and erectile dysfunction were each reported at 3.1%.

These technologies have captured the interest of many patients seeking an alternative to TURP and a more convenient single treatment compared to daily medical therapy. Additionally, the significantly lowered risk of erectile and ejaculatory dysfunction makes these two treatments highly attractive to men who place value on these outcomes. There is no doubt that both Rezum and UroLift are efficacious at improving male lower urinary tract symptoms with 5-year published outcomes and with a safety profile that exceeds traditional transurethral surgery. Urologists with varying backgrounds and education have been able to be trained to perform these MISTs properly around the world with a very short learning curve.

However, if we take a step back from the advantages of MIST, there remain drawbacks worthy of mention. The first is equipment limitations. Standard urological equipment already available in urology departments is unfortunately not enough to gain entry into the MIST space. A specialized, extra-long and thin bronchoscope lens is required in the case of UroLift. Similarly, for Rezum, a dedicated, computerized radio-frequency steam generator for the procedure is required. Furthermore, the environmental carbon footprint to

these procedures can be staggering. The amount of packaging and boxes discarded at the end of a list of MIST cases does give one pause about the expense and waste left behind. With regards to total procedure costs, MIST procedures are unfortunately not cheap. Whether it's a hospital, an insurer, or a patient paying, the economic cost is sizable. In Canada, a single-use Rezum handpiece is around \$3000 CAD and a single UroLift implant is around \$1000 CAD (typical case requires 4-6 implants). While these are defined as minimally invasive procedures, many are still performed in operating rooms or ambulatory surgical centers using up resources, which could be put towards other conditions. Most still require some form of local anesthesia and/or sedation to be comfortably performed.

Not to be misunderstood or misinterpreted, we believe MISTs are currently excellent alternative BPH options for many urologists and their patients around the world. Thus far, they have treated countless men, allowing them to come off of medications or avoid more invasive surgeries. They play an important and rapidly growing role in the procedural management of BPH, a role that is here to stay. However, we need to rethink what a MIST is and whether we can offer something that changes the paradigm of BPH treatment. Herein, we would propose a novel concept, the TMIST – True Minimally Invasive Surgical Therapy.

We believe a unique category of TMIST should be an off-the-shelf solution requiring nothing more than a standard flexible cystoscope. The TMIST should be performed in a cystoscopy suite or office setting without the need for general anesthesia or sedation, special capital equipment, or additional planning steps. Conceptually speaking, similar to a patient who undergoes cardiac angiogram where stents may be placed, the male patient coming in for a diagnostic LUTS evaluative cystoscopy would consent concomitantly for the placement of a TMIST in the same setting. The urologist would evaluate the prostate and degree of bladder outlet obstruction and ask for a TMIST device from the shelf, stored alongside the guidewires and stents. The flexible scope would already be positioned and the TMIST device would simply be implanted directly into the prostatic urethra. To further flip every notion of BPH therapy we would propose that the targeted durability of TMIST be between 12-18 months.

The first TMIST already introduced is the Temporary Implantable Nitinol Device or iTind (Medi-Tate, Hadera, Israel), which received FDA approval in 2020. The iTind is a nitinol device with three elongated struts placed through a flexible or rigid standard cystoscope into the prostatic urethra, whereby through pressure-induced ischemic necrosis it expands. The result is a remodelling/opening

of the prostatic lumen. The device is then retrieved after 5 days under local anesthesia through an open-ended foley catheter. The first-generation Tind was studied in 32 patients with an average prostate volume of 30 mL. There were significant and durable improvements in IPSS, IPSS QoL, and Qmax out to 3 years.¹⁰ The second generation iTind was evaluated in the MT-02 study in 81 patients. The 3 year follow up showed durable improvements in IPSS (22.3 to 12.1), IPSS QoL (4.0 to 2.2), Qmax (7.3 mL/s to 13.4 mL/s), and PVR (78.7 mL to 42.6 mL).¹¹ There were no changes in erectile or ejaculatory function, with a surgical retreatment rate of 8.6% after 3 years. De Nunzio et al reported the 6-month outcomes of 70 men treated with the iTind in a prospective, multi-center study.¹² There are significant improvements in IPSS, IPSS QoL, and Qmax with improvements seen as early as 4 weeks, and no change in SHIM score and an improved MSHQ-EjD score.

There are other devices in phase 3 trials (Zenflow Spring System, Medeon Mercury Expander System, Urotronic Optilume-BPH drug coated balloon) that could fit the mold of a TMIST. When it comes to TMIST, the comparison that should be made is against medical therapy for BPH, not MIST or TUR surgery. The opportunity to diagnose and treat men's BPH during a simple, in-office flexible cystoscopy could completely change the way we approach BPH. Durability does not necessarily have to be the Holy Grail for BPH therapy. When we balance drug persistence rates, adverse drug side effects, MIST costs, and surgical risks and resources, we end up with a not entirely favorable proposition. However, as high volume BPH treaters, we see an opportunity. One where we develop truly minimally invasive surgical therapies (TMISTs) that focuses more on easing the BPH patient journey, usurping the need for medications, while decreasing the cost to the healthcare system and/or patient and being readily available without the need for added equipment.

Disclosures

Dr. Dean Elterman is a consultant and investigator for Boston Scientific, Medeon, Medi-Tate, PROCEPT BioRobotics and Zenflow.

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