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Review Article

Update on the management of benign prostatic hyperplasia and the role of minimally invasive procedures

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ABSTRACT

Lower urinary tract symptoms due to benign prostatic hyperplasia constitute a substantial burden, affecting the quality of life of those affected by this condition. While watchful waiting and medical management using a wide array of pharmaceuticals can be effective, surgery has been one of the most definite solutions for those highly affected by this condition. Transurethral resection of the prostate (TURP) is the gold standard surgical procedure, but other alternatives using laser (HoLEP and ThuLEP) and robotic water jets (Aquablation) are emerging treatments aimed at reducing postoperative morbidity. Minimally invasive procedures conducted in outpatient settings and under local anesthesia or sedation are increasingly being used, especially in those patients with high surgical risk due to comorbidities. These procedures include prostatic arterial embolization, water vapor thermal therapy (Rezum), prostatic urethral lift (Urolift), temporary implantable nitinol device (TIND/iTIND), and transurethral microwave thermotherapy (TUMT). The evidence supporting these treatments is growing, but some uncertainties remain as to what is the magnitude of their advantages and disadvantages compared to TURP. Innovations in the technologies involved in these new procedures may improve their profile for effectiveness and safety. Moreover, new devices are being investigated for marketing approval. Issues around costs and patients' preferences are also yet to be elucidated, thus their evolving role needs to be weighed against the aforementioned considerations.

1. Introduction

Benign prostatic hyperplasia (BPH) is a noncancerous enlargement of the prostate gland due to androgenic stimulus exerted by dihydrotestosterone, a metabolite derived from testosterone by the action of the enzyme 5-alpha reductase.[1] The most important risk factors for developing BPH include age and the presence of functioning testicles (due to their hormonal influence); a family history of this condition and obesity.[2] A total of 50% of 60-year-old men and 90% of 85-year-olds have microscopic BPH; however, only 50% of patients with this histological finding will have a macroscopic enlargement of the gland, and about 50% of these will develop symptoms.[3] Therefore, the most appropriate name for this entity is "lower urinary tract symptoms" (LUTS), considering that prostate enlargement is only one of the factors related to the presence of symptoms. The prevalence of LUTS is between 10% and 30% for men in their 60–70s and 30% in their 80s.[4]

Patients may present with obstructive or irritative symptoms.[1] Diagnosis is based on clinical history, and complementary studies are very useful to evaluate the degree of obstruction, rule out complications, and exclude other differential diagnoses.[1] Disease severity can be assessed using valid questionnaires, including the International Prostate Symptom Score (IPSS), which consist of seven questions rated on a 0–5 Likert scale, and the total score ranges from 0 to 35.[5] Based on the sum score, symptoms can be classified as mild (0–7), moderate,[8–19] or severe.[20–35] An additional question rates from 0 to 6 the overall impact in the quality of life (IPSS-QoL).[5] Long-term complications of BPH include acute urinary retention (AUR), recurrent urinary tract infections, bladder stones, and post-obstructive kidney failure. AUR is one of the most frequent complications, and the risk is up to 14% in 10 years in patients with large prostates and moderate to severe symptoms.[6].

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2. Medical management

The natural history of BPH shows that the progression of symptoms is very slow, and serious complications are infrequent. Watchful waiting and lifestyle modifications may be warranted in those with mild symptoms. Physical activity could reduce the symptoms of prostatism, so the recommendation to exercise regularly could be part of this management strategy.[7] Clinicians frequently advise avoiding irritants, such as coffee, spicy foods, and alcohol, although there is little to no evidence to support these recommendations.[8]

For those with moderate symptoms, alpha-blockers are the first treatment option, reducing symptoms by 30–40% and improving urinary flow by 20–25%.[9] Common side effects include hypotension and ejaculatory dysfunction. However, 5-alpha reductase inhibitors (5-ARI) can cause a moderate reduction in symptoms (15–30%) and prostate size, reducing the risk of AUR and the need for surgery, but there is a latency for this improvement (3–6 months), and they are most effective in patients with larger prostates (>30 cc) that will be treated on a long-term basis.[9,10] Patients should be warned that side effects include sexual dysfunction (e.g. erectile and ejaculatory disorder). In highly symptomatic patients with large prostates, the combined use of alpha-blockers and 5-ARI can result in faster symptomatic improvement and a reduction in the incidence of long-term complications.

Other drugs can be considered in the presence of specific symptoms. The result of clinical trials of phosphodiesterase inhibitors (PDE-Is) such as tadalafil indicate that they may be marginally beneficial over placebo in reducing LUTS.[11] While there is a potential risk of hypotension in combination with alpha-adrenergic blockers, a recent meta-analysis reported that a concomitant treatment with α-blockers and PDE-Is does not increase the rate of adverse events due to hypotension.[12] Tadalafil may be considered in patients with persistent symptoms in the context of concomitant erectile sexual dysfunction, although it requires close monitoring of adverse events. Moreover, LUTS due to BPH may coexist with symptoms of urgency, frequency, and incontinence due to detrusor overactivity (i.e. overactive bladder). In these cases, beta-3 adrenergic agonists, such as mirabegron and vibegron, stimulate detrusor relaxation without compromising bladder contractility. According to the available clinical trials, they would be effective in reducing irritative symptoms.[13] They can be used alone or in combination with anticholinergics. Common side effects include an increase in blood pressure.

Phytotherapeutic agents, such as *Serenoa repens*, also called *Sabal serrulatum* or Saw palmetto, have failed to demonstrate symptomatic relief in multiple clinical trials against placebo.[14] Pumpkin seeds (*Cucurbita pepo*) and African plum (*Pygeum africanum*) in some small clinical trials have moderate efficacy in reducing symptoms.[15] These drugs have fewer adverse events, but considering their limited effectiveness, their role in treating LUTS is limited.

3. Surgery and minimally invasive procedures

Transurethral resection of the prostate (TURP) is one of the most widely used techniques, and the probability of symptomatic improvement with this treatment is between 75% and 96%, and it is considered the “gold standard” treatment. The intervention is brief (usually within 60 minutes) and requires general or spinal anesthesia. The tissue is removed through the urethra using a resectoscope, and the patient remains with a bladder catheter for approximately a couple of days, and after this period, he is discharged from hospital.[16] The morbidity associated with TUR varies between 5% and 30%. Intraoperative complications include uncontrollable bleeding and capsular perforation with the consequent massive absorption of irrigation fluid (“post-TURP syndrome”) and its consequences dilutional hyponatremia, acute renal failure due to hemolysis, cerebral edema, and even death.[17] Early postoperative complications include hematuria, which may persist for up to six weeks, and infection; whereas, late complications include urethral stricture (<10%), bladder neck fibrosis, and urinary incontinence (~1%).[18,19] The most frequent late adverse effect of TURP is retrograde ejaculation (66% to 86% of operated patients); it can produce sterility but be not accompanied by alterations when achieving orgasm. Between 10% and 15% of patients present with psychogenic erectile dysfunction after TUR, and up to 2% to 5% with surgery-derived erectile dysfunction.[20,21] The reoperation rate is close to 3.3%, mostly related to the aforementioned late complications.[22,23] Improvements in TURP technique, including the use of bipolar energy, have reduced the risk of post-TUR syndrome and bleeding.[23]

4. Alternatives to TURP with spinal anesthesia

There are currently several surgical procedures with laser devices for the treatment of BPH, which allow the use of saline solution as an irrigation medium (with the same advantages as bipolar TURP) and are performed on an outpatient basis under spinal anesthesia with a requirement bladder catheter that averages 24 to 48 hours.[24] Laser *enucleation* uses a technique that, similar to open surgery, consists of resecting the middle and lateral lobes from the verumontanum to the bladder neck and then grinding the surgical material in the bladder for pathological study using Holmium (HoLEP) or Thulium (ThuLEP) lasers. This procedure offers results comparable to TURP with less morbidity and hospital stay.[24,25]

Laser *ablation*, on the other hand, is a technique that uses lasers to cauterize glandular tissue until an adequately patent prostatic canal is achieved. Similarly, photo-selective vaporization of the prostate (PVP) uses green light for this purpose.[26] The disadvantages of ablation and vaporization procedures include the impossibility of obtaining material for biopsy and a time of dysuria that is usually longer than with TURP; whereas, the advantages over the latter are a shorter hospital stay, subsequent bleeding, and the need for a bladder catheter, with similar results in terms of symptom improvement.[25,26]

Finally, water ablation therapy (also known as Aquablation®) is a recently developed surgical procedure that, using real-time visualization and ultrasound, uses a high-velocity, non-heated, sterile saline water jet to ablate prostate tissue. This procedure is probably as effective as TUR with a lower incidence of ejaculation problems, but no little difference in erectile function.[27]

5. Alternatives to TURP using local anesthesia or sedation: minimally invasive procedures

Many patients with moderate or severe symptoms are older adults with a high surgical risk, which led to the emergence of minimally invasive alternatives that, unlike the aforementioned procedures, can be performed with local anesthesia, on an outpatient basis, and selective post-procedure catheterization. These procedures, with the exception of arterial embolization, in principle, are not designed for large prostates. These procedures include as follows:

Prostatic arterial embolization (PAE): using femoral or radial artery puncture and guided by a preoperative assessment (using CT or MRI) of the pelvic artery anatomy, super-selective microcatheterization and embolization is then performed on the prostatic arteries to induce tissue necrosis.[28] Particle emboli are used

almost exclusively, with wide variation in the type and size of particles.[29]

Prostatic urethral lift (PUL, Urolift®, Teleflex Inc., Pleasanton, CA, USA): using a handheld pistol grip to which a needle-shaped probe is attached, four hook-shaped implants are placed to pull the urethral wall to expand the inner lumen, and two in each one of the lateral lobes of the prostate. This procedure is generally not used to treat a hypertrophied median lobe of the prostate, which causes obstructive intravesical protrusion of the prostate.[30]

Temporary implantable nitinol device (TIND®, Medi-Tate Ltd., Hadera, Israel): a cage-like device expands the lumen of the urethra causing necrosis to the adjacent prostatic tissue. This device was modified in its original 4-strout to a 3-intertwined strout to reduce the risk of mucosal damage into a second generation (iTIND®).[31]

Water vapor thermal therapy (WVTT, Rezum®, NxThera Inc., Maple Grove, MN, USA): it uses radiofrequency to create thermal energy through a jet of water vapor that triggers prostatic necrosis. This procedure is performed with the person in the dorsal

Table 1
Summary of the main trials and systematic reviews for minimally invasive procedures.

Study name (trial period)	Country	n	Follow-up	Main characteristics
Convective radiofrequency water vapor therapy (Rezum)				
McVary 2016 (2013-2014)	USA	197	3 months	• **Pivotal study** – sham comparison • Lower IPSS scores (MD -6.70, 95% CI -8.90 to −4.50), similar erectile function, and minor adverse events compared to sham. • Uncertainties about retreatment rate (cross-over at 3 months) • Low certainty of evidence.
Prostatic arterial embolization (PAE)				
Jung 2022 (Cochrane review of trials)	Europe and China	217	24 months	• **Two main long-term follow-up trials** • PAE may result in little to no difference in urologic symptom scores (MD 2.58 points, 95% CI −1.54 to 6.71; meta-analysis of 2 trials with 176 participants; $I^2 = 73\%$), adverse events, and sexual adverse events (low certainty evidence) • PAE likely increases retreatments (RR 3.80, 95% CI 1.32 to 10.93; one trial with 81 participants; moderate-certainty evidence)
Pisco 2020 (2014–2018)	Portugal	80	6 months	• Sham comparison • Lower IPSS scores (MD -12.70, 95% CI -15.69 to −9.71), similar erectile function, and minor adverse events compared to sham (low certainty evidence) • Uncertainties about retreatment rate (short-term follow-up)
Prostatic urethral lift (PUL)				
Gratzke 2017 (2012–2013) • **First longer-term comparison with TURP.** • Higher IPSS scores (MD 4.80, 95% CI 1.11 to 8.49), but similar erectile function, retreatment rates and adverse events compared to TURP (moderate to low certainty evidence)		Europe	91	24 months
Roehrborn 2013 (2011) • **Pivotal study** – sham comparison. • Lower IPSS scores (MD -7.30, 95% CI -9.73 to −4.87), similar erectile function, and minor adverse events compared to sham (moderate certainty evidence). • Uncertainties about retreatment rate (cross-over at 3 months)		North America and Australia	206	3 months
Temporary implantable nitinol device (TIND)				
Chughtai 2020 (2015–2018)	USA/Canada	185	3 months	• **Pivotal study** – sham comparison • Lower IPSS scores (MD -7.30, 95% CI -9.73 to −4.87), similar erectile function, and minor adverse events compared to sham (before cross-over). • Uncertainties about retreatment rate (cross-over at 3 months)
Transurethral microwave thermotherapy (TUMT)				
Franco 2021 (Cochrane Review of studies between 1994–2002)	Europe and the US	1919	6 months–5 years	• Ten studies compared TUMT with sham and **six studies compared TUMT with TURP**, mostly studies at a high-risk of bias and short-term follow-up. • TUMT probably results in little to no difference in IPSS scores compared to TURP (MD 1.00, 95% CI −0.03 to 2.03; meta-analysis of 4 studies with 306 participants) and fewer adverse events (RR 0.20, 95% CI 0.09 to 0.43;

(*continued on next page*)

Table 2
Guidance to engage in conversations about minimally invasive treatments

Steps in shared decision-making	Example of triggers for conversations with the patient
Invite the patient to shared decision-making *(choice-talk)*	I would like to discuss what is the best treatment option for you, would you be interested in talking about it? The decision about having surgery can be complex and we might need to discuss the alternatives and your thoughts about it. Would you like me to discuss the available options?
Help explore and compare treatment option *(option-talk)*	An option may be to continue taking the medication, in your case and because you are stable in relation to your symptoms, surgical treatment may not have additional improvements, however, in the case of not opting for surgical treatment it is important to know that there is a risk of acute urinary retention in the coming years (the probability of this will depend on the size of the prostate and how much urine you retain). On the other hand, if you choose surgical treatment, the risk of acute urinary retention will be lower; however, it is important to consider the risks of postoperative complications of the different procedures, which include: ejaculatory problems (66% to 86%), erectile dysfunction (up to 5%), blood in urine and in some rare cases urinary incontinence All of these could occur less frequently with some minimally invasive procedures, although it is important to consider that these have a high rate of need for long-term retreatment (that means, again for surgery).
Inquire into the patient's values and preferences *(option-talk)*	Looking at the alternatives, benefits, and harms, what is most important to you? How important are the benefits? What do you think about the side effects?
Evaluate the decision *(decision-talk)*	Do you need additional information or consult someone else before making a decision? Do you want to make a decision now or later? How comfortable are you with the decision we made?"

lithotomy position, and using a cystoscopy, a treatment needle delivers injections of water vapor lasting approximately 9 seconds.[32]

Transurethral microwave thermotherapy (TUMT): this is one of the first procedures developed in this category. TUMT uses a transurethral probe to radiate heat to the prostatic tissue causing necrosis.[33] A rectal probe may be inserted and can be used to monitor rectal temperature.[34] There are different types of devices and manufacturers, including those using high-energy to reduce the time of the procedure and urethral cooling to reduce damage.[33]

Most of these procedures have a low rate of major complications compared to TURP (see below). Pain, dysuria, urinary retention, and urinary tract infection are common side effects.[32,35–39] In the case of PAE, some of these local and systemic adverse events (dysuria, pain, fever, and nausea) are clustered in a poorly defined "post-PAE-syndrome."[40]

5.1. Benefits and harms of minimally invasive procedures

Based on a Cochrane review with network meta-analysis, PUL and PAE are likely to be more effective in reducing urinary

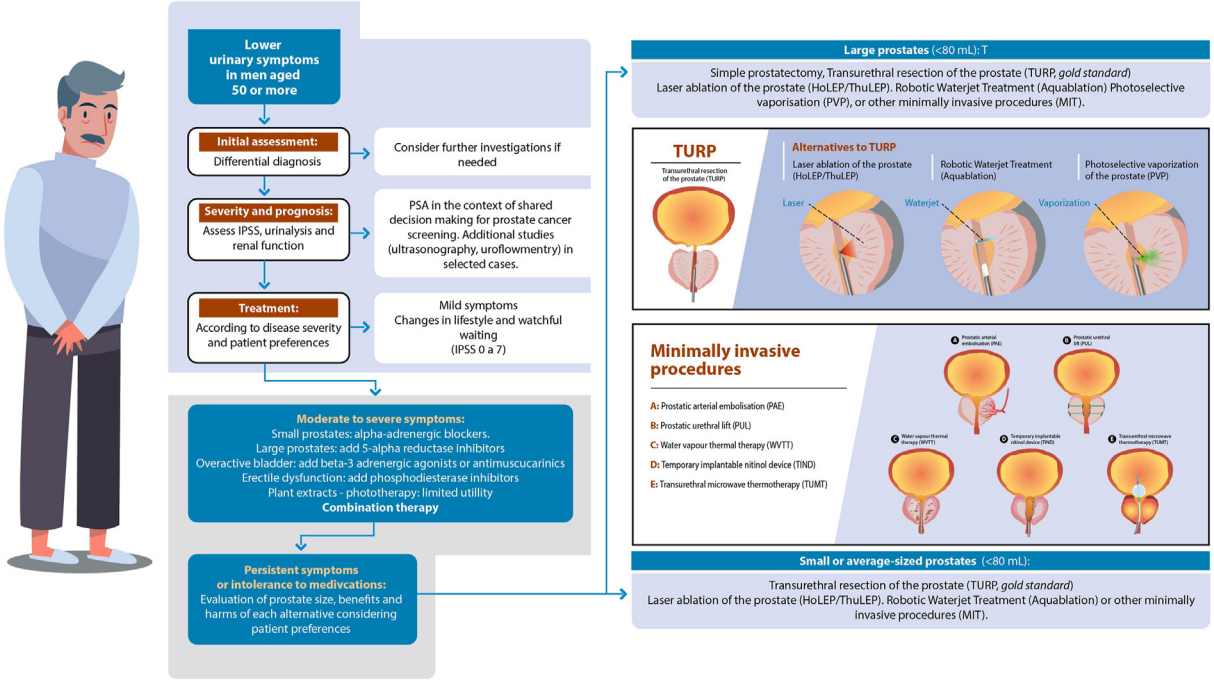

Fig. 1. Summary of the current management of lower urinary tract symptoms due to benign prostatic hyperplasia in men.

symptoms, among other minimally invasive procedures. See Table 1 for a summary of key trials[41–45] and systematic reviews[46–49] for each of these procedures. The evidence is limited and of low to very low certainty and short-term follow-up (<12 months).[22,50] Major adverse events across procedures may also be less frequent than TURP. The evidence is insufficient on the effects of minimally invasive procedures on sexual outcomes, including erectile and ejaculatory function. This brings into question the labeling of "ejaculation-preserving" procedures as they have not been able to demonstrate better sexual outcomes.[51] This is due to the fact that most studies did not systematically evaluate these outcomes using validated outcome measures or only assessed them in a subset of participants, breaking the principle of randomization. The rate of retreatments is very uncertain for some procedures for which the trials were unblinded and participants crossed over at three months (WVTT and TIND). Nevertheless, at long-term follow-up, retreatment rates were higher than TURP for PAE and PUL, but specially for TUMT, which was nearly ten times more than TURP.[22,50] Following the numerous trials on TUMT in the 1990s and 2000s, prostatic arterial embolization has the largest evidence based on randomized controlled trials, counting seven studies with 488 participants, some with two-year follow-up, in contrast to other technologies with smaller trials with short-term follow-up.[46–49]

5.2. *Finding the right spot for new treatments – what comes next?*

Currently, TURP remains the most frequently used procedure, but minimally invasive treatments are on the rise, particularly prostatic urethral lift in the US and Australia.[52,53] Insurers, third-party authorization, and the incorporation in guidelines are important factors for their implementation. For instance, while PUL is recommended as an alternative for TURP by the American Urological Association (AUA), the National Institute for Care and Excellence (NICE) in the UK, and the European Association of Urology (EAU), TIND and TUMT are either not mentioned or discouraged due to high retreatment rates.[9,54,55] Moreover, the NICE and the AUA have conflicting recommendations regarding the use of PAE and the AUA and EAU on the use of WVTT.[56] Moreover, considerations about cost-effectiveness are paramount, but determinations may be challenging. For instance, one cost-effectiveness analysis found that PUL and WVTT may not be cost-effective compared to TURP or PVP (green light).[57] Other head-to-head economic evaluations found that WVTT was cost-effective compared to PUL at a four-year horizon; however, the effectiveness data for WVTT was extrapolated from the trial that was unblinded and allowed cross-over at three months.[58] The results of these analyses should be interpreted with caution due to the emergent data on effectiveness and safety and the evolving changes in the cost base for these procedures.

Technical innovations may also modulate the benefits and harms of each procedure. However, there have not been new models for TUMT and WVTT (Rezum®), and a new generation of PUL (marketed as Urolift®) was launched in March 2022 (UroLift 2®), using the same implant with improved features in the delivery system.[59] Moreover, the elements of PAE, including particle type and size, can also provide a better effectiveness profile. Procedures using smaller particle size (<300 μm) may be associated with a greater reduction of IPSS scores[60] but a greater incidence of adverse events.[61] Promising results have been reported in single-arm trials using newer embolic particles (e.g. polyethylene glycol microspheres also called HydroPearl®) with a tighter calibration of size[62]. More investigation is needed as to how to better perform this procedure to reduce the dose of radiation and avoid collateral damage to anastomotic pudendal arteries[63]. Finally, a growing area of development includes newer temporary implantable devices similar to iTIND, including ClearRing®, ZenFlow Spring®, and Butterfly®.[64] Small single-arm trials for ClearRing® and Butterfly® indicate a 53% and 40% reduction in IPSS scores, respectively.[65,66]

The decision to undergo traditional surgery or a minimally invasive procedure can be led by the balance of benefits and harms based on patients' values and preferences. Men prefer a quick relief, ideally obtaining stable results, but at the same time, they are mindful of the risks and they prefer avoiding sexual side effects and AUR.[67] Sexual effects may be less important in those sexually inactive, such as elderly adults, but at the same time, the elderly may also be less prone to choosing surgical options.[67] Nevertheless, these studies on values have limitations in their internal validity and generalizability, and an individualized approach eliciting a patient's preferences through shared decision-making is still warranted.[68] Evidence-based decision aids are needed to help clinicians throughout these conversations.[69] We provide some pointers in Table 2 and a summary of the management of LUTS due to BPH in Fig. 1 so patients can engage in meaningful conversations with their health providers about these treatments.

In a recent analysis of the uncertainties of the evidence surrounding these new procedures, we found ten ongoing trials

Table 3
Ongoing studies involving minimally invasive procedures

Trial identification	Intervention	Comparison
Comparisons between procedures		
ACTRN12617001235392	PAE	TURP
NCT02006303	PAE	Green light photo-selective vaporization
NCT04084938	PAE	TURP
NCT04236687	PAE	Holmium laser enucleation
NCT02054013	PAE	TURP
NCT04757116	TIND	TURP
NCT04178811	PUL	Holmium laser enucleation
NCT04338776	PUL	WVTT
NCT04987138	ZenFlow*	Sham
NCT04807010	PAE	Sham
Minimally invasive treatments versus medical treatment		
NCT04245566	PAE	5-alpha reductase inhibitors + Alpha-blockers
NCT02869971	PAE	Dutasteride + Tamsulosin
NCT04838769	WVTT	5-alpha reductase inhibitors + Alpha-blockers
NCT04987892	PUL	Tamsulosin

Footnotes: PAE: prostatic arterial embolization, WVTT: water vapor thermal therapy (Rezum); PUL: prostatic urethral lift (Urolift); TIND: temporary implantable nitinol device; TURP: transurethral resection of the prostate. Status in November 2021. (*) ZenFlow is an implantable device similar to TIND. (**) Follow-up before cross-over.

comparing them to TURP or alternatives to TURP, which would further clarify their role in the treatment of LUTS due to BPH.56 Interestingly, we have identified four trials comparing these procedures with medical management (NCT04245566, NCT02869971, NCT0483876, and NCT04987892), which highlights the emerging role as initial treatment of this condition.[56] More recently, it has been proposed that WVTT can be a cost-effective first-line therapy, but this is reliant in the previously described weak evidence base.[70] More trials will shed more light into the role of these treatments (see Table 3).

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