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REVIEW

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Evaluation of new treatments for benign prostatic obstruction: ICI-RS 2023

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Abstract

Aims: To address how invasive therapies for benign prostatic obstruction (BPO) have been evaluated, what their effect is on BPO, if they can prevent progression to BPO and how new therapies need to be evaluated before implementation into clinical practice.

Methods: The think tank conducted a literature review and looked at the previous and current American Urological Association, European Association of Urology and the International Consultation on Urological Diseases guidelines to see what procedures have been used to treat BPO. They then assessed whether trials have been conducted before implementation of the procedures and whether they have been compared to a "gold" standard treatment. The use of urodynamics has also been addressed in the think tank in relation the clinical trials as well as terminology.

Results: Guidelines vary in the use of terminology when it comes to BPO with some continuing to use the term benign prostatic hyperplasia (BPH). There are several procedures for example, TUNA, which have become obsolete although continues to be mentioned in the guidelines until recently. Majority of procedures have been introduced without comparing to "gold" standard treatment and without any long-term data. There continues to be many unknowns with regard to the success of some of the BPO procedures and why some of the adverse events develop.

Conclusion: There needs to be more robust long-term clinical trials conducted of new BPO therapies, with men who have both lower urinary tract symptoms and urinary retention, before introduction into clinical practice.

KEYWORDS

benign prostatic hyperplasia, benign prostatic obstruction, HoLEP, TURP, urodynamics

1 | INTRODUCTION

The ICI-RS session considered the important topic of how new invasive therapies for benign prostatic obstruction (BPO) should be evaluated. First, we assume that all therapies are effective because they relieve or reduce the obstruction to voiding due to the prostate; we are not aware of other mechanisms being proposed for invasive therapies. Hence there is an "a priori" argument that BPO must be shown before the introduction of any new modality to treat BPO.

Second, for the purpose of effective and safe communication the standard terminology as used by the International Continence Society (ICS), European Association of Urology (EAU), and the American Urological Association (AUA), most recently published by the AUA on 14.9.23, should be followed:

- Benign prostatic hyperplasia (BPH) is nearly ubiquitous in the aging male with worldwide autopsy proven histological prevalence increases starting at age 40–45 years to reach 60% at age 60 and 80% at age 80. While BPH, or histological hyperplasia, in and of itself does not require treatment and is not the target of therapeutic intervention, it can lead to an enlargement of the prostate called benign prostatic enlargement (BPE) Lerner and colleagues.[1,2]
- BPE: The onset of the enlargement is highly variable as is the growth rate, and not all men with BPH will develop any evidence of BPE. Lerner and colleagues.[2,3]
- Benign prostatic obstruction (BPO): The prostate gland may eventually cause obstruction at the level of the bladder neck/prostatic urethra, which in turn is termed BPO, assuming a noncancerous anatomy. It is important to realize that not all men with BPE will develop obstruction or BPO, just as not all men with BPH will have BPE. To complicate matters further, obstruction may also be caused by other conditions referred to collectively as bladder outflow obstruction (BOO). Thus, BPO is a subset of BOO.[1,2]

Third, it is informative to look at the FDA's requirements for the assessments of new devices for treating the benign prostate: "Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH) Guidance for Industry and Food and Drug Administration Staff 27th DECEMBER 2021, a 38-page document." Nonclinical and clinical investigation of devices used for the treatment of BPH—Guidance for Industry and Food and Drug Administration Staff (fda.gov)[4]. This makes a number of recommendations: https://www.fda.gov/media/79397/download.

- P1: "Epidemiological studies estimate that 50% of men have histological BPH by age 60. The prevalence increases to 90% in men over 85." However, the FDA doesn't distinguish between BPH, BPE, and BPO. As the reader will note the FDA misuses the term BPH, by its own definitions. Hence, we have added parentheses to BPH where misused, when we assume that the FDA means BPO.
- P16: "We believe these challenges are most efficiently overcome by using a randomized, controlled trial design. The benefit of a randomized, controlled trial is its tendency to balance confounding factors, measurable and unmeasurable, between study groups and minimize the potential for bias."
- P17: "TURP (transurethral resection of the prostate) is considered the gold standard surgical treatment for 'BPH' and there are many successful clinical trials using TURP as a control."
- P17: "While potentially useful to certain stakeholders, the use of an approved drug therapy as a control is complicated because devices used to treat 'BPH' generally have significantly dissimilar expected risks and different mechanisms of action compared to approved drug therapies." "Bothersome LUTS is usually the primary reason a patient seeks treatment for his 'BPH', and most devices used to treat 'BPH' are designed to provide symptomatic relief."
- P18: "Specifically, we recommend you base the primary effectiveness endpoint upon the improvement in AUA-SI (or IPSS) compared to baseline."
- P20: "We recognize that other outcome measures may be appropriate as well due to specific device design characteristics or desired marketing claims. For example, claims for reduction of obstruction could be based on documented improvement in flow rate, results of 'pressure/flow' studies (cystometry), and post-void residual urine volume."
- P23: "For devices intended either as a curative treatment for 'BPH' or for long-term management, we recommend you follow subjects during the premarket follow-up period for 1 year following treatment to document the stability of the treatment effect and to monitor adverse events". Curative does not appear to be defined.
- P26: "a post void residual (PVR) volume >250 ml measured by ultrasound or acute urinary retention." is mentioned in the desirable exclusion criteria.
- P28: "Uroflowmetry including voided volume with a prospectively defined minimum to ensure meaningful analysis (e.g., >125 ml), total time of voiding, peak flow rate, and average flow rate, and PVR; and cystometry (liquid or gas) on all patients with simultaneous assessment of intravesical and intra-

abdominal pressure for determination of detrusor pressure." Both are recommended inclusion criteria, however we assume they are talking about CO_2 cystometry as the current air-filled urodynamic techniques have no relevant publications in men with no standardization.

- P30: "Uroflowmetry including voided volume with a prospectively defined minimum to ensure meaningful analysis (e.g. 125 mL), total time of voiding, peak flow rate, average flow rate, and post-void residual volume; and cystometry on all patients at later visits, e.g. 6 and 12 months post-treatment, with simultaneous assessment of intravesical and intra-abdominal pressure for determination of detrusor pressure[49]" are recommended posttreatment outcome measures, although reference 49, with no authorship given, confusingly states "detrusor pressure-flow studies should be conducted in the subgroup of patients evaluated pretreatment."

Fourth, while BPH/BPE/BPO is the terminology used by all three societies mentioned above, the recent AUA Guideline Updates still use a title of "Management of Lower Urinary Tract Symptoms Attributed to 'Benign Prostatic Hyperplasia': AUA Guideline."[2] In view of their clear statement above this is counter-intuitive and confusing. How has this situation arisen? Is the explanation that the AUA feel they have to follow the outdated terminology used by the FDA?

2 | CLINICAL CONSIDERATIONS

BPH involves increase in the size and number of prostate cells and may be followed by increase in the size of the prostate, leading to BPE which, in turn can lead to BPO and to secondary lower urinary tract symptoms (LUTS) The ICI-RS in 2018 has shown that BPO can be associated with bladder changes including detrusor underactivity during voiding and low compliance and detrusor overactivity during filling.[5] It is therefore important to be able to treat the LUTS/BPO progression which occasionally leads to "decompensation of the bladder" and the rest of the urinary tract. However, as Thomas and colleagues showed, these complications are rare and a conservative approach may be taken to LUTS/BPO, if that's what the man prefers.[6]

It is still unexplained why some men with BOO deteriorate in terms of bladder function and morphology with time and why most do not. Besides the level of obstruction, bad bladder habits such as voiding postponement[7] and comorbidities such as diabetes and cardiovascular insufficiency are likely to affect the progression of the disease.[8] Thus, the pathophysiological mechanism of progression from the histological BPH to clinical BPO is quite complicated and likely multifactorial (Figure 1). Therefore, new therapeutic options may arise to prevent its progression once we precisely understand the multifactorial pathophysiology of BPO.

A recent review assessed the molecular regulation of concomitant LUTS and erectile dysfunction (ED) with a special focus on pelvic ischemia as a denominator of both conditions. A close link between increased prostatic vascular resistance and greater incidence of LUTS and ED has been documented. Experimental models of atherosclerosis-induced chronic pelvic ischemia (CPI) showed increased contractile reactivity of prostatic and bladder tissues, impairment of penile erectile tissue relaxation, and simultaneous development of detrusor overactivity and ED. In the bladder, short-term ischemia caused overactive contractions while prolonged ischemia provoked degenerative responses and led to underactivity. CPI compromised structural integrity of the bladder, prostatic, and penile erectile tissues. Downstream

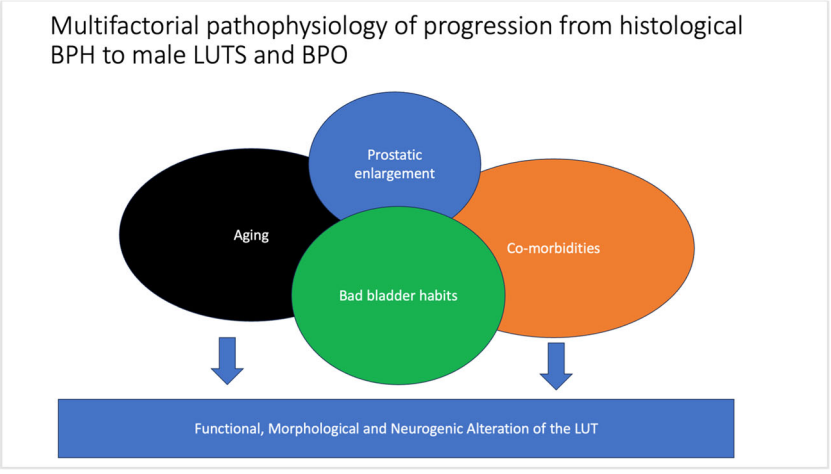

FIGURE 1 Multifactorial pathophysiology of progression from histological BPH to male LUTS and BPO. BPH, benign prostatic hyperplasia; LUTS, lower urinary tract symptoms.

molecular mechanisms appear to involve cellular stress and survival signaling, receptor modifications, upregulation of cytokines, and impairment of the nitric oxide pathway in cavernosal tissue. These observations in animal models may suggest pelvic ischemia as an important contributing factor in LUTS-associated ED and also be relevant for progression of BPO and lead to the development of preventive strategies.[8]

The natural history of untreated BPO is yet to be clarified. Thomas et al have shown analyzed a subgroup of 141 men with BOO who remained untreated, with a mean follow-up of 13.9 years. The only significant urodynamic changes were a reduction in detrusor contractility and an increased prevalence of detrusor overactivity. Most patients reported no change in their symptoms, but a significant minority experienced a gradual deterioration. Of the 29 men in whom the conservative approach failed, 22 proceeded to surgery for LUTS, and 7 for acute urinary retention. The authors concluded that patients with untreated BOO do not significantly deteriorate urodynamically in the long term, with only a minority deteriorating symptomatically. However, it is to note that the initial number of patients with BPO was 1068 and only 141 men with BOO were initially eligible for conservative management excluding BPO patients who needed treatment.[6]

Detrusor underactivity (DU) is another pressure/flow study (PFS) finding that may complicate male LUTS. The same group also followed 58 men initially diagnosed with DU but remained untreated, for 13.6 years. There were no significant changes in symptoms over the follow-up. The only significant urodynamic finding was an increase in the proportion of patients with detrusor overactivity, but with no apparent worsening of chronic retention. Of the 11 men in who failed the conservative approach, eight proceeded to surgery for LUTS, and three for acute urinary retention. This may suggest that the urodynamic definition of Du based on the BCI should be divided into grades. Although this study suggested that in men with DU presenting with LUTS, there were few symptomatic and urodynamic changes with time, this was again a very selected group of patients from an initial 224 men who were initially diagnosed with DUA and likely to present the healthier ones.[9] There have now been a number of studies that looked at men with symptoms and UDS DU or even acontractile bladder with successful (DU) and modestly successful results after outlet reduction in Du and acontractility, respectively.

There has been a large increase in the number of procedures, especially minimally invasive surgical treatments (MIST) that have been introduced over the last 10 years to treat LUTS/BPO, however there has been no data as to when these interventions should be offered and no long-term outcomes comparing it to the gold-standard treatment of transurethral resection of the prostate (TURP). Inadequate early meticulous assessment of outcomes is the likely reason why many "new" modalities have been discarded and TURP remains the most widely used operation to treat obstruction of the prostate worldwide and has withstood the test of time.[10] Speakman and colleagues have published regarding the evidence of implementation of novel techniques with requirements and potential recordable outcomes (Table 1) needed for devices for the treatment of BPO before their introduction (Speakman and colleagues). The Think Tank of the ICI-RS will address how surgical techniques for treating BPO prevent progression and how to critically assess them before implementation.

3 | PROGRESSION AFTER SURGERY FOR LUTS/BPO

TURP has been accepted as the gold standard procedure in the surgical treatment of voiding LUTS often attributed to BPO. Nonetheless, it has to be highlighted that there are no specific symptoms that are attributable to BPO or BPE and no symptoms that can distinguish between BPO and detrusor underactivity as potential causes of voiding LUTS. TURP achieves adequate and durable symptom relief in the vast majority of patients. Furthermore, there is no evidence as to what proportion of the prostate needs to be removed to relieve obstruction and significantly improve LUTS. If removal of the entire adenoma is not required, then this might lead to prostatic regrowth and symptom resurgence. Therefore, the need for completeness of TURP is an important issue. There is no universally accepted way to assess the adequacy of TURP and various parameters can be used for this purpose, such as the volume of resected tissue and the postoperative drop in PSA. Green and colleagues evaluated the completeness of TUR-P by calculating the resection ratio in 432 patients. They weighed the resected prostate tissue and defined the resection ratio as a percentage of the preoperative prostate volume determined by transrectal ultrasonography. The mean weight of prostate tissue resected was 25.6 g and when the results were stratified in terms of prostate size, it was found out that the resection ratio was less than 50% in all groups.[12] Park and colleagues investigated the effect of the ratio of resected tissue in comparison with the transitional zone volume (TZV) on improvement of voiding symptoms and flow rate in a cohort of 263 patients who underwent TURP. They did not detect significant differences between those with a resection ratio (volume of resected tissue/TZV) of >50% versus

TABLE 1 Suggested recordable outcomes in clinical trials for BPO.

		ICI-RS 2023 recommendations	[11]	FDA 2021
Objective measures				
	Bladder diary	Yes	Yes	No
	PSA	Yes	No	Yes
	Resected weight	Yes	No	No
	Qmax flow rate	Yes	Yes	Yes
	Postvoid residual	Yes	Yes	Yes
	Average flow rate	No	No	Yes
	Voided volume	Yes	No	Yes
	Cystometry and pressure/flow studies	Yes	Yes	Yes
	Physical examination	No	No	Yes
	Renal function tests	Optional	No	Yes
Subjective measures and QoL				Yes
	ICIQ-MLUTS	Yes	No	No
	IPSS	No	Yes	Yes
	ICIQ-satisfaction	Yes	No	No
	ICIQ-LUTSQol	Yes	No	No
	SF36	No	Yes	No
	IIEF	Yes	Yes	No
Sexual function assessment				Yes
	ICIQ-MLUTSsex	Yes	No	No
	MSHQ-EjD	Yes	Yes	No
Others				
	Health-economics including QALYs	Yes	Yes	No
	Complications (Clavien-Dindo)	Yes	Yes	Yes
	Reoperation rate due to prostatic regrowth/obstruction	Yes	Yes	No
	Reoperation rate due to other indications (urethral stricture, bladder neck contracture, urinary incontinence)	Yes	Yes	No
	Transfusion rate	Yes	No	No
	5 and 10 year data (or stratifying follow-up into short term [<12 months], medium term [12–36 months] and long term [>36 months])	Yes	No	No
	Length of hospital stay	Yes	Yes	No
	Length of catheterization	Yes	No	No
	Learning curve	Yes	No	No
	Speed of return to work	No	Yes	No
	Need for additional medical treatment	No	Yes	No

Abbreviations: ICIQ, International consultation on Incontinence Questionnaire; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; MLUTS, male lower urinary tract symptoms; MSHQ-EjD, Male Sexual Health Questionnaire for assessing ejaculatory dysfunction; PSA, prostate specific antigen; QALY, quality adjusted life years; QoL, quality of life; SF-36, 36-Item Short Form Survey.

<50% in terms of the postoperative changes in IPSS, QoL score, maximum urinary flow rate (Qmax), and PVR. The difference between the two groups remained insignificant after repeating the analysis based on prostate size.[13] However, we don't know if there was middle lobe obstruction and whether this has any relevance to outcomes data.

4 | "NEW PROCEDURES" FOR RELIEF OF LUTS/BPO

Obviously, TURP is not the only option to treat LUTS/BPO.[14] Many procedures have been introduced but have either failed to be included in the care pathways published by the EAU and AUA or were previously included and have been removed as they have become obsolete. These procedures were not properly assessed for their BPO relieving qualities before being introduced into routine clinical practice. Some of the procedures are listed in Table 2. There is an expanding armamentarium within this context and prostate size is an important factor when choosing amongst different surgical treatment modalities. Anatomical endoscopic enucleation of prostate (AEEP) with Holmium laser (HoLEP) and Thulium laser (ThuLEP) are accepted as size-independent procedures.[3]

AEEP with lasers includes multiple energy sources and surgical techniques. There are numerous laser types with different physical properties. Tissue dissection can be accomplished bluntly with the instrument or with the energy source itself. Additionally, there are en-bloc, bilobar, trilobar approaches with or without early apical release. These variations complicate the comparison between different enucleation techniques.[15] Furthermore, the learning curve of AEEP tends to be lengthy. This complicates the assessment of the outcomes of surgeons at various phases of their learning curve. Several criteria have been defined to better assess the learning curve of HoLEP. Trifecta denotes a HoLEP procedure done within 90 min without conversion to TURP and pentafecta has been reached when patients meet the trifecta criteria without postoperative complications or stress urinary incontinence.[16] It has been suggested that the learning curve plateaued after four

TABLE 2 Procedures for the treatment of BPO from American Urological Association (AUA), European Association of Urology (EAU), and International Consultation on Urological Diseases Male LUTS guidelines.

		2003		2013	2023	
Category	**Type of surgery**	**AUA**	**EAU**	**ICUD**	**AUA (size; recommendation)**	**EAU**
Resection	Transurethral incision of the prostate (TUIP)	Y	Y		Y (<30 gm; moderate)	Strong
	Transurethral resection of the prostate (TURP)	Y	Y	Gr A	Y (<80 gm; moderate)	Strong
Enucleation	Laser enucleation (HoLEP, ThuLEP)	?	Y	Gr A	Y (any size; moderate)	Strong
Vaporization	Transurethral vaporization of the prostate (TUVP)	?	_		Y (<80 gm; conditional)	Weak
	Photoselective vaporization of the prostate (PVP)	_	_	Gr C	Y (<80; moderate)	Strong
Alternative ablative	Transurethral microwave therapy (TUMT)	Y	Y	Gr A	_	_
	Transurethral needle ablation (TUNA)	Y	Y	Gr A	_	_
	Robotic waterjet treatment (RWT)	_	_		Y (30–80 gm; Conditional)	Weak
	Water vapor thermal therapy (WVTT)	_	_		Y (30–80 gm)	_
Nonablative	Prostate artery embolization (PAE)	_	_		Y (conditional)	Weak
	Temporary implanted prostatic devices (TIPD)	_	_		Y (expert)	_
	Prostatic urethral lift (PUL)	_	_	Gr D	Y (30–80 gm; conditional)	Strong
	Simple prostatectomy	Y	Y	Gr D (lap/rob)	Y (>80 gm; moderate)	Strong
	HIFU	N	N	Gr C	N	N

consecutive HoLEP procedures fulfilling either the trifecta or pentafecta criteria. For HoLEP, this could happen after the 22nd and 40th surgery for trifecta and pentafecta criteria, respectively.[17] Training with a simulator and mentored and structured training programs may help to tackle the challenges of the learning curve of HoLEP.[18]

Approximately 8%–10% of the patients who underwent TURP will require a second resection in 8 years. Reoperation rates after laser-based endoscopic enucleation, which implies a more complete way of tissue removal, are somewhat similar.[19] The possibility of an endourological procedure after HoLEP is around 5% by 10 years, this includes not only reintervention due to prostatic regrowth and related symptoms but also interventions due to urinary incontinence (UI), urethral stricture and bladder injury.[20]

Kim and colleagues compared TURP with HoLEP in terms of long-term outcomes in a cohort of over 58 000 patients using a nationwide insurance database. Mean follow-up duration was 51.6 and 47.6 months in the TURP and HoLEP groups, respectively. The rate of reoperation due to prostatic obstruction was 4.5% in the TURP group which was significantly higher than that recorded in the HoLEP group (1.27%). Notably, 2% of patients underwent reoperation within 1 year of TURP, whereas 0.7% of the HoLEP group underwent reoperation within 1 year of surgery. The rates of postoperative alpha-blocker and 5-alpha reductase inhibitor use were also higher in the TURP group at all time points (3, 12, 24 months).[21] Although, these results may not be generalizable to other populations, it does raise the question of whether the outcome depends on the "completeness" of the resection or enucleation, by whatever route, and the more tissue that is removed the more open the fossa will be, with some increase in adverse events.

Due to the discrepancy in the definition of post-HoLEP UI, there is a wide range of reported rates from 8% to 42%, which is similar to the situation we have regarding UI after radical prostatectomy. Nevertheless, it seems to be higher than TURP and therefore merits attention. Several patient-related (diabetes mellitus, prostate size, age), urodynamic (maximal urethral closure pressure, detrusor overactivity), and surgical risk factors (bladder injury, enucleation time, enucleation volume, learning curve) have been determined within this context.[22]

The term "gold-standard" was borrowed from economists. It signifies a monetary standard under which the basic unit of currency was defined by a stated quantity of gold. This made it possible to compare different currencies for international trading.[23] A gold-standard technique must be efficient, safe, cost effective, and reproducible versus the current best choice of treatment. AEEP is not a novel surgical treatment option, it's been established for almost 40 years. However, it has not yet been consolidated as the gold-standard for several proposed reasons, such as learning curve and cost effectiveness. Arguably, it is still being underused as it represents less than 5% of all BPO-related surgeries in the United States.[24] So, we should still accept TURP, especially bipolar,[25] as the gold standard and try to design prospective randomized controlled trials (RCT) against bipolar TURP if we are to assess outcomes of outlet procedures in a comparative manner. These RCTs should ideally include well-balanced cohorts and multiple centers with several surgeons to allow reproducibility of results. Recruiting difficult-to-treat cohorts such as those with indwelling catheters following acute urinary retention, elevated PVR, and on anticoagulants will enhance our understanding of the role of that particular technique in routine clinical practice.[11] Reduced hospital stay with rapid discharge and community management of postoperative catheters to reduce hospital stay and cost will also need to be assessed.

5 | HOW SHOULD PROGRESSION BE ASSESSED AND DEFINED IN THE ERA OF MINIMALLY INVASIVE SURGICAL TREATMENTS (MISTS)

BPO is a progressive and chronic condition, and the principal aim of treatment is to reduce the bother of LUTS by removing the obstructive element of BPO and to minimize the consequences if BPO progressed. With an increasing number of MIST being performed, it is crucial to understand their place in the treatment armamentarium.[26] Important outcome measures to assess MIST efficacy in future clinical trials are suggested, highlighting the limitations of the current literature. Outcomes to assess safety and complications are also discussed below.

Progression can be defined in many ways, both subjective and objective, and more detailed analysis of these factors should be recommended for future MIST trials. Subjectively, progression is defined as worsening in LUTS, and this has often been reported in the literature based on change in the International Prostate Symptom Score (IPSS). However, IPSS alone does not adequately assess the most bothersome LUTS of incontinence and postmicturition symptoms, and only superficially assesses storage symptoms[27,28]: the IPSS also fails to assess bother of individual symptoms. The current EAU Guidelines recommend that a questionnaire that

assesses individual symptom bother should be used to give a more thorough assessment in clinical trials, such as the International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms (ICIQ-MLUTS) which is a validated tool that provides a more detailed evaluation of all aspects of male LUTS and impact on quality of life.[29] This is especially important for the large group of men with bothersome storage LUTS in addition to voiding LUTS.

6 | WHAT OUTCOMES ARE IMPORTANT WHEN DECIDING WHETHER NEW MISTS SHOULD BE INTRODUCED OF?

6.1 | Efficacy

Important questions in clinical practice are: what is the likelihood that bladder outflow surgery will be effective for storage LUTS, and is effectiveness the same for MIST procedures as for TURP? A recent analysis of the UPSTREAM randomized trial has shown that men suffering with nocturia, incontinence and postmicturition dribble have a poor response from TURP, but the efficacy of MIST in the presence of these symptoms remains to be reported.[30]

6.2 | Safety

Objective outcome measures of progression that are frequently reported in trials are change in Qmax and PVR, but other important factors that are infrequently reported are the development of complications from BPO (acute urinary retention, urinary tract infections, incontinence, renal failure), and urodynamic outcomes. These are important outcomes that require long-term registries to assess. Furthermore, rates of secondary bladder dysfunction as a result of long-standing BPO are poorly reported in surgical trials, but the effect of bladder outflow surgery on improving secondary storage LUTS is important to know when counseling patients, especially with the large range of treatment options currently available. Older studies have shown that prostatectomy resolves detrusor overactivity to a greater extent than less invasive treatments,[31] but it is unclear how effectively MIST procedures resolve secondary storage LUTS and detrusor overactivity in the long-term. This is an important consideration when personalizing treatment recommendations.

Indirect measures of progression can also provide valuable data, but again are variably reported in the literature on MISTs. Retreatment rates are often reported, but it is not always clear whether this refers to retreatment for ongoing bladder outlet obstruction (BOO), treatment targeted at persistent storage LUTS, or even whether the retreatment is surgical or pharmacological. A recent study showed that the use of pharmacological therapy after surgery for BPO is up to 66%, but this varies considerably by surgical technique[32] and it is unclear what are the indications for drugs, storage or voiding symptoms, or both. The lowest rates are for enucleation procedures (38%), compared to MIST (50% for WVTT, 63% for PUL) or TURP (61%). Future studies on MIST should define retreatment, and specifically report the following: discontinuation rates of pharmacotherapy with reasons, indications for pharmacotherapy, such as for persistent or de novo voiding LUTS, or pharmacotherapy for persisting or de novo storage LUTS, and for surgical retreatment (with indication and mode of surgery).

Another important consideration for future trials of MIST relates to the appropriate comparator group. While most MIST are compared to sham or TURP, it may be more appropriate to compare these treatments to both pharmacological treatment (alpha blocker ± 5-alpha reductase inhibitor) and to TURP, to accurately define their place in the treatment pathway. Different surgical modalities treat obstruction to varying degrees, with greatest improvements (based on Qmax and IPSS) for enucleation procedures, followed by resection or vaporization procedures, and lowest for MIST.[33] Treatment recommendations would therefore depend on the primary aim of treatment in each case, with, for example, an enucleation procedure being recommended for a patient in chronic urinary retention where the primary goal for the patient is to be catheter-free,[34] compared to a patient with bothersome LUTS alone who desires a minimally invasive treatment with preservation of sexual function. The minimum follow-up should also be long enough to account for considerable placebo effects of treatment, at least 1-year, before reporting initial results. For example, a recent sham-controlled trial of the Optilume "BPH" system reported very similar improvements in IPSS at 3 months in both arms (mean 10.5 points with treatment compared to 8 with sham), which then separated at 12-month follow-up as the placebo effect resolved.[35] Clearly, long-term follow up registries are required to assess rates of disease progression (retention, renal failure, incontinence, retreatment). Other measures of safety that should be consistently reported include perioperative (bleeding, infection, return to theater), early (urethral stricture/bladder neck stenosis, sexual dysfunction, stress urinary incontinence), and late postoperative (urethral stricture/bladder neck stenosis, stress urinary incontinence, sexual dysfunction) complications.

With an increasing number of MISTs entering the clinical armamentarium, future studies need to thoroughly assess both subjective and objective parameters with adequate follow-up (as above), with standardized outcome measures, to aid comparability across future MIST trials.

7 | URODYNAMICS AND BPO SURGERY

Bladder outflow obstruction is a diagnosis of pressure flow studies based on the relation of the maximum flow rate with the detrusor pressure when the maximum flow rate occurs. However, allegedly due to practical reasons, few studies utilized pressure flow studies to assess the efficacy of BPO treatments. Rather, the majority of studies considered symptomatic outcome usually assessed by IPSS and Qmax revealed by uroflowmetry as study endpoints which make it difficult to assess the role of BOO in the outcome of BPO treatments.

The think tank (TT) agreed that there is yet no single clinical or urodynamic parameter that predicts progression of histological BPH to BPO. The TT emphasized that the possible role of bad bladder habits needs to be investigated by bladder diaries and, comorbidities such as metabolic syndrome and cardiovascular risk factors need to be better assessed to explain the multifactorial pathophysiology of BPO progression.

The TT agreed PFS are the most objective tool in the assessment of the new treatment options for BPO. Supporting that, Fusco and colleagues reported that PFS demonstrated that both medical therapy with alpha-blockers (ABs) and endoscopic surgical procedures provided BPO relief with a higher magnitude of improvement after surgery. They further indicated that a complex relationship existed between improvement in the bladder outlet obstruction index (BOOI) and variations of both Q_{max} and detrusor pressure. When the reduction of BOOI was small, the improvement of Q_{max} was clinically irrelevant and the BOOI is mainly influenced by a decrease of detrusor pressure. In contrast, when the magnitude of BOOI reduction was greater, a meaningful improvement of both detrusor pressure and urinary flow was evident.[36]

Over the last three decades, several minimally invasive techniques have been introduced for the surgical management of BPO. Many have not stood the test of time often because they were overpromoted before there were sufficient data. Our TT further indicated that the new treatment options for BPO need a careful long-term assessment. In a randomized prospective study, it was shown that in up to a quarter of the patients, a secondary TURP is performed within the first 2 years after "less invasive" procedures including transurethral electrovaporization (TUVP), visual laser ablation of the prostate (VLAP), transrectal high intensity focused ultrasound (HIFU), and transurethral needle ablation (TUNA).[37]

This was also stated by the European Association of Urology (EAU) Guidelines Committee who indicated that the evidence of any new modality must provide adequate length of follow-up to allow proper information to be provided for patients before treatment choices are made and to be able to create recommendations in high-quality guidelines such as those of the EAU. They further commented that it was not just within the domain of LUTS treatments that this was important, other urological devices, such as mesh devices, have been equally "guilty" and likewise devices in most other (surgical) specialties. The EAU Guidelines Committee agreed that there was a need for a set of requirements built around primary randomized controlled trials (RCTs) looking at both efficacy and safety, and secondary studies to confirm the reproducibility and generalizability of the first pivotal studies. They further emphasized that there is a danger that a single pivotal study can be over-exploited by device manufacturers. Future studies are needed to include (1) proof of concept, (2) RCTs on efficacy and safety, as well as (3) cohort studies with a broad range of inclusion and exclusion criteria to confirm both reproducibility and generalizability of the benefits and harms.[11]

Our TT agreed with recommendations of the EAU guideline panel and further suggested that that post-operative invasive urodynamic evaluation when compared with preoperative urodynamic findings will increase the quality and reliability of the postoperative assessment of any new treatment modality.

8 | RECOMMENDATIONS—TABLE 1

- Proof of concept study is essential.
- Pragmatic patient selection, including those with retention, hence rebutting the FDA suggestions of excluding PVR > 250 mL and retention patients! This may well allow poor (less effective) operations to hide their poor efficacy. The UNBLOCS trial can be used as the basis for other BPO clinical trials as it included both men with LUTS and those with urinary retention.[38]
- Objective outcomes of success include Qmax and PVR assessment: it needs to be shown whether or not post-op Qmax is adequate if pretreatment PFS have been done?
- Standardized safety outcomes.

- Standardized timescales for the assessment of both effectiveness and safety: assessments at both one and 5 years seem the minimum.
- Costs.

Research questions with brief outline methodology to answer the research questions:

- RCT of new MISTs versus TURP as the gold standard treatment in patients with LUTS and urinary retention with 1, 5, and 10-year follow-up with clinical and health economic outcomes
- RCT of current treatments versus gold standard treatment in patients with LUTS and urinary retention with 5 and 10-year follow-up with clinical and health economic outcomes
- When should BPO surgery be performed with respect to subjective and objective criteria?
- Do MISTs prevent progression of BPO to urinary retention?
- Why do some patients with apparent acontractile bladder void after outlet reduction especially with enucleative procedures.

AUTHOR CONTRIBUTIONS

All authors contributed text to this review. The corresponding author constructed the final full text draft. All authors commented on the final text and approved the final version for submission.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

There are no primary data in this review.

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