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INVITED REVIEW

Male Health

Minimally invasive surgical therapies (MISTs) for lower urinary tract symptoms (LUTS): promise or panacea?

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The increasing importance of treatment of lower urinary tract symptoms (LUTS), while avoiding side effects and maintaining sexual function, has allowed for the development of minimally invasive surgical therapies (MISTs). Recently, the European Association of Urology guidelines reported a paradigm shift from the management of benign prostatic hyperplasia (BPH) to the management of nonneurogenic male LUTS. The aim of the present review was to evaluate the efficacy and safety of the most commonly used MISTs: ablative techniques such as aquablation, prostatic artery embolization, water vapor energy, and transperineal prostate laser ablation, and nonablative techniques such as prostatic urethral lift and temporarily implanted nitinol device (iTIND). MISTs are becoming a new promise, even if clinical trials with longer follow-up are still lacking. Most of them are still under investigation and, to date, only a few options have been given as a recommendation for use. They cannot be considered as standard of care and are not suitable for all patients. Advantages and disadvantages should be underlined, without forgetting our objective: treatment of LUTS and re-treatment avoidance.

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INTRODUCTION

In 2013, the European Association of Urology (EAU) guidelines reported a paradigm shift from the management of benign prostatic hyperplasia (BPH) to the management of nonneurogenic male lower urinary tract symptoms (LUTS).[1] The development of this concept is focused on the increasing importance of treating the symptoms while considering BPH as one of the LUTS's causes. An increasing awareness of LUTS and storage symptoms is warranted to further discuss different management options that could treat symptoms. It is in this context that minimally invasive surgical therapies (MISTs) found the space to become an interesting possible approach to the problem.

LUTS have a strong impact on patient's quality of life (QoL), even if variables between individuals and treatment preferences are different as well. MIST availability has increased patient's treatment options, improving the importance of including patient's values and preferences between assessments.[2] The guidelines offer practical evidence-based guidance, presenting the best evidence available to the experts, while personal values and individual preferences are lacking. A recent review reports that men prefer low-risk surgical management and prefer surgery with high rate of success and low risk of complications. Regarding symptoms, patients are seeking treatments effective in improving urge incontinence and nocturia, which are considered the most bothering ones.[2] Finally, sexual side effects, following surgery, are more important for those with a high level of sexual function.[2] In this regard, understanding patients' values and preferences in the context of personal, physical, emotional, relational, and social factors is important to optimizing counseling, facilitating treatment decision-making, and improving guideline recommendations.

Finally, to perform "the best treatment for the best patient" is necessary to get the correct diagnosis first. There are several possible causes of LUTS, including BPH, overactive bladder, nocturnal polyuria, neurogenic problems, infections, urethral strictures, and others.[3] Most elderly men often have more than one cause, and a multifactorial etiology should be considered. BPH predominates as primary cause; however, bladder dysfunction and nocturnal polyuria are often primary or co-existing. For this reason, the clinical assessment of patients with LUTS has two main objectives: making the differential diagnosis and defining the patient's clinical profile (including the risk of disease progression) to provide appropriate care.

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To date, the first approach to patients with bothering or complicated LUTS is based on drug treatment followed only in certain cases by surgical intervention.[3] The surgical treatment is usually reserved for those patients not having a satisfactory effect with pharmacological treatment or for those not willing to uptake drugs.

Monopolar and bipolar transurethral resection of the prostate (TURP) are considered the current gold standard for patients with a prostate of up to 70 ml and bothersome moderate-to-severe LUTS secondary of benign prostatic obstruction (BPO).[3] In recent years, different techniques have been developed aiming to reduce short- and long-term surgical side effects and with the intent to be minimally invasive. Even if few of these techniques demonstrate to be safe and effective, TURP is unsurpassed and still considered the gold standard. Anyhow, the concept of gold standard simply means what most people do and should probably be abandoned as it discourages change and improvement.[4]

The aim of this review was to evaluate the efficacy and safety of the most commonly used MISTs to treat LUTS. We focused on ablative techniques such as aquablation, prostatic artery embolization (PAE), water vapor energy, and transperineal prostate laser ablation (TPLA), and nonablative techniques such as prostatic urethral lift (PUL) and temporarily implanted nitinol device (iTIND).

To create a comprehensive clinical guide on MISTs, we conducted a manual search of the guidelines published by major urological associations (the EAU and the American Urological Association [AUA]).[1,5] The aim was to evaluate the existing evidence and recommendations regarding these therapies. In addition, we conducted a nonsystematic literature review in April 2023, utilizing databases such as PubMed and Scopus, to identify relevant papers on MISTs cited and endorsed by the guidelines. The therapies included in the review were aquablation, PAE, water vapor energy, TPLA, PUL, and iTIND. The search was limited to English-language studies. Titles and abstracts of retrieved articles were screened to identify potentially relevant studies, followed by a full-text review based on predefined inclusion and exclusion criteria. Included studies encompassed randomized controlled trials, prospective cohort studies, and retrospective studies evaluating minimally invasive therapies for LUTS. Data extraction and analysis were performed to collect relevant information, including study characteristics, patient demographics, interventions, outcomes assessed, and follow-up duration. The findings from the included studies were synthesized and presented in a narrative format, considering the efficacy and safety outcomes of the MISTs. The review concluded by discussing the key findings, current guideline recommendations, limitations, and potential future directions in the field while adhering to ethical considerations and reporting guidelines for transparency and replicability.

AQUABLATION

Among the most extensively tested minimally invasive technologies for treating obstructive prostatic hyperplasia, aquablation (AquaBeam©, PROCEPT Biorobotics, Redwood Shores, CA, USA) has gained significant experience over the course of more than 5 years.[6–8] This technology, introduced in 2015, utilizes ultrasound-guided robotic assistance to ablate prostate tissue using a high-pressure waterjet with exceptional precision. Aquablation comprises three key components: a planning unit, a robotic 24-Fr handpiece, and a console. By employing this method, urinary obstruction can be resolved while preserving erectile and ejaculatory function.

AquaBeam procedure can be performed with the patient placed in the lithotomy position, allowing for transrectal ultrasound and cystoscopy to be conducted. Meanwhile, the robotic handpiece is inserted transurethrally, positioned proximal to the external urethral sphincter. This positioning enables the console to map the prostate gland, while the robotic arm precisely ablates the tissue without compromising the urethral sphincter or damaging the neurovascular bundles. The surgeon's only controlled variable is the speed and depth of the waterjet, which is adjusted using a pretreatment plan and a foot pedal. Following the robotic procedure, hemostasis can be achieved through mono-bipolar or laser diathermocoagulation or by placing a cuffed catheter in the prostate lodge for a few hours. A cystoclysis is typically maintained for a day, and the patient is usually discharged on the second day without a catheter.[9]

Aquablation is supported by a substantial body of literature. The initial prospective study conducted by Gilling *et al*.[10] in 2017 involved 21 men with prostate volumes ranging from 30 ml to 102 ml. Follow-up data were collected at 3 months, 6 months, and 12 months. The procedure had a mean operating time of 38 min and a mean blood loss of 0.8 g dl^{-1} of intraoperative hemoglobin. Improvement in voiding was evaluated using the International Prostate Symptom Score (IPSS), which showed a decrease of 6.8 compared to pretreatment values. Uroflowmetry indicated a mean maximum urinary flow rate (Qmax) improvement of up to 18.3 ml s^{-1} after 1 year. Sexual and ejaculatory function, as assessed by the International Index of Erectile Function (IIEF) and Male Sexual Health Questionnaire-short form (MSHQ-s), appeared to be preserved.[10]

In a second study conducted in 2018, called the WATER trial, AquaBeam was compared to TURP in a double-blind randomized trial involving 181 patients from 17 centers.[11] Intraoperative data demonstrated the noninferiority of aquablation compared to TURP. AquaBeam patients showed a more significant improvement in Qmax and better ejaculation outcomes compared to the TURP cohort, which had a higher incidence of retrograde ejaculation (25% *vs* 6.9% in aquablation).[11]

The WATER II trial in 2019,[12] a multicenter study involving 101 patients followed for 6 months, further confirmed the effectiveness of AquaBeam, even in prostates larger than 80 ml. The results were comparable to those of the WATER trial. The average surgical time was 37 min with an average ablation time of 8 min. The mean postvoid residual volume improved from 131 ml to 47 ml, the mean Qmax improved from 8.7 ml s^{-1} to 18.8 ml s^{-1}, and the IIEF score increased by 0.7 points.[12,13]

Comparative studies have also been conducted, such as the one by Tanneru *et al*.[14] in 2021, which analyzed AquaBeam, Urolift, and Rezūm. At 1 year, AquaBeam demonstrated the best results in terms of IPSS compared to the other techniques, and at 2 years, it showed a Qmax improvement of 6.4 ml s^{-1}. Urolift achieved the best ejaculation outcomes at 1 year, but the re-treatment rate after 2 years was higher (7.5%) compared to those receiving Rezūm (4%) or AquaBeam (4.3%).[14]

A study conducted by Elterman *et al*.[15] in 2022 analyzed three significant studies on minimally invasive surgical techniques (REZŪM II, WATER, and LIFT) and compared their effects on sexual function (erectile function of IIEF and ejaculatory function of MSHQ-EjD) over 3 years. None of the three technologies seemed to significantly affect erectile function, while AquaBeam and Urolift appeared to provide the most benefit in terms of ejaculation preservation.[15]

However, it is important to note that one limitation of AquaBeam is its suboptimal control of postoperative bleeding. Gloger *et al*.[16] conducted a retrospective study in 2021, including patients who underwent AquaBeam followed by electrocoagulation of the bladder

neck and ablation bed. Intraoperative and postoperative data were compared with those of a cohort of patients who underwent holmium laser enucleation of the prostate (HoLEP). Although the percentage of patients who had to return to the operating room was slightly higher in the AquaBeam case (13.6% *vs* 9.8%), the Hb loss was similar in the two groups (1.3 g dl^{-1} in AquaBeam *vs* 1.22 g dl^{-1} in HoLEP). The preservation of ejaculation was 72%, which is below the 90% demonstrated in the WATER trial. The authors suggest that this outcome may be due to thermal and mechanical damage to the anatomical structures responsible for ejaculation (verumontanum and bladder neck) caused by energy delivery after aquablation.[16,17] Most significant trials are summarized in **Table 1**.

PAE

PAE is an endovascular procedure performed through the injection of polyvinyl-alcohol microspheres into selective prostatic arteries. This technique aims to reduce prostate volume by inducing necrosis in the targeted cells.[18]

The procedure is performed as follows: the femoral artery is cannulated as the first step. Subsequently, the prostate arteries are identified. Selective arteriography is performed from the internal iliac artery, followed by the injection of microspheres using a catheter into the prostatic arteries. This injection induces a slowed blood flow and subsequent necrosis of the prostate tissue.[19]

Abt *et al*.[20] conducted a study involving 103 patients over a 2-year period to compare the outcomes of PAE with bipolar TURP. The results showed significant differences between the two procedures, with bipolar TURP demonstrating a considerable superiority in terms of Qmax (3.9 ml s^{-1} improve for PAE *vs* 10.23 ml s^{-1} for TURP). However, similar outcomes were observed for postvoid residual volume (PVR). In terms of the IPSS, both procedures led to a notable decrease, with a reduction of 9.21 points for PAE and 12.09 points for TURP. PAE demonstrated superiority only in terms of preserving ejaculatory function. Side effects were slightly lower for PAE, but the difference was not statistically significant.[20]

A trial by Salem *et al*.,[21] with a follow-up of 3 years, has been conducted on 45 patients who underwent PAE. A progressive improvement of IPSS was noticed starting from 1 month (mean ± standard deviation [s.d.]: 23.6 ± 6.1 to 12.0 ± 5.9) to 1 year (mean ± s.d.: 12.4 ± 8.4) and QoL too. Qmax got important results from 1 month to 3 months after surgery, while PVR had a progressive decrement. No significant improvements in terms of IIEF and MSHQ and side effects were noticed.[21]

Carnevale *et al*.[22] conducted on a cohort of 30 patients followed for 1 year, reported improvements in IPSS, QoL, prostate volume, and Qmax following PAE. They compared these outcomes with those of TURP, which had higher rates of side effects such as urinary incontinence, prostate rupture, and retrograde ejaculation.[22]

Uflacker *et al*.[23] conducted a meta-analysis including six studies to evaluate the outcomes of PAE at 12 months. The results showed a significant reduction in IPSS (20.39 points), improvement in QoL (2.49 points), decrease in PVR (85.54 ml), and improvement in Qmax (5.39 ml s^{-1}). Adverse events classified using the Interventional Radiology class (218 out of 668 patients, with 216 classified as A/B class) included proctalgia, dysuria, and acute urinary retention.[23]

In general, the most common side effect of PAE is hemorrhage, which can manifest as hematuria and hematospermia. Another specific condition called "post-PAE syndrome" can occur, characterized by vagal symptoms and perineal pain.[24] Other potential adverse events include ischemia of the prostate and pelvic organs, but these are usually reversible.[25] Most significant trials are summarized in **Table 2**.

WATER VAPOR THERMAL THERAPY (WVTT)

Rezūm is a thermal therapy which has followed FDA clearance in 2015[26] and is based on the use of water vapor for the treatment of prostatic hyperplasia related to prostatic obstruction.

The Rezūm™ Water Vapor Therapy (Boston Scientific, Marlborough, MA, USA) utilizes radiofrequencies to convert water into vapor, which is then injected transurethrally using a handpiece equipped with a 30° optic.[27] At the end of the handpiece, a thin needle emerges, and small injections lasting approximately 9 s are performed. These injections release steam at a temperature of 103°C, creating circular dispersion and intraglandular lesions measuring about 10 mm.[27] The injections are made at least 1 cm away from the bladder neck in the transition zone of the prostatic adenoma. Subsequent punctures are performed proximally along the prostatic urethra up to the verumontanum.[28]

Within the prostate gland, the vapor is converted back to water at body temperature, releasing heat (approximately 540 cal ml^{-1}). This process leads to the breakdown and death of cells. The regenerative capacity of the cells takes around 3 months to reabsorb the cellular damage. The ultimate effect is the relief of irritation and voiding symptoms, along with an improvement in urinary flow. An indwelling catheter is typically maintained for 3–7 days.[29]

The first concrete scientific data comes from the 2016 study by McVary *et al*.,[30] a randomized controlled trial evaluating 4-year efficacy with a control group underwent shamed treatment (with cross-over at 3 months of the control group). The results showed benefit on LUTS as early as 2 weeks post-Rezūm, with improvements in IPSS and Qmax lasting up to 4 years. The Qmax mean value improved from 9.5 ml s^{-1} (pretreatment) to 13.5 ml s^{-1}; similarly, PVR improved from 83 ml to 73 ml. Despite this, at 2 years, a decrease of the IIEF was noted with respect to the reference values ($P = 0.033$) while ejaculation showed no variation in the MSHQ-EjD questionnaire.[30]

Gupta *et al*.,[31] in another randomized clinical trial study of 2018, using data from the Medical Therapy of Prostate Symptoms (MTOPS) trial, compared the efficacy and adverse effects of Rezūm with those of medical therapy (doxazosin, finasteride, or their combination). At an initial 3-month follow-up, a mean increase in Qmax and decrease in IPSS after Rezūm were greater than those achieved with 5α-reductase

Table 1: Aquablation and results at 6 months and 12 months

Study	*Patient (n)*	*IPSS*			*Qmax*			*IIEF-5*		*MSHQ-s*	
		Previous	*6 months*	*12 months*	*Previous*	*6 months*	*12 months*	*Previous*	*6 months*	*Previous*	*6 months*
Gilling *et al*.[10] 2017	21	22.8 (13–34)	7.1	6.8	8.7 (4.9–14.1)	18.9	18.3	13	Improved	NK	NK
Glling *et al*.[11] 2018	181	22.9±6.0	5.9±5.0	NK	9.4±3.0	20.3±10.9	NK	17.2±6.5	Stable	8.1±3.7	Stable
Desai *et al*.[12] 2019	101	23.2±6.3	5.9±5.4	NK	8.7	18.8	NK	14.8±7.7	0.7±5.6	8.1±3.9	–1.4±5.4

The data are shown as mean, mean±s.d., or mean (range). IPSS: International Prostate Symptom Score; Qmax: maximum urinary flow rate; IIEF-5: International Index of Erectile Function-5; MSHQ-s: Male Sexual Health Questionnaire-short form; s.d.: standard deviation; NK: not known

inhibitor (5-ARI) single therapy and those with combination therapy ($P \leq 0.02$ and $P = 0.73$, respectively).[31]

Another recent trial by McVary *et al*.[32] reported 4-year follow-up results, and despite thermal therapy caused transient adverse effects such as dysuria (17%), hematuria (12%), and hematospermia (7.4%), the re-treatment rate was very low (4.4%). Regarding sexual function, it was impaired by medical therapy, while the IIEF and MSHQ-EjD of the Rezūm cohort were stable after 4 years of follow-up.[32]

In accordance with prostate volume, there is a retrospective study on patients undergoing Rezūm treatment. Garden *et al*.[33] divided 204 patients based on prostate size (larger or smaller than 80 ml), reporting no differences at follow-up in patients with bigger prostates ($P = 0.825$), and only three patients suffered *de novo* erectile dysfunction (ED). Even Darson *et al*.[34] evaluated 131 patients, and with a short-term follow-up, no one presented *de novo* ED or retrograde ejaculation.

The most important randomized clinical trial is the "REZŪM II" where a total of 196 patients were randomized 2:1 between Rezūm and control arm. A significant improvement in urodynamic function at 5 years is reported. The IPSS score, as QoL, showed a 45% reduction, with a corresponding 49% improvement in Qmax. Re-treatment rate remained below 4.5%. Finally, no patient experienced ED or ejaculatory disease.[35] Even the first multicenter Italian experience, by Siena *et al*.,[29] with 135 patients, confirmed these data. The authors reported a reduction in the IPSS score from 21.5 to 4.4 after 6 months, with no observed negative effects on sexual function or ejaculation following water vapor therapy.[29]

Regarding patients with indwelling catheter, there is an important review confirming the feasibility and efficacy of Rezūm treatment.[36] Most significant trials are summarized in **Table 3**.

TPLA

Among the most recent MISTs, we must mention TPLA of the prostate. TPLA is a transperineally and ultrasound-guided procedure that involves thermocoagulation of obstructing prostate tissue by transperineally. Laser sources are placed in the prostate lobes, operating at 1064 nm wavelength (EchoLaser system – ELESTA, Calenzano, Italy).[37]

The procedure is performed placing the patient in a lithotomic position, and a local anesthesia is performed.[37] A three-way bladder catheter is placed with cystoclysis. Up to three 21-gauge needles per prostate lobe are introduced, under ultrasound guidance, parallel to the urethra and an additional needle in the case of a third lobe. The number of laser optic fibers is prostate volume dependent: generally, at least two per prostate lobe for a volume of more than 60 ml, otherwise 1 fiber is sufficient. Their positioning must respect distances from the urethra (10 mm), capsule (10 mm), bladder neck (15 mm), and other probes (10–15 mm) to avoid complications.[37] The ablation power is operator dependent, varying from a constant 3 W up to an initial 5 W with subsequent gradual reduction.[38–41] For bulkier prostates (> 80 ml), an additional ablative cycle, called "pull back", may be necessary, determined by the retraction of the fiber by about 10–15 mm along its axis of action.[37] The distal end of the fiber produces an ellipsoid of coagulative necrosis secondary to hyperthermia, the diameter of which can be defined before surgery using specific software (Echolaser Smart Interface [ESI]).[37–41] Postoperatively, the effectiveness of thermocoagulation can be assessed by measuring with magnetic resonance or contrast-enhanced ultrasound the area of necrosis.[38–41] To reduce irritative symptoms and possible obstructions secondary to edema, anti-inflammatory therapies can be administered at the end of the procedure, with removal of the bladder catheter and urine test scheduled 1 week after the treatment.[37]

We report the results of a study by Frego *et al*.,[37] in which they enrolled 22 patients with BPH or patients with a history of LUTS who were willing to discontinue drug therapy. Within the cohort, we highlight the preoperative data, which include a mean prostate volume of 65 ml, a mean PVR of 60 ml, a mean Qmax of 9 ml s^{-1}, an IPSS score of 22, a mean QoL score of 4, and a mean International Index of Erectile Function-5 (IIEF-5) score of 22. Evaluating the same parameters at 6 months and 12 months, a significant improvement in symptoms was observed: the mean Qmax increased to 15 ml s^{-1} and 20.5 ml s^{-1} and PVR reduced to 40 ml and 30 ml, respectively. The mean IPSS decreased to 5, and the mean prostate volume decreased to 41.5 ml. Interestingly, the IIEF-5 score remained almost unchanged.[37] In the literature, the procedure is described as safe and effective for sexual function and ejaculation preservation. Among the intraoperative complications, there were only a few cases: one involving urethral burns and another related to urinary tract infection, along with three cases of prostatic abscesses that required surgical drainage (classified as Clavien–Dindo III). The most common postoperative complications encountered were irritative symptoms and several cases of acute urinary retention treated with catheterization.[37,42,43] Most significant trials are summarized in **Table 4.**

Table 2: Parameters at baseline, 3 months, and 12 months of patients who underwent prostatic artery embolization

Study	*Patient (n)*	*IPSS*			*Qmax*			*IIEF-5*		*MSHQ-s*	
		Previous	*3 months*	*12 months*	*Previous*	*3 months*	*12 months*	*Previous*	*3 months*	*Previous*	*3 months*
Abt *et al*.[20] 2021	103	19.38±6.37	NK	18.9±6.3	NK	NK	NK	NK	NK	NK	NK
Salem *et al*.[21] 2018	45	23.6±6.1	10.2±6.0	12.4±8.4	5.8±1.0	15.3±12.3	NK	NK	NK	NK	NK
Carnevale *et al*.[22] 2016	30	25.3±3.6	NK	12.8±8.0	7.0±3.6	NK	10.1±6.5	14.3±6.8	NK	NK	NK

The data are shown as mean±s.d. IPSS: International Prostate Symptom Score; Qmax: maximum urinary flow rate; IIEF-5: International Index of Erectile Function-5; MSHQ-s: Male Sexual Health Questionnaire-short form; s.d.: standard deviation; NK: not known

Table 3: Rezūm treatment: results at 3 months and 12 months

Study	*Patient (n)*	*IPSS*			*Qmax*			*IIEF-5*		*MSHQ-s*	
		Previous	*3 months*	*12 months*	*Previous*	*3 months*	*12 months*	*Previous*	*12 months*	*Previous*	*12 months*
McVary *et al*.[32] 2019	188	22.0±4.8	NK	21.8±4	9.9±2.2	NK	10±2.2	22.7±7.4	23.3±6.9	9.3±3.1	9.3±4.0
Gupta *et al*.[31] 2018	129	21.5±4.3	−10.6±68.7[a]	−3.1±84.1[a]	9.9±2.3	+6.5±7.3[a]	+5.6±6.5[a]	NK	NK	NK	NK
Siena *et al*.[29] 2021	135	21.5 (17–25)	4.2 (3.2–5.3)	NK	8.1 (6–10)	NK	NK	20 (16–22)	NK	NK	NK

The data are shown as mean±s.d. or mean (range). [a]Change compared to the previous data. IPSS: International Prostate Symptom Score; Qmax: maximum urinary flow rate; IIEF-5: International Index of Erectile Function-5; MSHQ-s: Male Sexual Health Questionnaire-short form; s.d.: standard deviation; NK: not known

Table 4: Transperineal laser ablation: results at 3 months and 12 months

Study	Patient (*n*)	IPSS			Qmax			IIEF-5		MSHQ-s	
		Previous	*3 months*	*12 months*	*Previous*	*3 months*	*12 months*	*Previous*	*3 months*	*Previous*	*3 months*
Frego *et al.*[37] 2021	22	22 (19.5–25.25)	8 (4.5–11)	6 (4.25–7)	9 (5–12.5)	12 (9–16.5)	20.5 (14.25–23.75)	22 (16.5–24)	22 (19.5–24)	NK	NK
Sessa *et al.*[42] 2023	30	21.5 (18–27.8)	13 (11.3–6.4)	NK	9.5 (7.6–11.2)	14.2 (11.2–16.3)	NK	16 (7.5–23.5)	23 (17.5–25)	5 (3–7.4)	8.9 (7–16.4)
Cai *et al.*[41] 2022	20	22.7±5.3	NK	NK	8.5±3	NK	NK	NK	NK	NK	NK
De Rienzo *et al.*[43] 2021	21	18±3.9	8.3±3.8	NK	9.2±3.4	13.3±6.7	NK	17.8±6.6	17.7±6.7	5.7±4.5	6.8±3.5
Manenti *et al.*[40] 2021	44	18.5±5.5	NK	6.2±3.8	7.6±4.2	NK	16.2±4.9	21±4	NK	4.9±3.7	NK
Pacella *et al.*[38] 2020	160	22.5±5.1	NK	7.0±2.9	8±3.8	NK	15±4	NK	NK	NK	NK
Patelli *et al.*[39] 2017	18	21.9±6.2	10.7±4.7	NK	7.6±2.7	133±76.2	NK	NK	NK	NK	NK

The data are shown as mean±s.d. or mean (range). IPSS: International Prostate Symptom Score; Qmax: maximum urinary flow rate; IIEF-5: International Index of Erectile Function-5; MSHQ-s: Male Sexual Health Questionnaire-short form; s.d.: standard deviation; NK: not known

PUL

PUL, also known as Urolift, is a simple and standardized procedure preserving verumontanum, bladder neck, and urethral sphincter while treating prostatic obstruction. It is the only minimally invasive procedure suggested with strong evidence by European guidelines, underlining benefits in patients with prostate volumes smaller than 80 ml.[3]

PUL is performed by placing a variable number of implants in the prostatic urethra, in function of its length, to induct a retraction of prostatic lobes that allow outflow and minimize side effects due to resection or enucleation.[44]

We analyzed four multicentric studies. McVary *et al.*[45] focused on ejaculatory and erectile function 1 year after surgery, which were preserved (in few cases even improved). IPSS and QoL, as well, were better at 3 months and at 1 year.[45]

Roehrborn *et al.*[46] compared the effect of PUL versus sham in 206 patients with prostate volume between 30 ml and 80 ml. They estimated an increase of peak urinary flow rate at 3 weeks (4.4 ml s^{-1}) and its stabilization at 12 months (4 ml s^{-1}); the American Urological Association Symptom Index parameters received benefit too; in fact, from 22 preoperative, there was a decrement to 18 (at 2 weeks) and then 11 (no variation at 3 months and 12 months). No adverse effects were reported, including erectile and ejaculatory function.[46]

Rukstalis *et al.*[47] compared the short- and long-term effects of PUL, with relevant improvements in terms of IPSS, decreased of 9 points in 3 months, and Qmax which upgraded of 4.2 ml s^{-1}. No collateral effects were reported on sexual and ejaculatory function.[47]

Sønksen *et al.*[48] compared 80 patients who underwent TURP or Urolift, reporting more benefits for the second one in terms of erectile and ejaculatory function, but no significant differences were reported in terms of IPSS and QoL mean values.

Annese *et al.*[49] in a 35-patient retrospective study showed benefits of this procedure, especially in terms of IPSS (from a median of 20 points to 9 points after 12 months of follow-up), PVR (reduction from 70 ml to 22.5 ml at 12 months), and Qmax (improvement from 8 ml s^{-1} in preoperatory to 13.5 ml s^{-1} at 12 months). Most significant trials are summarized in **Table 5**.

ITIND

The iTIND is a device with 3 nitinol end-tips (instead of 4 like its predecessor) that is implanted on the prostatic urethra and bladder neck, creating enough pressure to induce ischemic necrosis on the obstructing tissue. Two different generations of this device have been commercialized, the previous was known as TIND, while the actual is the iTIND.[50]

The entire procedure can take approximately 10 min, including local anesthesia.[51] The device is placed under cystoscopy vision with the 3 terminal struts anchored at 12 o'clock, 5 o'clock, and 7 o'clock on the bladder neck and along the prostatic urethra, determining the required pressure. Catheterization after implant is not always necessary, and after 5 days or 7 days, the device is removed, leaving a reshaped urethra.[52]

We reviewed 3 multicenter studies with similar assessment of functional outcomes. In the study by Amparore *et al.*,[52] 81 patients, with an average prostate volume of 75 ml, were enrolled. Evaluation of the results at 3 years showed an improvement of the mean Qmax from 7.71 ml s^{-1} to 15.2 ml s^{-1}, the mean IPSS QoL decreased from 3.96 to 1.76, and the mean IPSS decreased from 20.7 to 8.55.[52]

In the trial by De Nunzio *et al.*,[53] 70 patients with a prostate volume of smaller than 120 ml were enrolled. At 6 months, there were a clear improvement in the mean Qmax from 7.34 ml s^{-1} to 12.08 ml s^{-1}, a

decrease in the mean IPSS QoL from 4.13 to 1.96, and a decrease in the mean IPSS from 21.2 to 8.3.[53]

In the study by Chughtai *et al*.,[54] 185 patients with a prostate volume of smaller than 75 ml were enrolled, of whom 128 underwent iTIND placement. The results at 12 months showed that the mean Qmax increased from 8.42 ml s^{-1} to 11.93 ml s^{-1}, the mean IPSS QoL changed from 4.51 to 2.45, and the mean IPSS decreased from 21.64 to 12.69.[54]

In the previous studies that included validated questionnaires for sexual function (sexual health inventory for men [SHIM] and IIEF) and ejaculatory function (MSHQ-EjD), there were no difference before and after the treatment, while in some cases, even an improvement was reported.[53,54] Furthermore, in all cohorts, minor perioperative complications (Clavien–Dindo grades I and II) were reported, the most common of which were irritative urinary tract symptoms with associated urinary urgency and macrohematuria, while major complications and the need for re-treatment were very rare (Clavien–Dindo grades III and IV).[52–54] Most significant trials are summarized in **Table 6**.

EVIDENCE SYNTHESIS AND GUIDELINE RECOMMENDATIONS

In terms of AquaBeam, the available literature lacks long-term data at more than 3-year follow-up, and the procedure is not recommended for office-based settings due to the risk of bleeding. The EAU guidelines in 2023 propose AquaBeam as an alternative to TURP with a weak recommendation.[1]

PAE currently faces challenges in terms of standardization, as the procedure requires expertise from urologists or radiologists. Vessel atherosclerosis or anomalies can also impact the outcomes of PAE, making it a procedure that is not currently considered safe and reproducible.

Rezūm has a low recommendation level and low scientific evidence (level C) according to the AUA guidelines.[5] It is considered an alternative technique rather than a gold standard. The European guidelines express similar concerns and indicate the need for more randomized controlled trials to evaluate and compare Rezūm with other minimally invasive techniques.[1] However, in the American review of the surgical approach to BPH, Rezūm is proposed as a therapeutic alternative for men with prostates smaller than 80 g who wish to preserve ejaculation or have difficulty adhering to medical therapy.[5]

Transurethral prostate laser ablation has shown promising results in reducing urinary symptoms and prostate volume without impacting sexual function. However, there is a lack of long-term follow-up studies and guidelines specific to TPLA are currently unavailable.

PUL lacks long-term follow-up trials, and patient selection is crucial for the practicality of this procedure. However, the EAU guidelines in 2023 report strong evidence for PUL among MISTs for LUTS due to its low rate of side effects, particularly in terms of urinary continence, despite the potential need for re-treatment.[1]

Although the literature on the iTIND procedure is limited, the available results are promising, suggesting that it is a simple, safe, and effective technique that can preserve ejaculation and sexual function. The EAU guidelines in 2023 consider iTIND as an option for high-risk patients who are unable to undergo spinal anesthesia, pending further randomized clinical trials.[1]

MISTs are becoming a new promise, but strong evidence is still lacking. Most of them have still not yet reached maturity and cannot be considered definitive treatments. To date, only a few options have been given a recommendation for use, while others remain under investigation. In contrast with several other predecessors, it is hoped that some of the actual options will pass the test of time.

Among the major advantages of MISTs, antegrade ejaculation is considered the most important by patients. All the MISTs analyzed in the present review are considered to offer a high chance of preserving ejaculatory function.[55] The most comprehensive literature review and meta-analysis, conducted by Manfredi *et al*.,[56] shows that overall,

Table 5: Functional outcomes at 3 months and 12 months for prostatic urethral lift

Study	*Patient (n)*	*IPSS*			*Qmax*			*IIEF-5*		*MSHQ-s*	
		Previous	*3 months*	*12 months*	*Previous*	*3 months*	*12 months*	*Previous*	*3 months*	*Previous*	*3 months*
McVary *et al*.[45] 2014	140	22.2±5.48	11.0±7.6	11.1±7.0	8.02±2.43	12.4±5.4	12.1±5.4	18±5.6	19.2±6.3	9.1±3.1	10.5±3.2
Roehrborn *et al*.[46] 2017	140	22.2±5.4	11±7.6	11.1±7	8.9±2.2	12.4±5.4	12.1±5.4	13±8.4	13.4±9.2	8.7±3.2	Not significant
Rukstalis *et al*.[47] 2016	51	25.41±5.48	12.32±8.01	15.22±8.14	8.04±2.39	11.95±5.79	12.07±5.28	15.38±7.86	16.51±8.17	8.79±3.01	10.94±2.91
Sønksen *et al*.[48] 2015	45	22±5.7	10.5±7.4	10.7±8.1	9.2±3.5	13.6±5.3	13.6±5.5	20±4.9	19.7±5.6	11±2.7	11.9±3
Annese *et al*.[49] 2021	35	20±2.75	10.5±4.6	9±4	8±2	13.5±2.9	14.5±2.4	20±1.8	21.5±1	11±1.38	12±1.78

The data are shown as mean±s.d. IPSS: International Prostate Symptom Score; Qmax: maximum urinary flow rate; IIEF-5: International Index of Erectile Function-5; MSHQ-s: Male Sexual Health Questionnaire-short form; s.d.: standard deviation

Table 6: Functional outcomes at 3 months, 6 months, and 12 months for temporarily implanted nitinol device

Study	*Patient (n)*	*IPSS*			*Qmax*			*IIEF-5*		*MSHQ-s*	
		Previous	*3 months*	*6–12 months*	*Previous*	*3 months*	*6–12 months*	*Previous*	*3 months*	*Previous*	*3 months*
Amparore *et al*.[52] 2021	81	22.5±5.6	22.41±5.72	21.7±5.56	7.3±2.6	7.44±2.43	7.61±2.25	NK	NK	NK	NK
De Nunzio *et al*.[53] 2021	70	21.2±6.0	7.8±5.4	8.3±6.7	7.3±2.2	11.8±5.1	12±5.4	16.1±7.7	18.7±7.7	9.2±4.9	11.1±4.9
Chughtai *et al*.[54] 2021	118	22.1	11.7	8.8	7.3	11.2	14.9	Capable of performing sex (91.3%)	No patients experienced *de novo* ED	NK	No patients experienced *de novo* ED

The data are shown as mean or mean±s.d. IPSS: International Prostate Symptom Score; Qmax: maximum urinary flow rate; IIEF-5: International Index of Erectile Function-5; MSHQ-s: Male Sexual Health Questionnaire-short form; s.d.: standard deviation; ED: erectile dysfunction; NK: not known

MISTs are associated with a significantly lower risk ($P < 0.00001$) of retrograde ejaculation than TURP and laser procedures. In particular, retrograde ejaculation shows no statistically significant increase for PAE and PUL, while there is a difference for aquablation. When looking at the MSHQ-EjD, PUL shows no difference before and after the surgery, while WVTT reports a worsening of ejaculatory function. Finally, erectile function is not affected by any minimally invasive surgical procedure.[56] Another review focused on PUL, PAE, aquablation, and WVTT confirms that all of them are effective in maintaining erectile and sexual function.[57]

MISTs are considered an intermediate step between BPH medication and conventional surgery. For this reason, they are safe and characterized by low intraoperative and postoperative complications. The MAUDE database for reported complications of MIST procedures analyzes a total of 692 reports. The majority of complications reported are minor (level 1 or 2), and there is no significant difference between the MISTs. On the other hand, they describe an overall higher major complication rate (levels 3 and 4) for PUL in comparison with WVTT.[58]

There are certain limitations of MISTs that should be pointed out. Most of the available trials have been sponsored by companies, and real-world studies are often missing. A comparison between different techniques can be helpful to better identify all of them.

A very recent systematic review and network meta-analysis comparing the efficacy, safety, and tolerability of WVTT, PUL, PAE, and iTIND to TURP has identified 63 trials. The authors conclude that TURP is better in terms of uroflowmetry parameters, while symptoms and QoL for PAE, PUL, and WVTT are similar to TURP. Finally, WVTT and PUL were superior in terms of ejaculatory function.[59] Another systematic review and meta-analysis including 18 trials and comparing aquablation, Rezūm, and iTIND reports that aquablation seems to lead to better functional results compared to the others, while the safety profile of Rezūm and iTIND is higher. Regarding aquablation, bleeding should not be underestimated.[60] A third recent review compares aquablation, Rezūm, and TPLA. Even though the authors suggest that long-term, real-world data should be implemented, all three surgical procedures are reported to be safe and effective for the treatment of BPH.[61] The 2022 Cochrane network meta-analysis, including 3017 patients and 27 trials, reports that PUL and PAE may result in little to no difference in urological symptom improvement compared with TURP, while WVTT and iTIND may result in worse urological symptoms. Regarding QoL, MISTs compared to TURP may result in little to no difference, while they may result in a large reduction in major adverse events.[62]

Another highly debated issue is the reintervention rate, and once again, the data presented do not always reflect real-world results. The importance of the success and the duration over time of the treatment must be kept in consideration, as the cost of a second intervention or pharmacologic re-treatment can negatively impact health systems. The literature lacks high-quality, independent randomized trials, and only a few trials could be considered reliable. An interesting review has been conducted in this regard on a total of 36 studies and 6380 patients. The authors report that 5-year long-term data are lacking and that the risk of bias is very high. Nevertheless, re-treatments of 5% after 3 years are reported for iTIND, about 4% for WVTT, and 13% for PUL after 5 years of follow-up. Even pharmacologic re-treatments are poorly reported, with up to 7% after 3 years for iTIND and up to 11% after 5 years of follow-up for WVTT and PUL.[63] Only one real-world experience with WVTT could be considered of good quality, and even though the follow-up is short (16.7 months), the authors report a re-treatment rate of 4.6%.[64]

Madersbacher *et al*.[65] suggest that among the experts, there are a need for better-designed clinical trials, a clearer definition of the target population, and a more realistic marketing approach to better define the actual MISTs. Even Gómez-Sancha[66] reports how we are at a high risk of being influenced by companies. There are centers adopting certain MISTs that are included by manufacturers between "centers of excellence", generating the wrong concept that if you do not embrace that technology, you are not a good center.[66]

Last but not least, patients' values, preferences, and expectations should be highly taken into consideration. The assessment of patients has a role not only in making the differential diagnosis and offering treatment but also in focusing on defining their clinical profile to provide the most suitable care. The patient's clinical profile should include their values and preferences within the context of personal, physical, emotional, relational, and social factors. All of this will optimize their counseling, facilitate treatment decision-making, and lead to the best results. A review on patients' values, preferences, and expectations for the diagnosis and treatment of LUTS reports that men prefer low-risk and highly effective surgical therapies. Patients report two symptoms to be more bothersome: urge incontinence and nocturia. On the other hand, sexual side effects are more important for those with a high level of sexual function.[2]

MISTs are not suitable for all patients, and individuals should be well informed about advantages and disadvantages. Maintaining ejaculation is an important point, but we should not forget our first goal: treatment of LUTS and avoidance of further treatments. Anyhow the "one size fits all" surgical management will be soon obsolete in favor of a more personalized approach.

AUTHOR CONTRIBUTIONS

GMB, AC, MR, ET, UGF, FC, and LDG take responsibility for the integrity of the data and the accuracy of the data analysis. GMB, NdA, GC, CB, MF, EDB, and LC reviewed the concept and design of the review. All authors contributed to the acquisition, analysis, and/or interpretation of data. GMB, AC, UGF, GA, PA, OST, MF, AP, and FDG drafted the manuscript. GMB, VM, and UGF have been the study supervisor of the entire project. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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