Review – Benign Prostatic Hyperplasia

New Ultra-minimally Invasive Surgical Treatment for Benign Prostatic Hyperplasia: A Systematic Review and Analysis of Comparative Outcomes

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1. Introduction

Benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS) is the most diagnosed urologic condition among men aged 45–74 yr, with a prevalence ranging from 8% to 80% between the fourth and ninth decades of life [1]. Medical therapy is usually the first treatment choice. However, medication-related side effects and insufficient symptom control resulting in BPH-related adverse events (such as hematuria, recurrent infection, and bladder stones) often lead to pharmacological discontinuation in favor of operative treatment options [2]. Most of these patients are offered surgical treatments, such as the traditional gold-standard transurethral resection of the prostate (TURP), holmium laser enucleation of the prostate (HoLEP) [3], water ablation [4], and simple prostatectomy (either open or minimally invasive [5]). Nevertheless, these techniques carry a non-negligible risk of complications and significantly impact a patient’s sexual function.

In this scenario, several new minimally invasive techniques have been introduced with the aim of providing better symptom relief compared to pharmacological therapy while minimizing the impact on sexual function [6]. Translating the concept from gynecology [7] and orthopedics [8], these new approaches can be broadly defined as ultra-minimally invasive treatments (uMISTs).
Among them, steam injection (Rezūm), prostate artery embolization (PAE), intraprostatic injection of fexapotide triflutate (NX-1207) and PRX302, implantation of a prostatic urethral lift (PUL), and the temporary implantable nitinol device (TIND) were introduced in the 2020 European Association of Urology (EAU) guidelines, although their role in the management of BPH remains controversial.

The aim of this review was to summarize and evaluate the perioperative and functional outcomes of these new uMISTs.

2. Evidence acquisition

2.1. Search strategy

After establishing an a priori protocol, a systematic electronic literature search was conducted in December 2020 using the Medline (via PubMed), Embase (via Ovid), Scopus, and Web of Science databases.

The search strategy used the PICO (Patients, Intervention, Comparison, Outcome) [9] criteria: studies among patients with BPH (Patients) undergoing uMIST (Intervention) or MIST (Comparison) to evaluate surgical, micturition, and sexual outcomes (Outcome) were identified.

The following search string was used: “Prostatic Hyperplasia”[MeSH] OR “benign prostatic hyperplasia”[tiab] OR “Lower Urinary Tract Symptoms”[MeSH] OR “lower urinary tract symptoms”[tiab] AND (rezum)[tiab] OR vapor/water/steam)[tiab] OR “Embolization, Therapeutic”[MeSH] OR PAE[tiab] OR “prostatic urethral lift”[tiab] OR PUL[tiab] OR Urolift[tiab] OR “temporary implantable nitinol device”[tiab] OR TIND[tiab] OR iTIND[tiab] OR Medi-Tate[tiab] OR Meditate[tiab] OR “fexapotide triflutate”[Supplementary Concept] OR “fexapotide triflutate”[tiab] OR “NX-1207”[tiab] OR “PRX302”[Supplementary Concept] OR PRX302[tiab] OR “PRX 302”[tiab]).

2.2. Article selection

The record selection process was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The study protocol was registered with PROSPERO (registry number CRD42021225014).

Two of the authors (E.C. and S.D.C.) independently reviewed the literature according to the inclusion and exclusion criteria. Disagreements about eligibility were resolved in conjunction with a third reviewer (C.F.) until consensus was reached. We included only prospective studies referring to one of the five uMISTs mentioned in the EAU guidelines [6] and reporting outcomes of interest. Articles not in English, not original investigations (such as editorials, commentaries, abstracts, reviews, and book chapters), studies reporting experimental studies on animals or cadavers, and non-BPH-related surgeries were excluded. As the EAU guidelines do not recommend the use of botulinum toxin A for this indication, this treatment option was not considered and related articles were not eligible. The titles and abstracts were reviewed in accordance with the inclusion criteria. After screening, full-text analysis was performed to confirm whether the selected articles should be included. References from the pooled articles were manually reviewed to identify additional studies of interest. In the case of multiple studies from the same institution and with overlapping study periods, we only included the latest published study. However, studies from the same institution considering different study populations were included in the analysis.

2.3. Risk-of-bias assessment

The risk of bias and the quality of the studies were independently assessed using the standard Cochrane Collaboration risk-of-bias tool for single-arm studies [11], the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool for comparative studies [12], and the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) for randomized controlled trials (RCTs) [13].

2.4. Assessment of study quality

For nonrandomized controlled trials, study quality was assessed using the Newcastle-Ottawa scale (total score: ≤5 = low quality; 6–7 = intermediate quality; 8–9 = high quality) [14]. RCTs were evaluated using the Jadad scale (0 = very poor quality, 5 = rigorous quality) [15]. The level of evidence of each study was assessed according to the Oxford Centre for Evidence-Based Medicine [16].

2.5. Data extraction and analysis

A dedicated data extraction form was used to collect the data of interest. Baseline demographics (age, indwelling catheter, prostate-specific antigen, prostate volume, maximum urinary flow (Qmax), postvoid residual volume (PVR), International Prostate Symptom Score (IPSS), IPSS-Quality of Life (Qol), International Index of Erectile Function (IIEF-5), Male Sexual Health Questionnaire-Ejaculatory Dysfunction (MSHQ-EjD) bother and function, and Sexual Health Inventory for Men (SHIM)), perioperative variables (operative time, number of intraoperative complications, Visual Analog Scale (VAS) score, length of stay, and duration of catheterization), and postoperative complications according to the Clavien-Dindo classification [17] were recorded. Qmax, IPSS, Qol, IIEF-5, PVR, and MSHQ, SHIM, and IIEF-5 scores were collected and analyzed at 1, 3, 6, and 12 mo after the intervention. An indirect comparison among treatments was performed given the absence of studies with a pairwise design.

For continuous variables reported as the median (range), results were converted to the mean ± standard deviation (SD) using a dedicated formula [18]. Data reported as the median and interquartile range (IQR) were excluded because no information regarding the parametric distribution was available. After obtaining the mean ± SD, data were further converted to the mean with 95% confidence interval (CI). The grand mean was used to calculate the overall mean.
for data for the same variable but split into two groups. For continuous variables, a pooled analysis of the mean (95% CI) was performed using the *meta* command, whereas for dichotomous values a cumulative analysis of percentages was conducted using the *meta* command. A random-effects model using the DerSimonian and Laird method was used to evaluate the $I^2$ value for heterogeneity. A heterogeneity level above 75% was considered to be high.

Funnel plot analysis was conducted for bias assessment using the *metafunnel* command.

Stata version 15.0 software (StataCorp LLC, College Station, TX, USA) was used for all statistical analyses.

3. Evidence synthesis

The initial electronic search identified a total of 3978 papers. Of these, 1575 were identified for detailed review, and ultimately 48 studies met the inclusion criteria and were included in the analysis [19–66] (Fig. 1).

Among these, 35 were single-arm studies [19–24,26–31,33–35,37–44,46,47,50,51,53,54,57–61,66], 12 were RCTs [25,36,45,48,49,52,55,56,62–65], and one was a comparative study [32].

Four studies described Rezūm [53–56], 32 PAE (including one perfected PAE [PAPAI]) [19–50], two intraprostatic injections [51,52], seven PUL [60–66], and three TIND [57–59]. Only seven studies reported a comparison with TURP, of which five were on PAE [25,32,36,45,49] and two were on PUL [64,65].

A total of 2689 patients were evaluated.

3.1. Study quality

The quality of non-RCT studies evaluated with the Newcastle-Ottawa scale ranged from poor to good [19–24,26–35,37–44,46,47,50,51,53,54,57–61,66]. All the RCTs were found to be of acceptable quality (≥3 points) [25,36,45,48,49,52,55,56,62–65]. The quality assessment and level of evidence are summarized in Table 1.

3.2. Risk of bias

High risk of bias (selection, performance, and detection bias) was observed for all the single-arm studies [19–24,26–31,33–35,37–44,46,47,50,51,53,54,57–61,66] (Fig. 2A), whilst the risk of bias was low for the comparative study [32] and the RCTs [25,36,45,48,49,52,55,56,62–65] (Fig. 2B, C). Funnel plot assessment demonstrated a high risk of bias among the studies, as shown in Supplementary Figure 1.

3.3. Baseline characteristics

Baseline data are summarized in Supplementary Table I. Assessment (Supplementary Fig. 2) revealed that patients in the PAE group were the oldest (68.81 yr, 95% CI 67.79–71.82), were the only ones with indwelling catheters (24%, 95% CI 17–31%), and had the highest prostate volume (88.4 cm³, 95% CI 79.35–97.53). Patients in the PPAE group had both the highest IPSS (24.6 points, 95% CI 22.78–26.42) and the lowest Qmax (5.10 ml/s, 95% CI 3.58–6.62). The TIND group had the lowest IPSS-QoL (3.96 points, 95% CI 3.77–4.15). MSHQ-EJd function and bother scores were only available for Rezūm and UroLift studies. The Rezūm group had a lower MSHQ-EJd function score (7.72 points, 95% CI 7.22–8.23) in comparison to the UroLift group. SHIM scores were only reported in studies assessing the UroLift technique.

3.4. Micturition outcomes

At the start of follow-up, there was a decrease in the pooled IPSS median score with respect to baseline (−9.81 points, 95% CI −11.37 to −8.25) and a further decline by 12 mo (−13.13 points, 95% CI −14.98 to −11.64; Fig. 3A).

Pooled analysis showed that PAE led to the lowest 1-mo (−6.53 points, 95% CI −7.62 to −5.54) and the highest 12-mo postintervention changes in IPSS (−18.21 points, 95% CI −21.25 to −15.17; Fig. 3A). IPSS data for every time point for all the uMISTs are reported in Supplementary Figure 3.

For Qmax, an overall pooled improvement of 3.66 ml/s (95% CI 2.8–4.5) was recorded at 1 mo of follow-up and remained relatively stable during the study period (4.14 ml/s, 95% CI 0.72–7.56 at 12 mo). The highest postintervention change in Qmax was observed for UroLift at 1 mo (7.80 ml/s, 95% CI 5.78–9.82) and for TIND at 12 mo (7.30 ml/s, 95% CI 6.10–8.50; Fig. 3B and Supplementary Fig. 3).

A significant improvement in PVR was observed at 1 mo (−28.72 ml, 95% CI −52.23 to −5.21) and 6 mo (−23.45 ml, 95% CI −33.48 to −13.45), followed by a slight decrease up to 12 mo (−10.10 ml, 95% CI −27.90 to 7.71; Fig. 3C and Supplementary Fig. 3). The highest postintervention change was found at 12 mo for the TIND technique (−39.51 ml, 95% CI −47.86 to −31.16; Fig. 3C).

3.5. Sexual outcomes

Data for IIEF-5 were available for PAE and PPAE only. The 12-mo IIEF-5 score was higher for the PPAE group than for the PAE group (18.70 vs 15.71; Supplementary Fig. 3). No analysis of postintervention changes in IIEF-5 was possible.

No significant difference in postintervention changes in MSHQ-EJd bother among the treatments was found at 1, 3, 6, and 12 mo (Fig. 4A and Supplementary Fig. 3).

MSHQ-EJd function was not affected by the treatments either at the beginning of follow-up (change in overall pooled median score of 1.88 points, 95% CI 1.34–2.42) or after 1 yr (1.04 points, 95% CI 0.28–1.8). At 12 mo the change in MSHQ-EJd function was lower in the Rezūm group (−0.30 points, 95% CI −1.08 to 0.48; Fig. 4B). Data regarding SHIM scores were only available for UroLift studies (Supplementary Fig. 3).

3.6. QoL outcomes

At 1 mo the pooled change in IPSS-QoL was lowest in the TIND group (−2.74 points, 95% CI −3.17 to −2.32), whereas there was no difference at 3, 6, and 12 mo (Fig. 3D). Overall,
the change in QoL at 12 mo was less than –2.5 points (95% CI –2.85 to –2.16).

3.7. **Adverse events**

Assessment of complications demonstrated an overall rate of 29%, with no difference among the techniques included (Supplementary Fig. 3).

3.8. **Interpretation of further study findings**

All five uMIST procedures (PAE, UroLift, TIND, Rezūm, and intraprostatic injection) can be performed in the office using intravenous sedation and local anesthesia [67]. Oral sedation has also been described for PUL and Rezūm. Perioperative management is in line with what is expected for a treatment defined as ultra-minimally invasive. Mean
| Study                  | Year | Type of study | uMIS type | Patients (n) | Outcomes assessed                                                                 | SQ | LE |
|-----------------------|------|---------------|-----------|--------------|-----------------------------------------------------------------------------------|----|----|
| Pisco et al [19]      | 2011 | PSCS          | PAE       | 15 –         | Clinical success on intent-to-treat basis defined as improvement in IPSS (reduction with score >20) and/or Qmax to >7 ml/s after PAE | 5  | 4  |
| Carnevale et al [20]  | 2013 | Single-arm PSCS | PAE       | 11 –         | Urodynamic investigation, PSA, PV, LUTS, sexual function, QoL                        | 2  | 4  |
| Pisco et al [21]      | 2013 | PSCS          | PAE       | 89 –         | Safety, morbidity, and short- and intermediate-term results of PAE for BPH after failure of medical treatment | 7  | 4  |
| Pisco et al [22]      | 2013 | PSCS          | PAE       | 255 –        | Improvements in symptoms and QoL                                                  | 6  | 4  |
| Antunes et al [23]    | 2013 | Single-arm PSCS | PAE       | 11 –         | QoL, LUTS, PSA, prostate US and MRI, urodynamic investigation                      | 4  | 4  |
| Kurbatov et al [24]   | 2014 | Single-arm PSCS | PAE       | 88 –         | LUTS, QoL, urinary flow, PVR, PSA, sexual function                                | 5  | 4  |
| Gao et al [25]        | 2014 | RCT           | PAE       | 57 57        | Safety and adverse events evaluated from intra- and perioperative data (operative time, fluoroscopy time, radiation dose, changes in hemoglobin and serum sodium within 24 h after PAE, transfusion requirements), postoperative data (hospital stay, catheter requirements), and peri- and postoperative complications | 3  | 1b |
| Bagla et al [26]      | 2014 | Single-arm PSCS | PAE       | 20 –         | Fluoroscopy time, QoL, LUTS, sexual function, PV, adverse events                  | 4  | 4  |
| Moreira de Assis et al [27] | 2015 | Single-arm PSCS | PAE       | 35 –         | LUTS, urinary flow, urodynamic investigation, PSA, QoL, PV (MRI)                   | 4  | 4  |
| Li et al [28]         | 2015 | PSCS          | PAE       | 24 –         | Improving symptoms (IPSS total score reduction of >25% and score – 18 points) after PAE and reduction in QoL of at least 1 point (score <3 points), with increase in Qmax by &gt;2.5 ml/s and Qmax of ≥7 ml/s | 5  | 4  |
| Lin et al [29]        | 2015 | PSCS          | PAE       | 18 –         | Clinical and morphologic (IPP index and PV) effect of PAE in patients with significant median lobe hyperplasia | 5  | 4  |
| Wang et al [30]       | 2015 | PSCS          | PAE       | 117 –        | Primary endpoints: IPSS reduction of 7 points (or >25% of the total score) and increase in Qmax (>3 ml/s) at 24 mo after PAE | 5  | 4  |
| Gabr et al [31]       | 2016 | PSCS          | PAE       | 22 –         | Improvement in LUTS and urinary flow rate, and reduction in PV and serum PSA        | 5  | 4  |
| Carnevale et al [32]  | 2016 | Prospective comparative study | PAE/PPAE | 15/15 15 | Urodynamic investigation, LUTS, PV, QoL, urinary flow, sexual function            | 6  | 4  |
| Rampoldi et al [33]   | 2017 | PSCS          | PAE       | 43 –         | Technical feasibility, safety, and efficacy of PAE in patients with BPH-associated BOO managed with IBC and unfit for endoscopic or surgical therapy because of severe comorbidities | 5  | 4  |
| Klaw et al [34]       | 2018 | Single-arm PSCS | PAE       | 29 –         | PV, LUTS, adverse events                                                          | 4  | 4  |
| Franiel et al [35]    | 2018 | PSCS          | PAE       | 30 –         | IPSS, QoL score, IIEF, PSA, Qmax, and PVR assessed before PAE (baseline) and at 1, 3, and 6 mo after PAE | 4  | 4  |
| Abt et al [36]        | 2018 | Randomized, open-label noninferiority trial | PAE       | 48 51 | Urinary flow, PVR, QoL, LUTS, sexual function, adverse events                     | 3  | 1b |
| Maclean et al [37]    | 2018 | PSCS          | PAE       | 86 –         | Reduction in IPSS of >25%                                                         | 6  | 4  |
| Singhal et al [38]    | 2018 | Single-arm PSCS | PAE       | 4 –          | LUTS, QoL, PV, PVR                                                               | 2  | 4  |
| Salem et al [39]      | 2018 | Single-arm PSCS | PAE       | 50 –         | LUTS, QoL, sexual potency, ejaculatory preservation, PVR, urinary flow, adverse events | 5  | 4  |
| Shaker et al [40]     | 2016 | Single-arm PSCS | PAE       | 28 –         | LUTS, QoL, urinary flow, PV                                                       | 4  | 4  |
| Moreira de Assis et al [41] | 2019 | Single-arm PSCS | PAE       | 8 –          | LUTS, PSA, urinary flow, PV (MRI), prostate elastography                          | 4  | 4  |
| Bilhm et al [42]      | 2019 | Single-arm, single-blind prospective randomized trial | PAE       | 89 –         | LUTS, QoL, sexual function, PV, PSA, urinary flow, PVR                           | 3  | 1b |
| Lindgren and Bläckberg [43] | 2019 | PSCS          | PAE       | 37 –         | IPSS reduction of >25% or improvement in QoL of 3 points, or freedom from urinary catheter in patients with previous chronic use or CIC, and urinary flow > 10 ml/s | 5  | 4  |
Table 1 (Continued)

| Study                        | Year | Type of study     | uMIS type | Patients (n) | Outcomes assessed                                                                                   | SQ | LE |
|------------------------------|------|-------------------|-----------|--------------|-------------------------------------------------------------------------------------------------------|----|----|
| Malling et al [44]           | 2019 | PSCS              | PAE       | 11 –         | Primary outcome for men with urinary retention: ability to void 6 mo after PAE                      | 4  | 4  |
| Insauti et al [45]           | 2020 | Noninferiority randomized trial | PAE       | 23 22        | Urinary flow, LUTS, QoL, PV, adverse events                                                          | 3  | 1b |
| Cheng et al [46]             | 2020 | Prospective single-arm cohort study | PAE       | 21 –         | LUTS, urinary flow, PV, PSA, PV                                                                      | 4  | 4  |
| Al Rawashdah et al [47]      | 2020 | Single-arm PSCS   | PAE       | 147 –        | LUTS, QoL, urinary flow, PV, PV, sexual function, ejaculation preservation                           | 5  | 4  |
| Pisco et al [48]             | 2020 | Randomized, single-blind, sham-controlled superiority clinical trial | PAE       | 80 –         | LUTS, PSA, urinary flow, PV, PV, sexual function, fluoroscopy time, procedural time                | 3  | 1b |
| Radwan et al [49]            | 2020 |RCT                | PAE       | 20 40        | Efficacy and safety of PAE                                                                         | 2  | 1b |
| Tapping et al [50]           | 2020 |Single-arm PSCS    | PAE       | 50 –         | LUTS, sexual potency, PV (multiparametric MRI)                                                      | 4  | 4  |
| Denmeade et al [51]          | 2011 | Phase 1/2 comparative study | PRX302    | 33 –         | LUTS, QoL, PV, PV, urinary flow                                                                  | 5  | 4  |
| Elhilali et al [52]          | 2013 |RCT                | PRX302    | 61 31 (PBO)  | Primary endpoint: increase in Qmax Other endpoints: PV as measured by TRUS, reduction in IPPS    | 5  | 1a |
| Dixon et al [53]             | 2015 |PSCS               | Rez3tm    | 65 –         | Efficacy and safety                                                                                 | 4  | 4  |
| Dixon et al [54]             | 2016 |PSCS               | Rez3tm    | 65 –         | IPSS, QOL instruments (QOL from IPPS, BPHII), and sexual function with IIEF, IIEF-question 9 for ejaculatory function, and MSHQ-EJd (1 center) Uroflowmetry, PV, and PSA were repeated at 1 wk, and 1, 3, 6, 12, and 24 mo | 5  | 4  |
| McVary et al [55]            | 2016 |RCT                | Rez3tm    | 136 61 (PBO) | Voiding symptoms (IPSS, QoL, Qmax, incontinence, IIEF-EF score) and ejaculatory function (MSHQ-EJd); effect of median lobe treatment on IPPS and sexual function | 3  | 1b |
| Roehrborn et al [56]         | 2017 |Multicenter RCT    | Rez3tm    | 135 –        | LUTS, urinary flow, incontinence rate, sexual function, adverse events                           | 4  | 1b |
| Porpiglia et al [57]         | 2019 |PSCS               | TIND      | 32 –         | Safe, effective, and well tolerated                                                               | 6  | 4  |
| Kadner et al [58]            | 2020 |Single-arm, multicenter PSCS | iTIND     | 81 –         | LUTS, QoL, urinary flow, PV, PV, intraoperative complications, sexual function, ejaculatory preservation | 4  | 4  |
| Amparore et al [59]          | 2020 |Single-arm, multicenter PSCS | iTIND     | 81 –         | Operating room time, postoperative complications, urinary flow, LUTS, PV, QoL, sexual function, ejaculatory preservation | 4  | 4  |
| Woo et al [60]               | 2011 |PSCS               | PUL       | 19 –         | Safety and feasibility                                                                             | 5  | 4  |
| Woo et al [61]               | 2012 |PSCS               | PUL       | 64 –         | Effect of PUL procedure on erectile and ejaculatory function                                         | 6  | 4  |
| Cantwell et al [62]          | 2014 |Randomized double-blind study | PUL     | 66 –         | LUTS, sexual function, ejaculatory preservation, urinary flow, PV                                  | 4  | 1a |
| McVary et al [63]            | 2014 |RCT                | PUL       | 140 66 (PBO) | Improved LUTS and urinary flow rate with preservation of sexual function                           | 4  | 1b |
| Senksen et al [64]           | 2015 |Multinational prospective, randomized, nonblinded study | PUL       | 45 35        | LUTS, postoperative recovery, sexual potency, ejaculatory preservation, container preservation, high-grade complications | 3  | 1b |
| Gratzie et al [65]           | 2016 |RCT                | PUL       | 40 40        | Primary endpoint: composite of six validated instruments assessing net health outcome at 1 yr: IPSS, SHIM, MSHQ-EJd, ISI, QoR VAS, and Clavien-Dindo classification of adverse events. | 3  | 1b |
| Rukstalis et al [66]         | 2019 |Single-arm PSCS    | PUL       | 45 –         | LUTS, postprocedural severe complications, QoL, urinary flow, sexual function                       | 4  | 4  |

uMIST = ultra-minimally invasive treatment; PSCS = prospective study-case series; TURP = transurethral resection of the prostate; SQ = study quality; LE = level of evidence; PAE = prostatic artery embolization; PPAE = perfected PAE; PUL = prostatic urethral lift; PBO = placebo; LUTS = lower urinary tract symptoms; MRI = magnetic resonance imaging; PV = postvoid residual volume; PV = prostate volume; PSA = prostate-specific antigen; Qmax = maximum urinary flow; CIC = clean intermittent catheterization; QoL = quality of life; IPSS = International Prostate Symptom Score; IIEF = International Index of Erectile Function; IIEF-EF = IIEF-Ejaculatory Function; RCT = randomized controlled trial; IPP = intravesical prostate protrusion; BPB = benign prostatic hyperplasia; BPHII = BPH Impact Index; BOO = bladder outlet obstruction; IBC = indwelling bladder catheterization; MSHQ-EJd = Male Sexual Health Questionnaire-Ejaculatory Dysfunction; SHIM = Sexual Health Inventory For Men; ISI = Incontinence Severity Index; QoR VAS = Quality of Recovery Visual Analog Scale; TIND = temporary implantable nitro device; iTIND = second-generation TIND.
Fig. 2 – Risk-of-bias assessment for (A) single-arm studies, (B) randomized controlled trials, and (C) the comparative study.
operative times for PUL range from 29 to 57 min, while the average treatment times for RezTm and TIND are 2–6 and 5.8 min, respectively (Supplementary Table 2) [67]. Hospital stays range from 0 to 2 d (Supplementary Table 2), with only one study that reported 6 d for PAE [28].

Rates of postprocedural catheterization for PUL and RezTm differ, depending on the protocol, with 32–68% of PUL and 55–100% of RezTm patients still having a catheter in place at discharge [67]. Patients undergoing TIND do not require postoperative catheterization, and thus experience better postprocedural comfort. Our analysis showed that the 1-mo IPSS-QoL (2.08 points, 95% CI 1.87–2.29) and IPSS-QoL change from baseline (−2.74 points, 95% CI −3.17 to −2.32) were lowest in the TIND group (Fig. 3D).

Compared to other MIST (not uMIST) procedures, TURP [68] and Aquabeam [4] require a significantly longer operative time and a hospital stay for an average of 2.1 d, and a postoperative catheter is always needed.

The number of men requiring surgical intervention vastly exceeds our operative resources, which were further reduced due to pandemic restrictions [69], so uMISTs might represent an attractive and convenient alternative for both patients and physicians.

Focusing on micturition and functional outcomes, TIND devices guarantee a good decrease in IPSS compared to baseline from the first month postoperatively (−11.05 points, 95% CI −12.25 to −9.86), with relatively stable results at 12 mo (−13.63 points, 95% CI −15.09 to −12.16). Similar findings were recorded for PUL and RezTm. On the contrary, PAE led to a slight improvement in IPSS at the beginning of follow-up (−6.53 points, 95% CI −7.62 to −5.54), with a more significant improvement after 1 yr (−18.21 points, 95% CI −21.25 to −15.17). These differences did not affect the change in Qmax among the different techniques, for which PAE was in line with the other uMISTs. Noteworthy is the UroLift Qmax improvement at 1 mo after intervention (7.80 ml/s, 95% CI 5.78–9.82). PVR was lower in the TIND group at every time point evaluated up to 12 mo of follow-up.

The delayed achievement of a plateau in benefit from PAE can be explained by the different inclusion criteria for patient selection: higher prostate volume might lead to a
longer time for the ischemia to induce necrosis in large-volume adenomas. Moreover, the presence of an indwelling catheter could stunt bladder contractility in the first months after the intervention.

Regarding sexual outcomes, a comment should be made with regard to the ideal candidates for these uMISTS. In the past, when first attempts to introduce less invasive treatment options such as transurethral needle ablation and transurethral microwave thermotherapy [70] were made, the target population was often represented by older patients unfit for conventional surgery. Nowadays an ever-younger population is interested in uMISTS since patients prefer to avoid daily consumption of oral medications, which can have considerable sexual side effects (such as erectile and ejaculatory dysfunction). However, these patients do not want to undergo a “standard” surgical procedure requiring general anesthesia and longer recovery, and they prefer to avoid the non-negligible risks of complications, including permanent ejaculatory dysfunction.

In our analysis, data on erectile function in terms of IIEF-5 score were only available for PPAE and PAE groups (mean score at 12 mo: 18.70 vs 15.71). A recently published multicenter Italian RezTm study showed a statistically significant increase in IIEF-5 score from baseline at 6 mo (20 vs 23.5 [IQR 21–25.5]; p = 0.04), with postoperative scores of 4 and 5 for question 9 of the IIEF-15 questionnaire in 81% and 17.1% of cases, respectively, and a score of 5 for question 10 in 98.5% of cases [71]. These results are in line with the data reported for conventional BPH surgical options.

By contrast, ejaculation dysfunction was widely explored. Our analysis revealed no statistically significant difference for the changes in MSHQ-EjD bother at 1, 3, 6, and 12 mo. In terms of MSHQ-EjD function, substantial stability compared to baseline was recorded. RezTm seemed to be the most effective treatment at 12 mo, with the lowest score recorded (−0.30 points, 95% CI −1.08 to 0.48).

No case of EjD was recorded in the PUL, TIND, and PAE groups, except for one trial that reported 13.3% loss of ejaculatory volume after PAE [72]. In the RezTm cohort, EjD ranged from 0% to 4.4%; McVary [55] observed EjD incidence of 2.9% in an RCT, similar to Mollengarden et al [73] (3.1%). More recently, a retrospective review of 62 patients treated in France revealed an even higher anejaculation rate (10.8%) [74]. However, even if RezTm might carry a higher risk of sexual dysfunction compared to PUL and TIND, this risk is relatively low compared with the rate of retrograde ejaculation reported after TURP (65.4%) [75] and HoLEP (70%) [76].

Cacciamani et al [77] evaluated EjD in a systematic review and pooled analysis of randomized trials and reported that among patients undergoing PUL, MSHQ-EjD bother scores did not reflect significant changes in function score compared to the TURP cohort (−0.1 vs −0.3). The meta-analysis was unable to demonstrate an advantage of PAE over TURP in terms of retrograde ejaculation rates (relative risk 0.73, 95% CI 0.49–1.08; p = 0.11). The physio-

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Fig. 4 – Forest plots of the pooled postintervention change in Male Sexual Health Questionnaire-Ejaculatory Dysfunction (MSHQ-EjD) scales for (A) bother and (B) function. CI+ confidence interval.
logical mechanisms of ejaculation were recently explored in depth and conventional techniques (TURP or HoLEP) were modified with the aim of avoiding EjD [76].

Acceptable rates of Clavien-Dindo grade III/IV complications have been reported for PAE, PUL, and RezTm. Data for TIND revealed that 9.9% of cases experienced Clavien-Dindo grade III complications in the first month after the procedure, after which no further complications occurred [78]. For PUL, adverse events were mostly limited to the first 3 mo and consisted of mild to moderate dysuria and hematuria [79]. However, serious related adverse events in the first year included an overnight stay for clot retention related to restarting warfarin therapy and a bladder stone formed from bladder gravel that was detected at baseline. Although rare, TIND patients may experience complications during the implantation period that require treatment abortion [57] or immediate retreatment (2.5–6.2% of cases) [78]. Clavien-Dindo grade I/II adverse events included hematuria, dysuria, urgency, pain, and urinary tract infection, while grade III events included eight episodes (9.9%) of acute urinary retention [59].

Notwithstanding all the above-mentioned benefits of these uMISTs, some obstacles limit their wider adoption, of which equipment limitations represent the first. For example, a specific extra-long bronchoscope lens is necessary for UroLift, and a dedicated computerized radiofrequency steam generator is required for RezTm.

The second limitation of these new technologies is the cost, which may exceed €1000 for just the equipment, besides the requirement to perform the procedures in a dedicated operative setting [80]. In fact, as emerged in a cost-effectiveness analysis, the cheaper MITs were ~$900 more expensive than the cost of drug therapies over 2 yr. TURP and photovaporization of the prostate provided slightly greater relief of LUTS than MITs at approximately twice the cost over 2 yr [81].

To date, only TIND perfectly meets the uMIST concept [80]: the entire procedure can be performed under local anesthesia or light sedation (without a dedicated setting) with a standard flexible or rigid cystoscope with no extra costs. The procedure is extremely fast and easy to perform, with promising findings for symptom relief up to 3-yr follow-up [59].

Our study is not devoid of limitations. First, the studies included are heterogeneous regarding surgical procedures and study design. In fact, some of these new uMISTs (TIND, RezTm) lack a comparison with gold-standard options such as TURP; moreover none of the studies directly compared the uMISTs to each other. Although all the studies report similar outcomes, the timings for evaluation differed and complications were not always classified according to the standard Clavien-Dindo system. The paucity of long-term follow-up data did not allow analysis after the first 12 mo postoperatively, despite the promising data from single-center experiences [33,39,55–57,59,65,78]. Lastly, owing to the lack of comparative data with standard TURP, no direct comparison with network meta-analysis was possible among the different uMISTs.

4. Conclusions

Available data suggest that uMISTs might offer effective relief from LUTS in patients with BPH. For RezTm, UroLift, and PAE, a minimal impact on patients’ sexual function in relation to baseline, especially in terms of preservation of ejaculation, was registered. Longer follow-up and further trials comparing these treatment options with more established techniques are warranted.

Author contributions: Enrico Checcucci had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Volpi, Carbonara, Vecchia, Piramide, De Cillis, Pecoraro.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.uroeuros.2021.08.009.

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