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An Indirect Comparison of Newer Minimally Invasive Treatments for Benign Prostatic Hyperplasia: A Network Meta-Analysis Model

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Key words: BPH, Benign prostatic hyperplasia, Prostatic urethral lift, Urolift, Rezum, Water vapor therapy, Aquablation, Network meta-analysis

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Abstract

Objective

This study was designed to provide an indirect comparison of the urinary and sexual domain outcomes and complications following newer minimally invasive surgical therapy (MIST) of Aquablation, Rezum, and UroLift for benign prostatic hyperplasia (BPH) to transurethral resection of prostate (TURP).

Methods

We searched Embase, Medline, and Cochrane in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA), in December 2019. Only randomized clinical trials (RCTs) that reported outcomes following treatment of BPH for prostate less than 80g with Aquablation, Rezum, or UroLift, were included in the analysis.

Results

A total of 4 RCTs reporting the outcomes after treatment with newer MIST for BPH were identified. Patients undergoing the resective procedures i.e. TURP and Aquablation, had greater improvement in urinary domain outcomes: International Prostate Symptom Score, Quality of Life, peak flow rate and Post Voiding Residual compared to patients undergoing non-resective procedures: UroLift and Rezum. Patients in UroLift group maintained a higher sexual function domain score compared to TURP but not Aquablation. Our multiple comparison analysis did not reveal a significant difference in urinary and sexual domain scores between patients undergoing UroLift and Rezum at 24 months of follow-up.

Conclusions

Aquablation and TURP necessitate general or regional anesthesia, both produced significantly better urinary domain scores compared to Rezum and UroLift. On the other hand, UroLift demonstrated better sexual function domain scores compared to TURP but not Aquablation. There was no significant difference in urinary domain scores between UroLift and Rezum at 24 months follow up.

Key words:

BPH, UroLift, Rezum, Aquablation, Network meta-analysis

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a chronic condition associated with development of lower urinary tract symptoms (LUTS). BPH is the most common diagnosis for men in 45-74 years of age diagnosed with urological problems. Since 20% of the population in the United States (US) is estimated to reach 65 years of age by 2030, a corresponding increase in the proportion of patients with BPH will lead to significant increase in health care costs.[1, 2] Although many men are initially managed with medical therapy, 25-70 % will become non-compliant or discontinue medication due to inadequate relief or side effects.[3, 4] Until recently, treatment options for those who fail or discontinue medical management included surgical management with open or minimally invasive simple prostatectomy or minimally invasive treatments including transurethral resection of prostate (TURP), laser enucleation, photovaporization, transurethral needle ablation (TUNA), and transurethral microwave therapy (TUMT). TURP remains the gold standard for the treatment of BPH in prostates with gland size of 30-80g.[5] Although TURP causes significant improvement in International Prostate Symptoms Score (IPSS), peak flow rate (Qmax), quality of life (QoL), and reduction of post voiding residual (PVR) volume, it may be associated with early complications including bleeding, capsular perforation, and need for blood product transfusion; as well as delayed postoperative complications including incontinence, erectile dysfunction, and/or retrograde ejaculation.[6] Sexual function remains an important component of overall QoL regardless of age in majority of men[7] and especially preservation of antegrade ejaculation, remains a challenge. However, in recent years newer minimally invasive surgical therapies (MIST) options have emerged which provide effective urinary domain score improvement along with favorable ejaculatory sexual domain scores. More recent choices of intervention are: prostatic urethral lift (PUL) (UroLift; Neotract Inc., Pleasanton, California, USA), convective water vapor energy (WAVE) (Rezum; NxThera Inc., Maple Grove, Minnesota, USA) and water jet dissection, AquaBeam System (Aquablation, PROCEPT BioRobotics, Redwood Shores, CA, USA.[8,9,10] A desirable gold standard for these procedures include ability to perform the procedure in an office setting under local anesthesia, provide rapid and durable relief of LUTS with minimal complications and preservation of sexual function and early return to normal

activity of patients. While none of the currently available MIST for BPH meet the gold standard criteria, several of the newer MIST preserve the ejaculatory sexual domain score while maintaining efficacy in the urinary domain scores.

In spite of the newer MIST being compared to gold standard TURP, there is lack of RCT reporting a head to head comparison of each of these MIST, which makes selection of the procedure based on comparative efficacy and side effect profile a challenge. Therefore, we carried out an indirect comparison using network meta-analysis framework (NMA) on urinary and ejaculatory domain scores using the existing randomized controlled trials (RCTs) in the literature.

MATERIALS AND METHODS:

Methodology

We registered our study protocol at International Prospective Register of Systematic Reviews (PROSPERO) CRD42020163588. A systematic literature search was initially performed in December 2019, using Embase, Medline through PubMed, and Cochrane databases in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA) by a librarian (GK).[11] Databases were screened for RCTs reporting outcomes after Aquablation, Rezum and UroLift. Two authors (KT and SBJ) undertook the screening process independently. Individual urological journals and relevant citations were manually searched to retrieve any further studies. Search terms included keywords 'Urolift', 'Prostatic urethral lift', 'Rezum', 'Aquablation', 'Water jet dissection of prostate', 'Water vapor therapy for prostate'. We contacted the authors for access to unpublished data whenever the data in the articles was not adequate.

Data extraction and analysis

A Google Sheet data extraction template was created. Two researchers (SBJ, KT) independently extracted the data from full text articles. A third researcher (JC) was available in case of conflict between the two researchers in risk of bias assessment and data extraction. Unpublished data was requested from authors and added to the database manually. Risk of bias assessment was assessed using the Cochrane risk of bias tool for

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randomized trials (ROB 2).[12] Robvis (visualization tool) was used to demonstrate the risk of bias.[13] Out of the 4 studies identified for NMA, TURP was used as the control group in two studies and sham procedure in the other two studies. As TURP is considered the gold standard procedure for treatment of BPH, we pooled the data from the two studies that had TURP as the control and generated a single control group.

Outcome measures

The primary outcome measures were IPSS, Qmax, PVR, QoL which will be referred as urinary domain outcomes, Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD), and Male Sexual Health Questionnaire for Ejaculation Bother (MSHQ-Bother) which will be referred as sexual domain. We excluded the Sexual Health Inventory for Men (SHIM) and International Index of Erectile Function (IIEF) as they were not uniformly reported among all the studies. The secondary outcomes were perioperative events like type of anesthesia, procedure time, need for post-operative catheterization, length of hospital stay, time needed to return to activity of pre-operative level and adverse events (AEs).

Statistical Analysis

We performed network meta-analysis (NMA) assuming a fixed-effect model with frequentist approach for indirect comparison among different interventions.[14] For each outcome, the effect size with 95% confidence interval (CI) was calculated at each timepoint by computing the mean difference from the baseline and standard deviation of this difference. We also estimated the relative ranking of different treatments for each outcome using the distribution of the ranking probabilities and the surface under the cumulative ranking curves (SUCRA). All analyses were performed using STATA statistical software (*Release 15*. College Station, TX: StataCorp LLC.). Graphical representations were made using GraphPad Prism v8. Statistical significance was set at $p < 0.05$.

RESULTS:

Initial search resulted in 22 articles after screening 17 articles were assessed for eligibility. The PRISMA diagram (Figure 1) outlines the flow of literature search. A total of 4 studies were included in the final analysis (UroLift -2 studies, Rezum - 1 study and Aquablation - 1

study).[10, 15-20] We excluded articles that reported outcomes in patients with prostates more than 80g. The inclusion and exclusion criteria among included studies were comparable among the trials (Supplementary Table 1). A total of 116, 133 and 181 patients underwent Aquablation, Rezum and UroLift, respectively. In the reported RCTs, 24-month follow up data was available on 109, 109 and 77 patients who underwent Aquablation, Rezum, and UroLift, respectively. We did not use the data available at 36, 48, or 60 months of follow up due to unavailability of data for one or more of the interventions. The quality of studies was assessed using the Cochrane risk of bias tool. We rated the study by Gratzke *et al*.,[18] to have high risk of performance and detection bias as it was a non-blinded study and Roherborn *et al*.,[16] to have high risk of performance bias. However, the other two studies were rated to have low risk of bias in all domains (Supplementary Figure 1).

Baseline characteristics

The baseline inclusion and exclusion criteria were similar among included studies with minor differences. Rezum and UroLift studies used a PVR cutoff of >250 ml whereas Aquablation used a cutoff of >300ml. UroLift studies excluded patients with obstructed median lobe as determined by pre-operative cystourethroscopy. The mean age of the patients was comparable among different groups, the mean prostate size was 6-10 ml higher in the Aquablation and TURP group (Table 1). However, this difference was not statistically significant.

Peri-operative outcomes

Majority of cases of UroLift procedure were performed under local anesthesia, Rezum under sedation, whereas 94% of patients undergoing Aquablation and 100% undergoing TURP were performed under general or regional anesthesia. The average total procedure time for UroLift was 66±24 min and 55±17 minutes in studies by Roehrborn *et al.*,[21] and Gratzke *et al.,*[18] respectively. Aquablation and TURP had an operative time of 33±16 and 35±15 minutes, respectively. The majority of patients undergoing Rezum and UroLift were discharged on the same day. The mean length of stay (LOS) for patient's admitted after undergoing UroLift was 1±1 day and those undergoing TURP or Aquablation had a median LOS of 1.4 days. The mean length of time taken for return of pre-operative activity level

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was 8.6±7.5 days and 11±19 days after undergoing UroLift in studies by Roehrborn *et al.,*[15] and Gratzke *et al.,*[18] respectively. Men undergoing, TURP went to preoperative activity level on an average of 17±19 days. Patients undergoing Rezum returned to preoperative activity level at median of 4 days after catheter removal.

IPSS

Supplementary Table 2 shows the result of indirect comparison of IPSS improvement at 1, 3, 6, 12, and 24 months of follow up between Aquablation, Rezum, TURP, and UroLift. At all follow up times after 1 month, TURP and Aquablation had higher improvement in IPSS score compared to Rezum and UroLift (p<0.05) (Figure 2). TURP and Aquablation had similar IPSS improvement scores except at 3 months where Aquablation had higher improvements compared to TURP. As shown in Figure 2, the patients in TURP group continued to improve on IPSS at each interval time up to 24 months of follow up while patients in Aquablation and Rezum had improvements for the first 6 months and had a decline in IPSS improvement score afterwards. Patients in the UroLift group had an initial improvement for the first 3 months and had a steady decline in improvement afterwards. Supplementary Table 2 shows the details of IPSS improvement score for each intervention. At 24 months, patients undergoing Aquablation had an average of 3.3, 95% CI 0.4 - 6.2, and 5.4, 95% CI 2.7 - 8.1 higher improvement compared to patients undergoing Rezum and UroLift, respectively.

QoL

Figure 2 shows the improvement in QoL following Aquablation, Rezum, TURP, and UroLift. At all follow up times Aquablation and TURP had comparable improvements in QoL. At 1 month of follow up, Aquablation, TURP, and UroLift had comparable and more improvement in QoL compared to Rezum (p<0.05). After 3 months, Rezum and UroLift, had lower improvements in QoL compared to both Aquablation and TURP at all follow up intervals (p<0.05). There was no difference between Rezum and UroLift at 24 months of follow up. As shown in Figure 2, Aquablation, Rezum, UroLift had an increase in QoL for the first 6 months whereas TURP group had an increase in QoL up to 12 months followed by a decline at 24 months of follow up. The details of data for each procedure is presented

in Supplementary Table 2. At 24 months of follow up, patients in Aquablation had an average of 1.0, 95% CI: 0.2 - 1.9 and 1.0, 95% CI: 0.2 - 1.8 higher improvement in QoL compared to Rezum and UroLift patients, respectively (p<0.05).

Qmax

Data for Qmax is shown in Figure 2 and Supplementary Table 2. As shown in Figure 2, at all follow up times, Aquablation and TURP had higher and comparable improvement in Qmax scores. Aquablation and TURP both outperformed Rezum and UroLift at all interval times in increasing the Qmax (p<0.05). There was no difference between Rezum and UroLift in any interval time. Patients in Aquablation group had an average of 6.3, 95% CI 1.8 - 10.9, and 6.9 95% CI, 3.0 - 10.9 higher improvement in Qmax in comparison to Rezum and UroLift, respectively (p<0.05).

PVR

The change in PVR is shown in Figure 2. Aquablation and TURP had comparable and higher decrease in PVR compared to Rezum and UroLift (p<0.05). The decrease in PVR remained relatively stable at 24 months of follow up in Aquablation, TURP, and UroLift, while there was a declining pattern in patients undergoing Rezum. There was no difference between Rezum and UroLift at any follow up time (Supplementary Table 2 and Figure 2). At 24 months of follow up, Aquablation patients had higher decrease in PVR compared to Rezum and UroLift with an average of 56.7 95% CI 19.4 – 94.0, and 46.4 95% CI 7.9 – 84.9 ml lower PVR, respectively (p<0.05).

MSHQ-EJD (Function)

MSHQ-EjD changes from baseline are shown in Figure 2. Data was available for follow up intervals after 3 months. Patients in UroLift had an improvement in their MSHQ-EJD scores at all follow up time, this improvement was significant compared to TURP group at all follow up times (p<0.05), and compared to Aquablation, and Rezum at 6 and 12 months, respectively (p<0.05). The MSHQ score decreased over time for all interventions, except Aquablation which demonstrated an increasing pattern during the follow up intervals (Figure 2). The indirect comparison results are shown in Supplementary Table 3.

MSHQ-EJD (Bother)

MSHQ-EjD bother score changes are shown in Figure 2. There was no specific trend in change of bother score. Initially, the patients in UroLift had a reduction in bother score which was significant compared to Aquablation and TURP at 3 months (p<0.05). This difference was not significant at 6 or 24 months. At 12 months, UroLift patients had significant reductions in bother score compared to Aquablation and TURP. Supplementary Table 3 has the details of the difference in change of MSHQ-EJD bother score used in the indirect comparison.

Adverse events

A summary of early (<30 days) adverse events is shown in Table 2. There was a higher incidence of dysuria and pelvic pain following UroLift. Patients undergoing UroLift had no reported incidence of erectile dysfunction (ED) or retrograde ejaculation (RE). Patients undergoing TURP reported higher incidence of bleeding, urgency, urge incontinence, ED, and RE. After Aquablation, there was a higher incidence of urinary retention and urinary tract infection. At two years of follow up, the retreatment rates following Aquablation, Rezum, TURP and UroLift were 4.3%, 4%, 1.5%, and 7.5%, respectively (Table 2).

DISCUSSION

Over the last decade many promising newer minimally invasive techniques have emerged for the treatment of BPH/LUTS. The 2018 AUA guidelines, which was amended in 2019, recommended use of Aquablation, Rezum, and UroLift in prostates less than 80g and, in 2020, UroLift has been approved by the FDA for use in prostates up to 100g.[22] In our previous review we have shown the durability of UroLift results at 24 months.[23] In this NMA, we compared the functional and perioperative outcomes of Aquablation, Rezum, and UroLift within 24 months of follow-up using TURP as the common comparator among the interventions.

As expected, resective procedures i.e. TURP and Aquablation, demonstrated greater improvement in IPSS compared to Rezum and UroLift, except in the first month after procedure. Compared to UroLift, it took longer for Rezum to demonstrate improvement in

IPSS, presumably due to time needed for sloughing of prostate tissue. Comparatively, the immediate opening of the prostatic urethra following UroLift may explain the better improvement in IPSS and QoL at one-month follow-up.

Resective procedures, i.e. TURP and Aquablation were found to have greater improvement in peak flow rate at all follow-up months compared to Rezum and UroLift. This is likely explained by the greater amount of tissue removed in resective procedures therefore creating a larger defect in the prostatic fossa. Similar outcomes were seen in PVR, with greater decrease following Aquablation and TURP. There was similar improvement in Qmax and PVR following Rezum and UroLift at all follow-up months. It is interesting to note that although UroLift had greater improvement in IPSS and QoL at one month compared to Rezum, Qmax and PVR had similar improvement at longer follow-up.

Retrograde ejaculation after TURP is a common and known side effect after resection. Preservation of the bladder neck and zone adjacent to the verumontanum are important in maintaining the ejaculatory function. Gilling *et al*., have observed better preservation of ejaculation when post-Aquablation non-resective cautery was avoided.[20,24,25] UroLift is shown to better preserve the sexual function in patients at all follow-up months compared to TURP but not Aquablation or Rezum, which is likely explained by the preservation of the bladder neck anatomy and absence of thermal injury in UroLift. There was no significant difference in sexual function between Aquablation, Rezum, and TURP. Patients who underwent UroLift were found to have better sexual bothersome scores as well when compared to Aquablation and TURP at 3and 12 months follow-up. It is interesting to note that all the procedures had no significant differences in sexual bother scores at 24 months follow-up.

Although urethral catheterization after UroLift can be avoided, there is a higher incidence of dysuria and pelvic pain in this group of patients. While the exact etiology is unclear, it is plausible that the exposed metallic tab in the prostatic urethra may be a contributing factor. Incidence of hematuria in men undergoing UroLift is comparable to TURP, this may be related to the technique of not using coagulation at the time of the procedure. However, there is no reported increased incidence of re-operation or persistent gross

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hematuria 3 months after UroLift. None of the men undergoing UroLift reported retrograde ejaculation compared to 29% of men undergoing TURP. Aquablation had a higher incidence of UTIs and urinary retention compared to the other procedures, whether the etiology of this finding relate to the mechanism of high pressure water jets in Aquablation is not known at this time.

One of the important factors to consider is retreatment rate which shows the durability of the procedure. In regard to retreatment, TURP has the lowest retreatment rate at 1.5% and UroLift reported the highest retreatment rate of 7.5% at 24 months. Aquablation and Rezum had similar retreatment rate of 4%. It looks that procedures that directly or indirectly resect and ablate prostatic tissue, have lower retreatment rate. Rezum and UroLift can be performed as office-based procedures under local anesthesia ± sedation, however, Aquablation and TURP require the procedure to be performed in the operating room under general or regional anesthesia.

The resource consumption of newer minimally invasive BPH procedures was not reported in the reviewed studies. The cost of health care delivery in the US may suggest a financial advantage to procedures performed in the office setting. UroLift and Rezum may be performed in office while Aquablation and TURP require anesthesia and are at best ambulatory surgical procedures. Office based MIST has been demonstrated to provide value when compared to medical intervention in prior reports.[26] Financial data was not reported in the manuscripts reviewed in this review so a direct comparison cannot be made between interventions. Perhaps future studies comparing financial cost to specific patient clinical factors will lend better guidance when choosing the best therapy for individual patients.

This study is not without limitations. There are limitations that are inherent to indirect analysis of the data. There are limited number of RCT published in the literature comparing Aquablation, Rezum, or UroLift to TURP. UroLift is the only intervention that had more than one study. As the design of the original studies was cross over or sham procedure, we computed a comparator TURP group with pooling data from original studies. This might have added bias to our analysis, however, patients in the included studies had comparative

demographic and baseline data. The total number of patients included in the studies were relatively low. Although longer follow-up data was available for UroLift and Rezum we limited our study to 24 months because the longest follow up available for the comparator, TURP, was only 2 years. Nevertheless, the study is the first NMA using the gold standard TURP as a comparator and novel options of BPH treatment, which provides necessary insights for providers and patients to make informed choices.

CONCLUSION

Patients undergoing Aquablation had greater improvement in IPSS, QOL, Qmax and PVR compared to patients undergoing Rezum and UroLift. Patients in Aquablation, had similar outcomes to patients receiving TURP in all domains. Patients in UroLift group performed better in the sexual function domain compared to patients in TURP group but not to patients in Aquablation group. There was no significant difference between Rezum and UroLift at 24 months of follow-up.

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Conflict of interest

The authors declare no conflict of interests.

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Abbreviations used:

MIST- minimally invasive surgical therapy

BPH- benign prostatic hyperplasia

TURP- transurethral resection of prostate

PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement

RCT- randomized clinical trials

LUTS- lower urinary tract symptoms

TUNA- transurethral needle ablation

TUMT- transurethral microwave therapy

MSHQ-EjD - Male Sexual Health Questionnaire for Ejaculatory Dysfunction

MSHQ-Bother- Male Sexual Health Questionnaire for Ejaculation Bother

SHIM- Sexual Health Inventory for Men

IIEF- International Index of Erectile Function

IPSS- International Prostate Symptoms Score

Qmax- peak flow rate

QoL- quality of life

PVR- post voiding residual

PUL- prostatic urethral lift

AE- adverse events

CI- confidence interval

NMA- network meta-analysis

SUCRA- surface under the cumulative ranking curves

ED- erectile dysfunction

RE- retrograde ejaculation

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An Indirect Comparison of Newer Minimally Invasive Treatments for Benign Prostatic Hyperplasia: A Network Meta-Analysis Model (DOI: 10.1089/end.2020.0739)

Figure Legends:

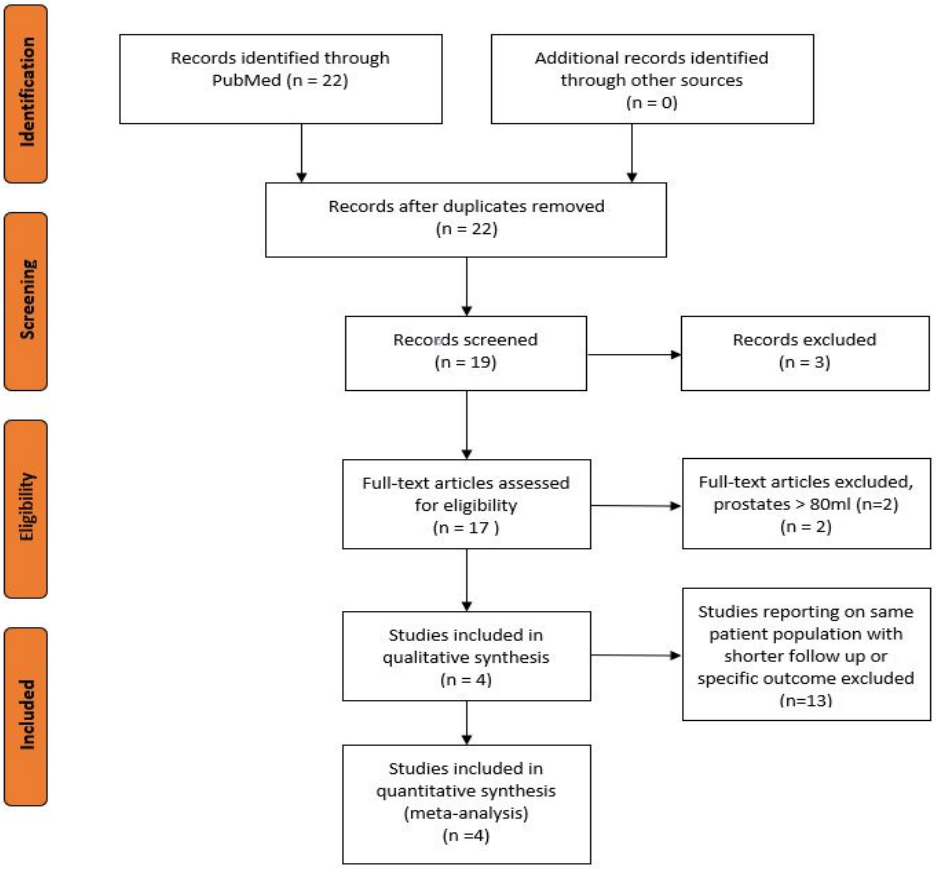

Figure 1 – Preferred Reporting items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram

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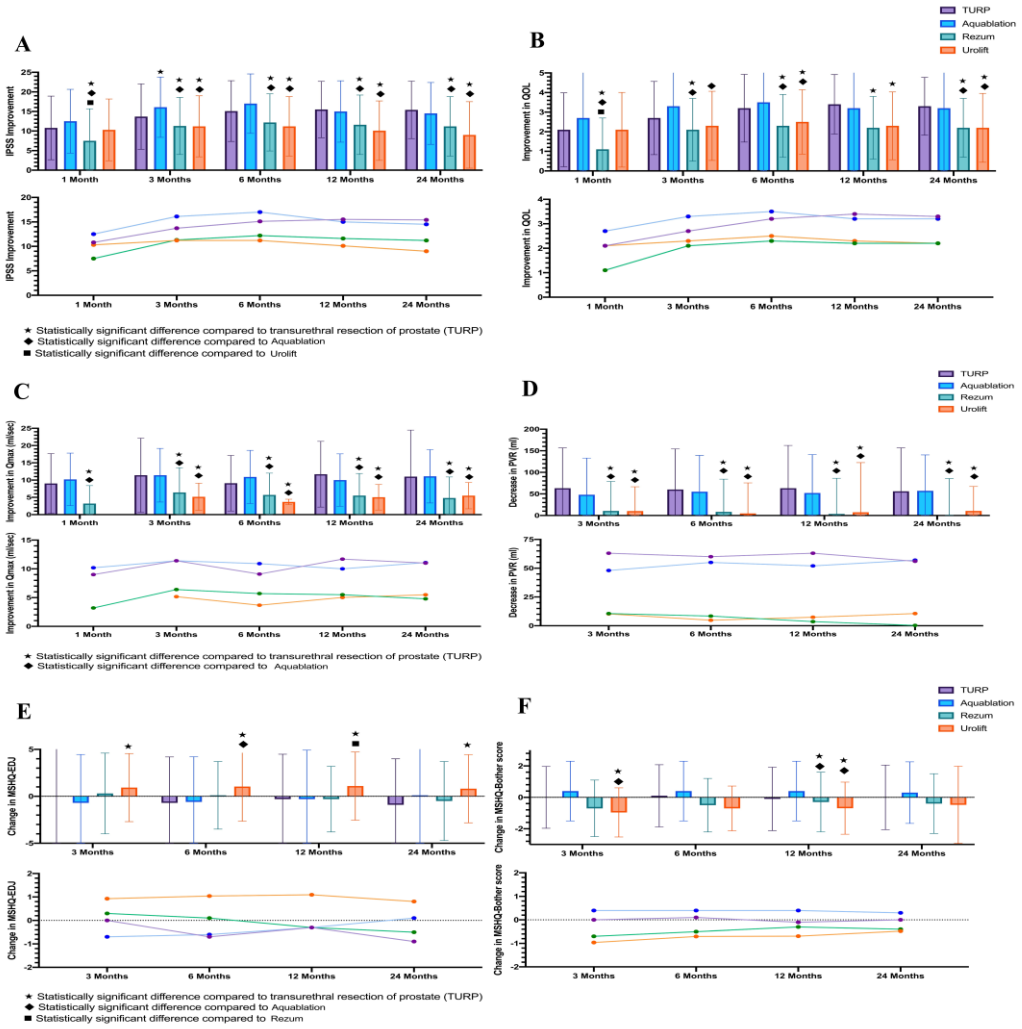

Figure 2 - Change from baseline at different follow-up intervals: (A) IPSS; (B) QoL; (C) Qmax; (D) PVR; (E) MSHQ-Ejd (function); (F) MSHQ-Ejd (Bother)

Table 1 Summary of base line characteristics

	UroLift (Roehrborn *et al*,2013) (n=181)	UroLift (Sonksen *et al*, 2015) (n=116)	Rezum (Mc Vary *et al*, 2015) (n=134)	Aquablation (Gilling *et al*, 2018) (n=116)
Age Mean ± SD	67 ± 8.6	63 ± 6.8	63 ± 7.1	66 ± 7.3
Prostate volume (ml)	44.5 ± 12.4	38 ± 12	54.8 ± 13	54.1 ± 16.2
IPSS (base line)	21.8 ± 5.6	21.4 ± 5.5	21.4 ± 4.5	22.9 ± 6
QoL (base line)	4.5 ± 1.0	4.6 ± 1.1	4.3 ± 1.0	4.8 ± 1.1
Q max (base line)	8.3 ± 2.4	9.3 ± 3.4	9.8 ± 2.3	9.4 ± 3
PVR (base line)	NA	80.5 ± 61.0	84.9 ± 54.0	97 ± 79
MSHQ-EjD Function (base line)	8.7 ± 3.3	11 ± 2.7	9.6 ± 3.0	8.1 ± 3.7
MSHQ-EjD Bother (base line)	2.2 ± 1.7	1.7 ± 1.8	2.2 ± 1.7	2 ± 1.6

SD- standard deviation, IPSS- International Prostate Symptoms Score, QOL- quality of life, Qmax- peak flow rate, PVR- post voiding residual,

TURP- Transurethral resection of prostate, MSHQ-EjD- Male Sexual Health Questionnaire for ejaculatory dysfunction

Table 2 Summary of early post-operative complications (0-3 months)

	UroLift (n=181)	Rezum (n=134)	Aquablation (n=116)	TURP (n=100)
Dysuria	48 (34%)	23(17%)	12(11%)	6 (6%)
Hematuria	54 (29%)	16(12%)	18 (15%)	33 (33%)
Urgency	10 (7%)	8 (5.9%)	5 (4%)	10 (10%)
Urge incontinence	6 (3%)	NR		
Erectile Dysfunction	0	0	NR	19 (19%)
Retrograde Ejaculation	0	4 (2.9 %)	7 (6%)	22 (22%)
Urinary retention	5 (3%)	5(4%)	10 (9%)	4 (4%)
UTI	7 (4%)	4 (2.9%)	11(10%)	6 (6%)
Pelvic pain	25 (18%)	4 (2.9%)	9 (8%)	5 (5%)

NR- Not Reported, UTI- Urinary tract infection, TURP- Transurethral resection of prostate

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