Surgical treatment for BPH refractory to medication: robotic water jet ablation vs. TURP functional outcomes from two FDA clinical trials

Alexis E.Te, MD,[1] Christina Sze, MD,[1] Steven A. Kaplan, MD,[2]
Bilal Chughtai, MD[1]

[1]Department of Urology, Weill Medical College of Cornell University/New York Presbyterian , New York, New York, USA
[2]Department of Urology, Mount Sinai School of Medicine, New York, New York, USA

TE AE, SZE C, KAPLAN SA, CHUGHTAI B. Surgical treatment for BPH refractory to medication: robotic water jet ablation vs. TURP functional outcomes from two FDA clinical trials. *Can J Urol* 2023;30(1): 11408-11413.

Introduction: *A common indication for benign prostate hyperplasia (BPH) therapies is failure to improve with medical therapy. However, pivotal Federal Drug Administration (FDA) registered randomized clinical trials (RCTs) for minimally invasive surgical therapies (MISTs) are designed to be compared to either sham or placebo while off medical therapy at baseline, and as an alternative to medical therapy. There are few if any RCTs reporting the MISTS efficacy in patients with true medical therapy failure. We report on the efficacy of robotic water jet ablation therapy (RWT) and TURP in patients who have failed to improve with medical therapy.*

Materials and methods: *Data was obtained from the WATER and WATER II clinical trials. Both clinical trials did not implement a drug washout period. Only patients with reported BPH medical therapy such as alpha-blockers (AB) and 5-alpha-reductase inhibitors (5-ARIs) usage were included. Functional outcomes as post-void residual volume (PVR), peak urinary flow rate (Qmax), internal prostate symptom score (IPSS), and quality of life score (QoL) were analyzed.*

Results: *AB and/or 5-ARIs usage at baseline were reported in 146 and 39 patients who underwent RWT (prostate sizes up to 150 cc) and transurethral resection of the prostate (TURP, prostate sizes up to 80 cc) respectively. Baseline median (IQR) IPSS, QoL, Qmax and PVR were 24 (18,28), 5 (4,5), 8.9 (6.4,11.5), and 95 (36,172), respectively. Functional outcomes did not statistically differ between Aquablation and TURP at baseline and at 36-month. In cohort of true medical failure, both RWT and TURP demonstrated group statistical improvements in PVR, Qmax, IPSS, and QoL at 36-month compared to baseline.*

Conclusions: *RWT and TURP are effective BPH therapy in patients who truly failed medical therapy, and RWT demonstrated this in a much broader prostate size range.*

Key Words: aquablation, BPH, washout period, drug failure

Accepted for publication January 2023

Disclosure of Funding
WATER and WATER II were funded by Procept. No funding provided for manuscript development.

Address correspondence to Dr. Alexis E. Te, Department of Urology, Weill Cornell Medicine, 425 East 61st Street, 12th Floor, New York, NY 10065 USA

Introduction

Lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) is a chronic condition that can have negative impact on the quality of life (QoL) in older men. Treatment therapies range from noninvasive options such as watchful waiting, lifestyle modifications, and pharmacotherapy to surgical interventions. One of

the relative indications for any surgical therapy is failure of pharmacotherapy and exhausting other noninvasive options.[1] Minimally invasive surgical therapies (MISTs) have emerged as intermediary options between conservative management including pharmaceutical therapy and the gold standard transurethral resection of the prostate (TURP).

Approval of novel MISTs rely on prospective randomized controlled trials (RCTs). Currently, washout periods are prevalent and the standard in pharmaceutical-based clinical trial protocols to reduce user bias and achieve greater internal validity of the research drug. Implementation of the washout period exclusion criteria has been broadened to surgery-based studies.[2] However, these cohorts do not reflect a population that truly failed medical therapy. In fact, most of the Federal Drug Administration (FDA) registered clinical trials on MISTs reflect therapies that are alternative to medical therapy and not truly for medical therapy failure. These trials are typically compared to sham or placebo while off medical therapy at baseline. This can potentially inflate symptoms score improvements with surgical therapy and do not accurately reflect improvement in those who failed medical therapy. In fact, these MIST have not been compared to medical therapy nor been proven superior to medical therapy in randomized clincal trials.

There is minimal evidence to explicitly substantiate the use of a washout periods for surgical therapy for BPH since most surgical therapies are utilized in patients with poor symptoms improvement from medical therapy and not as an alternative to surgical therapy. To accurately reflect this practical indication to selecting surgical therapy in a population that truly is medication refractory, we report the efficacy of robotic water jet ablation therapy (RWT) and TURP in this cohort.

Materials and methods

This is a post hoc analysis of subjects from WATER (Waterjet Ablation Therapy for Endoscopic Resection of Prostate Tissue) and WATER II trials. WATER is a prospective, double-blind, multicenter, international clinical trial comparing the safety and efficacy of RWT and TURP in the treatment of LUTS/BPH in men aged 45-80 yr with a prostate of 30-80 cm^3.[3,3] WATER II is a prospective, multicenter, single-arm international clinical trial of Aquablation in men with a prostate of 80-150 cm^3.[4]

Baseline characteristics for each trial were compared using a student's t test and Wilcoxon signed-rank test for normally and non-normally distributed continuous variables, respectively. Fisher's test was used for categorical variables. Repeated-measures analysis of variance was used to compare longitudinal responses at different time points, adjusting for patient clustering.

All statistical tests were 2-sided with a p value < 0.05 indicating statistical significance. All statistics were performed using the statistical package JMP (JMP Pro, Version 16 Software, Microsoft Windows for x 64; SAS Institute Inc., Cary, NC, USA, 1989-2019).

Results

A total of 185 men had AB or 5-ARI prior to undergoing RWT or TURP, Table 1, with the majority (79%) undergoing RWT. Median prostate volume was 75 (IQR 52-102). There was significant trend improvement of parameters such as IPSS, QoL, Qmax and PVR from baseline to follow up at 36-month, Figure 1A-D. When compared to the men who were not on any AB or 5-ARI prior to surgery (n = 97) in WATER, there was no significant difference in any of the urinary parameters at baseline and at 36-month follow up.

In patients who underwent RWT, erectile (ED) and

TABLE 1. **Baseline characteristics**

Characteristics	**Aquablation n = 146**	**TURP n = 39**	**p value**
IPSS	24.0 (18.2, 28.0)	21.0 (15.0, 27.5)	0.2
QoL	5.00 (4.00, 5.00)	5.00 (4.00, 5.00)	0.9
Qmax	8.9 (6.4, 11.5)	8.9 (7.2, 11.4)	0.5
PVR	95 (36, 172)	124 (73, 213)	0.2
Prostate volume (cc)	67.4 (46.03, 93.3)	53.1 (40, 66.2)	0.001
Median (IQR)			

IPSS = internal prostate symptom score; QoL = quality of life; Qmax = peak urinary flow rate; PVR = post-void residual volume; IQR = interquartile range

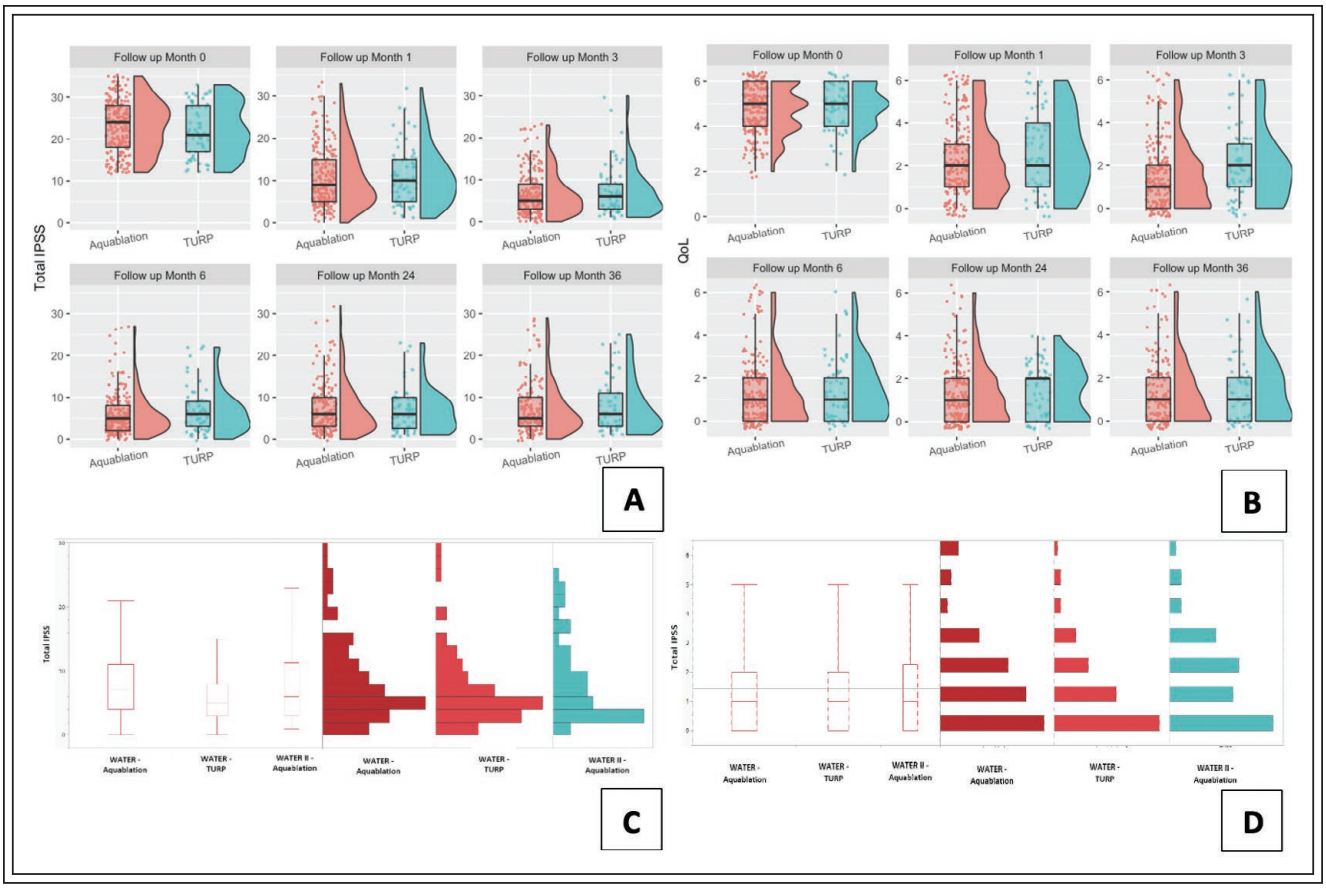

Figure 1. A) Friedman test demonstrating trend in IPSS with follow up (up to 36 months) comparing Aquablation and TURP. **B)** Friedman test demonstrating trend in QoL with follow up (up to 36 months) comparing Aquablation and TURP. **C)** Total IPSS at 36 months of follow up comparing Aquablation and TURP. Krushkal-Wallis tests p = 0.25. **D)** Total QoL at 36 months of follow up comparing Aquablation and TURP. Krushkal-Wallis tests p = 0.10.

ejaculation (EjD) dysfunction rate were higher in the patients who were not on BPH medications at baseline however this was not significantly different in both WATER and WATER II trials (p = 0.14 and p = 0.21, respectively), Figure 2A-C. Comparing subgroups (medical refractory patients versus patients not on BPH medical therapy) showed no differences. However, the TURP groups, regardless of baseline status of medical therapy, had a statistically significant worse EjD rate (p < .05).

Patients who were on BPH medication at baseline were more likely to return to medication or undergo another BPH intervention at 3 years of follow up in both aquablation and TURP cohorts however this difference was not significant in both RWT and TURP cohorts (p = 0.81 (WATER) and p = 0.22, respectively). In men with larger prostates (> 80 g) who were medication naïve were more likely to be on BPH medications at 3 years however this did not reach significance (p = 0.22).

TURP retreatment rate from the WATER was 1.5%. The patient underwent another TURP. Retreatment rates for aquablation from WATER and WATER II were 4.3% and 3%, respectively. The majority of retreatment procedures was TURP.

In the aquablation group, Calvien-Dindo (CD) grade 2 or greater complications were higher in men on BPH medications at baseline compared to men who were not on any BPH medications at 6 months follow up however this did not reach significance in both WATER and WATER II trials (p = 0.14, p = 0.52, respectively). Conversely, men on BPH medication at baseline in the TURP arm had lower rates of ≥ CD grade 2 complications compared to those not on BPH medications at baseline however this did not reach significance (p = 0.2). Additionally, all the Clavien-Dindo adjudicated bleeding events did not differ between subgroups.

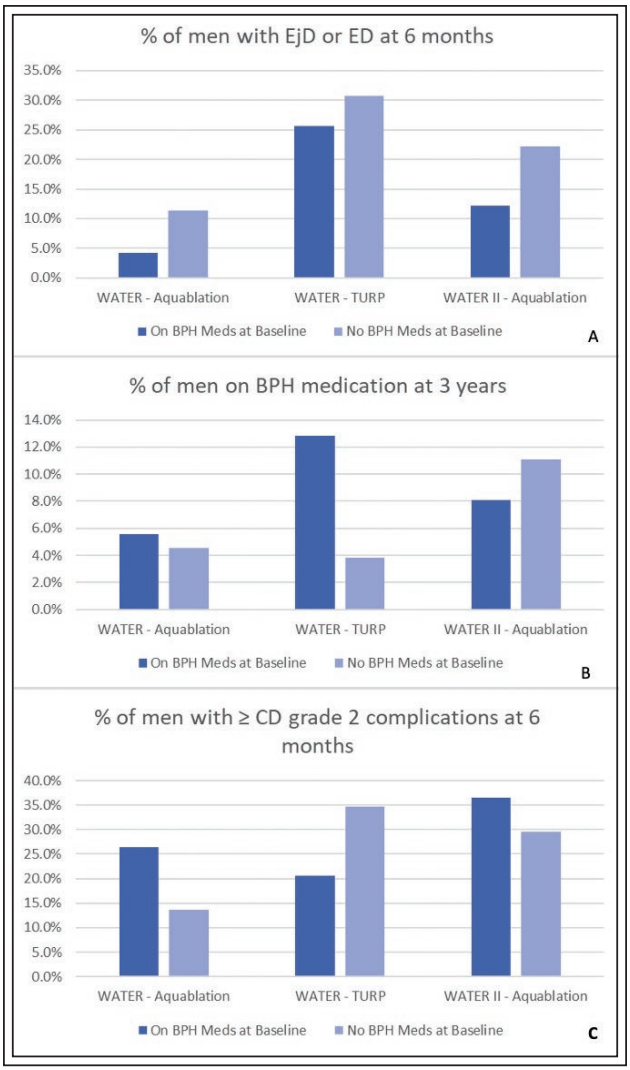

Figure 2. A) Percentage of men who experienced erectile dysfunction (ED) or ejaculation dysfunction (EjD) at 6 months of follow up; **B)** Percentage of men who are on BPH medications or underwent a BPH intervention after TURP/Aquablation at 3 years of follow up; **C)** Percentage of men with Calvien-Dindo (CD) grade 2 or greater complications at 6 months of follow up.

Discussion

TURP continues to be the gold standard for the treatment of LUTs due to BPH with a prostate volume limit of 80 cc especially for medical therapy failure since the 1930s.[5] Because of the advent of meds and MISTs, prostate sizes are becoming larger and larger by the time they treated with surgical therapy. With the advent of pharmacotherapy, the landscape of BPH therapy changed from a tradition where surgical prostatectomy was the preferred treatment choice of debulking obstructive tissue. The advent of medical therapy altered the perception for the need for invasive surgical therapy, and eventually the era of MISTs evolved as an alternative option to medical therapy. To emulate it as an alternative option, MISTs in prospective randomized clinical trials were designed to mimic pharmacologic trials with a comparison to sham and included a washout period to report medication free baseline for outcome parameters. The balloon prostatoplasty was the first trial to utilize this design, and it has remained the standard by which clinical trials for minimally invasive therapies are designed as an alternative to medical therapies.[6] Although this study was not designed as a treatment for failed medical therapy, the concept of minimally invasive therapy as a treatment for failed medical therapy was assumed once it was approved for use, and is applied extensively in current clinical practice.

Given this need for better information, we present a cohort of patients who truly failed medical therapy and underwent surgical management as a result. WATER and WATER II trials did not have a washout phase prior to enrollment therefore clearly representing a cohort that were symptomatic failure to medical therapy at baseline. As such, indications and inclusion situate these surgical therapies as the clear next step after failure to medical therapy. Both RWT and TURP demonstrated group statistical improvements in IPSS, QoL, Qmax, and PVR at 36-month compared to baseline. Functional outcomes did not statistically differ between RWT and TURP at baseline and at 36-month. TURP has classically been that option and in the WATER studies, RWT has demonstrated non inferiority. In a pre-specified analysis, RWT showed superior results in symptom reduction compared to TURP in prostate sizes 50-80 cc. This sub-analysis of medical therapy failure cohort further reinforces the role of these therapies as treatment of choice for medical therapy failures including men who desire to limit their sexual adverse events from surgical therapies.

Of note, as an alternative to medical therapy, MISTs do not seem as favorable to medical therapy. When compared to medical therapy, MISTs complications include dysuria, gross hematuria, and urinary frequency. More serious complication though rare include bladder neck contracture and urosepsis were reported in pivotal trials.[3] Additionally, retreatment rate as high as 15.5% for water vapor thermotherapy treatment (WVTT) (4.4% for surgical reintervention; 11.1% restarting medication) and 33.6% (13.6% for surgical reintervention;[7] 10.7% restarting medication;

9.3% clip removal) for prostatic urethral lift (PUL).[3] In a recent meta-analysis looking at surgical reintervention rate after PUL in 2000 patients, reintervention rates were 4.3% per year in studies with < 1 year follow up and can be as high as 10.7% in studies with longer follow up up to 3 years.[8] Using a novel composite, symptom-centric metric to measure durability, the rate of medical or surgical retreatment was 10.6% and 31.8% in WVTT and PUL, respectively.[9] In comparisons, the progression to surgical treatment in the Medical Therapy of Prostatic Symptoms (MTOPS) study was only 4% vs. placebo and from the Alfuzosin Long-Term Efficacy and Safety Study (ALTESS) study progression to BPH-related surgery was only 2.2%.[10,11] When placed in this context, medical therapy still seems superior to PUL and WVTT. In theory, these randomized prospective MIST RCTs compared to sham are designed to be an alternative to medical therapy.

Contrary, in the 3-year trial comparing WVTT to pharmacotherapy show that clinical progression was five times more likely in the pharmacotherapy vs. a single WVTT therapy suggesting that WVTT may be a reasonable alternative to pharmacotherapy.[12] It should be noted, however, that symptomatic progression on phamacotherapy therapy to surgical therapy was very low, and that progression on MTOPs did not define failure of therapy as a historial comparison. Of note, a combination of pharmacotherapy (AB and 5-ARI) in both the MTOPs trial and Combination of Avodart and Tamsulosin (CombAT) trial has been demonstrated to be superior to monotherapy in controlling of both storage and voiding LUTS.[13-15] It maybe that WVTT would benefit with having a 5ARI added to their postop regimen due to their high retreatment rate. There is currently a need for prospective studies directly comparing MISTs to pharmacotherapy to provide clarity for better identification and management of patients at risk of BPH progression.[16] Finally, the 5-year retreatment rates for surgery as well as back on meds from the WATER study (6% for RWT, 12.3% for TURP) should be noted as well.[17]

Since the current clinical practice is to offer MIST to those who fail pharmacotherapy or need surgical intervention who desire a minimally invasive approach, future MIST trials should not have a washout period to demonstrated their role as a alternative to invasive surgical therapy and not pharmacotherapy as represented in current trials against sham.

Conclusion

We present functional outcomes on patients who truly failed medical therapy and underwent surgical prostatectomy therapies. Washout periods are not necessary in these studies that evaluate efficacy of a BPH surgery therapy. RWT and TURP are effective BPH therapy in patients who truly failed medical therapy, and RWT demonstrated effectiveness in a larger prostate size range. We also suggest that future clinical trials of surgical options including minimally invasive therapy sham should not have a washout period to demonstrate their role as an option to medical therapy failure.

Disclosures

Dr. Alexis E. Te – Procept - PI and Consultant; Dr. Steven A. Kaplan – Procept – PI; Dr. Bilal Chughtai –Procept – PI; Dr. Christina Sze - no disclosure. □

References

1. Lerner LB, McVary KT, Barry MJ et al. Management of lower urinary tract symptoms attributed to benign prostatic hyperplasia: AUA GUIDELINE PART II-Surgical Evaluation and Treatment. *J Urol* 2021;206(4):818-826.
2. Campbell J, Reid J, Ordon M et al. The utilization of benign prostatic hyperplasia and bladder-related medications after a transurethral prostatectomy. *Urology* 2019;130:126-131.
3. McVary KT, Gittelman MC, Goldberg KA et al. Final 5-year outcomes of the multicenter randomized sham-controlled trial of a water vapor thermal therapy for treatment of moderate to severe lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Urol* 2021;206(3):715-724.
4. Nguyen DD, Barber N, Bidair M et al. WATER versus WATER II 2-year update: comparing Aquablation therapy for benign prostatic hyperplasia in 30-80-cm^3 and 80-150-cm^3 prostates. *Eur Urol Open Sci* 2021;25:21-28.
5. Mayer EK, Kroeze SG, Chopra S et al. Examining the 'gold standard': a comparative critical analysis of three consecutive decades of monopolar transurethral resection of the prostate (TURP) outcomes. *BJU Int* 2012;110(11):1595-1601.
6. Lepor H, Sypherd D, Machi G et al. Randomized double-blind study comparing the effectiveness of balloon dilation of the prostate and cystoscopy for the treatment of symptomatic benign prostatic hyperplasia. *J Urol* 1992;147(3):639-642.
7. Roehrborn CG, Barkin J, Gange SN et al. Five year results of the prospective randomized controlled prostatic urethral L.I.F.T. study. *Can J Urol* 2017;24(3):8802-8813.
8. Miller LE, Chughtai B, Dornbier RA et al. Surgical reintervention rate after prostatic urethral lift: systematic review and meta-analysis involving over 2,000 patients. *J Urol* 2020;204(5):1019-1026.

9. Miller LE, Te AE, Bhattacharyya SK et al. A novel metric for treatment durability in clinical trials of minimally invasive treatments for benign prostatic hyperplasia. *Expert Rev Med Devices* 2020;17(4):365-369.
10. McConnell JD, Roehrborn CG, Bautista OM. et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003;349(25):2387-2398
11. Roehrborn CG. Alfuzosin 10 mg once daily prevents overall clinical progression of benign prostatic hyperplasia but not acute urinary retention: results of a 2-year placebo-controlled study. *BJU Int* 2006;97(4):734-741.
12. Gupta N, Rogers T, Holland B et al. Three-year treatment outcomes of water vapor thermal therapy compared to doxazosin, finasteride and combination drug therapy in men with benign prostatic hyperplasia: cohort data from the MTOPS trial. *J Urol* 2018;200(2):405-413.
13. Kaplan SA, Lee JY, Meehan AG et al. Time course of incident adverse experiences associated with doxazosin, finasteride and combination therapy in men with benign prostatic hyperplasia: the MTOPS trial. *J Urol* 2016;195(6):1825-1829.
14. Kaplan SA, McConnell JD, Roehrborn CG et al. Combination therapy with doxazosin and finasteride for benign prostatic hyperplasia in patients with lower urinary tract symptoms and a baseline total prostate volume of 25 ml or greater. *J Urol* 2006; 175(1):217-220.
15. Montorsi F, Roehrborn C, Garcia-Penit J et al. The effects of dutasteride or tamsulosin alone and in combination on storage and voiding symptoms in men with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH): 4-year data from the combination of avodart and tamsulosin (CombAT) study. *BJU Int* 2011;107(9):1426-1431.
16. Roehrborn CG. BPH progression: concept and key learning from MTOPS, ALTESS, COMBAT, and ALF-ONE. *BJU Int* 2008;101(Suppl 3):17-21.
17. Gilling PJ, Barber N, Bidair M et al. Five-year outcomes for Aquablation therapy compared to TURP: results from a double-blind, randomized trial in men with LUTS due to BPH. *Can J Urol* 2022;29(1):10960-10968.