Randomized Controlled Trial of Aquablation versus Transurethral Resection of the Prostate in Benign Prostatic Hyperplasia: One-year Outcomes

Peter J. Gilling, Neil Barber, Mohamed Bidair, Paul Anderson, Mark Sutton, Tev Aho, Eugene Kramolowsky, Andrew Thomas, Barrett Cowan, and Claus Roehrborn

OBJECTIVE To report 1-year safety and efficacy outcomes after either Aquablation or transurethral resection of the prostate (TURP) for the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia (BPH)

METHODS This double-blinded, multicenter prospective randomized controlled trial assigned 181 patients with BPH-related moderate-to-severe lower urinary tract symptoms to either electrocautery-based prostate resection (TURP) or Aquablation. Efficacy endpoints included reduction in International Prostate Symptom Score and improvement in uroflow parameters. The primary safety endpoint was the occurrence of Clavien-Dindo persistent grade 1 or grade 2 or higher complications.

RESULTS BPH symptom score improvements were similar across groups with 12-month reduction of 15.1 points after TURP or Aquablation. In both groups, mean maximum urinary flow rates increased markedly postoperatively, with mean improvements of 10.3 cc/s for Aquablation versus 10.6 cc/s for TURP (P = .8632). At 1 year, Prostate-specific antigen (PSA) was reduced significantly ($P < .01$) in both groups by 1 point; the reduction was similar across groups (P = .9125). Surgical retreatment for BPH rates for TURP were 1.5% and Aquablation 2.6% within 1 year from the study procedure (P = not significant (NS)). The rate of late complications was low, with no procedure-related adverse events after month 6.

CONCLUSION The 1-year outcomes after TURP and Aquablation were similar and the rate of late procedure-related complications was low. (ClinicalTrials.gov number, NCT02505919). UROLOGY 125: 169–173, 2019. © 2018 Elsevier Inc.

INTRODUCTION

Benign prostatic hyperplasia (BPH) commonly results in lower urinary tract symptoms (LUTS) related to bladder outlet obstruction. The prevalence of symptoms is high (42% of men over age 50) and increases with age.[1,2] If medical treatment fails to provide sufficient relief, many men seek surgical treatments.

Several options are available for the surgical treatment of BPH, ranging from nonablative techniques to ablative (resective) techniques such as laser enucleation, photovaporization, and standard electrocautery (TURP). Although resective procedures have high rates of symptom relief, they commonly cause sexual dysfunction.[3-7] Retrograde ejaculation after TURP may occur in over two-third of men.[8]

Aquablation is a surgeon-planned, image-guided, and robotically executed technique to resect prostate tissue using a high-velocity waterjet. Previously, we reported 6-month results of a double-blinded prospective randomized controlled trial comparing outcomes after either Aquablation or TURP.[9] Herein, we report safety and efficacy at 12 months.

Conflict of Interest: Mohamed Bidair and Eugene Kramolowsky are consultants for PROCEPT BioRobotics. No other author has a conflict of interest with PROCEPT BioRobotics.

Financial Disclosure: *The study was funded by PROCEPT BioRobotics.*

From the Tauranga Urology Research, Tauranga, New Zealand; the Frimley Park Hospital, Frimley Health Foundation Trust, Surrey, UK; the San Diego Clinical Trials, San Diego, CA; the Royal Melbourne Hospital, Melbourne, Australia; the Houston Metro Urology, Houston, TX; the Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, UK; the Virginia Urology, Richmond, VA; the Princess of Wales Hospital, Bridgend, Wales, UK; the Urology Associates, P.C., Englewood, CO; and the UT Southwestern Medical Center, Department of Urology, University of Texas Southwestern, Dallas, TX

Address correspondence to: Peter J. Gilling, M.D., F.R.A.C.S., Urology, Urology Bay of Plenty, 850 Cameron Road, PO Box 56, Tauranga 3110, New Zealand. E-mails: peter@urobop.co.nz, peter.gilling@bopdhb.govt.nz

Submitted: August 31, 2018, accepted (with revisions): December 3, 2018

METHODS

WATER (NCT02505919) is a prospective double-blinded multicenter international randomized trial, as previously described.[9] Seventeen sites participated, 12 in the US, 3 in the UK, and 2 in Australia/New Zealand. The study, which enrolled subjects between October 2015 and December 2016, included men age 45-80 years with a prostate size between 30-80 cc (measured with transrectal ultrasound), moderate-to severe LUTS as indicated by an International Prostate Symptom Score (IPSS[10]) ≥ 12, and a maximum urinary flow rate (Qmax) < 15 mL/s. Men were excluded if they had a history of prostate or bladder cancer, neurogenic bladder, bladder calculus or clinically significant bladder diverticulum, active infection, treatment for chronic prostatitis, diagnosis of urethral stricture, meatal stenosis or bladder neck contracture, damaged external urinary sphincter, stress urinary incontinence, post void residual >300 mL or urinary retention, use of self-catheterization, or prior prostate surgery. Men taking anticoagulants or on bladder anticholinergics or with severe cardiovascular disease were also excluded. The control group, TURP using electrocautery, represents the gold standard for the surgical treatment of moderate-to-severe BPH. All participants provided informed consent prior to participating.

Subjects were assigned at random (2:1 ratio) to Aquablation or TURP. Assignments, stratified by study site and baseline IPSS score category with random block sizes, were obtained prior to treatment using a web-based system.

Aquablation was performed using the AquaBeam System (PROCEPT BioRobotics, Redwood Shores, CA).[11] Post-Aquablation hemostasis was achieved using either low-pressure inflation of a Foley balloon catheter in the prostatic fossa or focal, nonresective, and electrocautery.[12] All subjects received postprocedure bladder irrigation per standard practices. TURP was performed according to standard practice.

All follow-up assessments were administered by a blinded research team (physician and coordinator). Visits included IPSS, uroflow measurements, quality of life, adverse events, and blinding assessment.

The study's primary efficacy endpoint, noninferiority for the 6-month change in IPSS, was considered a success, as previously reported.[9] The focus herein is 1-year efficacy outcomes, which were compared using *t* tests or Fisher's test, as appropriate. For continuous outcomes, changes at postoperative time points were compared together using repeated measures analysis of variance. The primary safety endpoint, the occurrence of procedure-related complications rated as Clavien-Dindo[13] grade 1 persistent or higher, showed superiority. All safety events were adjudicated by a blinded clinical events committee. Herein we focus on late adverse events, which were compared using Fisher's test.

Study data were 100% verified by independent study monitors.

RESULTS

Baseline characteristics of the 184 randomized subjects were balanced across treatment assignment (Table 1). Three subjects (2 TURP, 1 Aquablation) voluntarily withdrew prior to treatment, leaving a safety and efficacy cohort of 181. Mean prostate size was 53 cc and 91% were sexually active. The 12-month follow-up was obtained in 177 subjects (98%, Fig. 1).

Mean standard deviation (SD) IPSS reduction at 12 months was 15.1 (7.0) in the Aquablation group and 15.1 (8.3) in the TURP group (P = .9898 for difference). The mean percent reduction in IPSS score was 67% in both groups at 93% and 86.7%, respectively, had improvements of at least 5 points from baseline. Repeated measures analysis showed no statistically significant difference in postoperative change scores across groups, nor any statistical interaction between time and treatment. Mean IPSS quality of life score improvement was also similar in both groups (3.2 (1.7) vs 3.5 (1.6), P = .3179).

Table 1. Baseline characteristics

Characteristic	Aquablation N = 117	TURP N = 67
Age, years, mean (SD)	66.0 (7.3)	65.8 (7.2)
Body mass index, mean (SD)	28.4 (4.1)	28.2 (4.5)
Prostate size (TRUS)*, gm; mean (SD)	54.1 (16.2)	51.8 (13.8)
Prostate specific antigen, g/dL; mean (SD)	3.7 (3.0)	3.3 (2.3)
Cystoscopy findings		
Lobes present		
Lateral lobe only	50 (42.7%)	31 (46.3%)
Median lobe only	9 (7.7%)	3 (4.5%)
Both lateral and median lobe	55 (47.0%)	88 (47.8%)
Degree of median lobe obstruction		
None	23 (19.7%)	15 922.4%)
Mild	25 (21.4%)	15 (22.4%)
Moderate	35 (29.9%)	22 (32.8%)
Severe	14 (12.0%)	7 (10.4%)
Bladder neck obstruction	30 (25.6%)	24 (35.8%)
Baseline questionnaires		
IPSS score, mean (SD)	22.9 (6.0)	22.2 (6.1)
IPSS QOL, mean (SD)	4.8 (1.1)	4.8 (1.0)
Sexually active, N (%) [MSHQ-EjD]	93 (80.2%)	54 (83.1%)
MSHQ-EjD mean (SD)†	8.1 (3.7)	8.8 (3.6)
IIEF-5, mean (SD)†	17.2 (6.5)	18.2 (7.0)

Abbreviations: IIEF = international index of erectile function; IPSS = international prostate symptom score; MSHQ-EjD = male sexual health questionnaire for ejaculatory dysfunction; QOL = quality of life; TRUS = transrectal ultrasound

* Volume = prostate length × width × height × $\pi/6$.

† Sexually active men only.

In both groups, mean maximum urinary flow rates increased markedly postoperatively, with mean improvements of 10.3 (11) cc/s for Aquablation versus 10.6 (11) cc/s for TURP (Fig. 2, P = .8632). The mean 12-month reduction in postvoid residual was 52 (79) and 63 (97) cc (P = .4625). In patients with an elevated (>100 cc) postvoid residual, mean reductions in postvoid residual were 107 and 114 cc, respectively. At 1 year, PSA was reduced significantly (P < .01) in both groups by 1 point; the reduction was similar across groups, Aquablation 27% and TURP 30% (P = .9125). The proportion of subjects using alpha blockers (5%) and 5-α reductase inhibitors (2%) at the 12-month follow-up was significantly lower than baseline and the same proportion in both groups.

By month 3, fewer men in the Aquablation group had a persistent Clavien-Dindo grade 1 or grade 2 or higher adverse event compared to TURP (primary safety endpoint, 26% vs 42%, P = .0149). Between month 3 and month 12, 40 additional urologic adverse events occurred. Of these, 8 and 12 were deemed probably or definitely related to the index procedure, but the

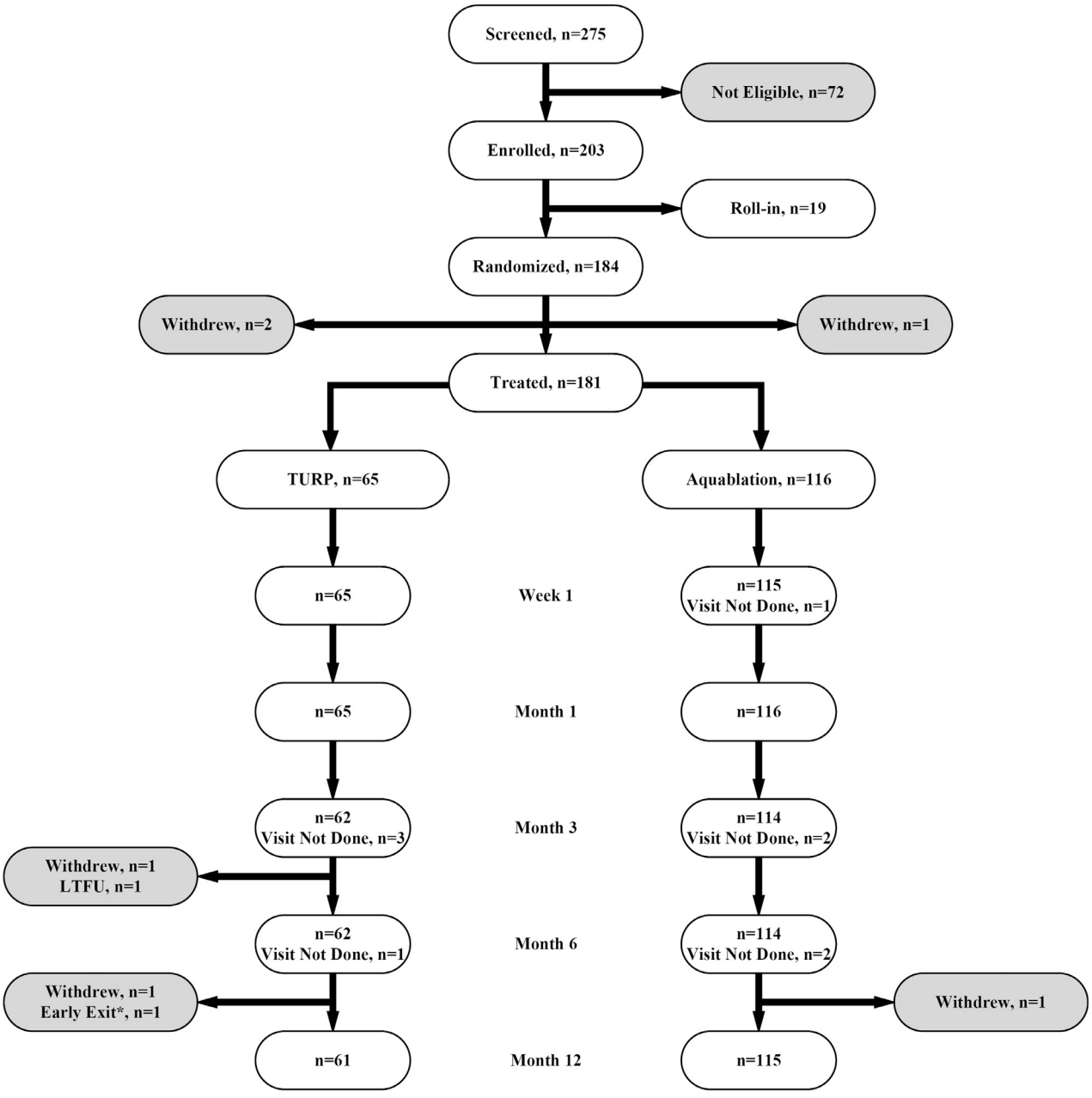

Figure 1. CONSORT diagram.

proportion of subjects with these events was similar across treatment groups (Table 2). One TURP subject (1.5%) and 3 Aquablation subjects (2.6%) underwent surgical retreatment for BPH within 1 year from the study procedure ($P = 1$). In all cases, additional surgery consisted of TURP.

DISCUSSION

Previously, we reported noninferior efficacy and superior safety of Aquablation compared to TURP for the treatment of men with LUTS due to BPH.[9] Herein we report that similar BPH symptom-related efficacy is maintained at 12 months with a low rate of late procedure-related adverse events. Importantly, the lower rate of sexual side effects prior to month 3 in the Aquablation group was not offset by late adverse events.

Improvements in urinary flow rate and postvoid residual seen in our study are similar to those observed for other resective-type surgeries, including laser enucleation[14] and laser photovaporisation.[15] Aquablation appeared to have larger improvements than nonresective techniques. For example, convective water vapor energy (rezum) showed an 11.6-point improvement in IPSS score[16] and UroLift showed an

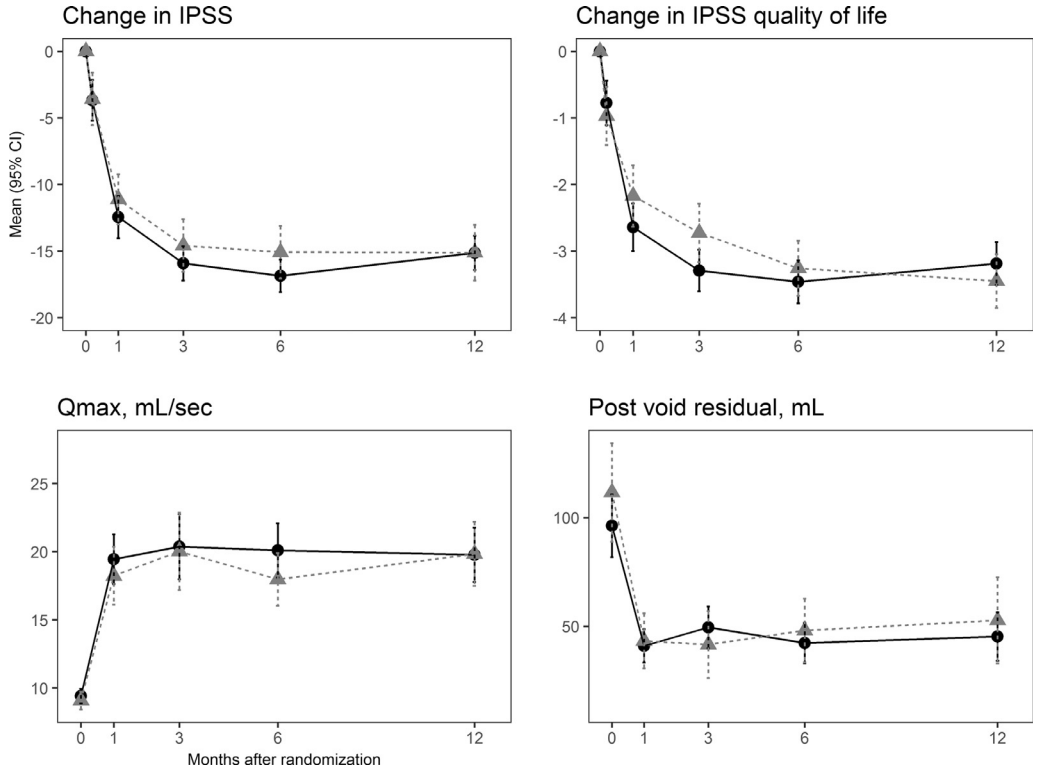

Figure 2. Change in International Prostate Symptom Score (IPSS, top left), IPSS quality of life (top right), maximum urinary flow (bottom left), and post void residual (bottom right) by treatment and time. Solid = Aquablation; dotted = TURP.

Table 2. Number of subjects and rate with urologic adverse events judged by the clinical events committee as possibly, probably, or definitely related to the index procedure between months 0 and 3 and between months 3 and 6. Events after month 6 were deemed unrelated to the study procedure

		Treatment				
		Aquablation		TURP		
Timing	Event Summary	N*	Rate	N	Rate	
<3 months	Arrhythmia	3	(2.6%)	-	-	0.5539
	Bladder pain/spasm	7	(6.0%)	3	(4.6%)	1.0000
	Bleeding	18	(15.5%)	10	(15.4%)	1.0000
	Dysuria	12	(10.3%)	6	(9.2%)	1.0000
	Other	19	(16.4%)	8	(12.3%)	0.5205
	Pain	9	(7.8%)	5	(7.7%)	1.0000
	Penile edema	1	(0.9%)	-	-	1.0000
	Penile trauma	1	(0.9%)	-	-	1.0000
	Retrograde ejaculation	7	(6.0%)	15	(23.1%)	0.0015
	Stricture or adhesions	3	(2.6%)	2	(3.1%)	1.0000
	Swollen Testicles	-	-	1	(1.5%)	0.3591
	Urethral damage	1	(0.9%)	1	(1.5%)	1.0000
	Urinary retention	10	(8.6%)	4	(6.2%)	0.7730
	Urinary tract infection	11	(9.5%)	4	(6.2%)	0.5779
	Urinary urgency/frequency/difficulty/leakage	5	(4.3%)	4	(6.2%)	0.7239
3-6 months	Bladder neck contracture	-	-	1	(1.5%)	0.3591
	Dysuria	1	(0.9%)	-	-	1.0000
	Other	-	-	1	(1.5%)	0.3591
	Retrograde ejaculation	1	(0.9%)	2	(3.1%)	0.2932
	Sexual dysfunction	-	-	1	(1.5%)	0.3591
	Urinary tract infection	1	(0.9%)	-	-	1.0000
	Urinary urgency/frequency/difficulty/leakage	3	(2.6%)	2	(3.1%)	1.0000

* N = number of subjects with event.

11.1-point improvement[17] compared with 15.1 points for Aquablation. Although direct comparisons of our data with those from other trials may not be possible, our data, along with data from other techniques that remove prostate tissue as opposed to altering its structure, suggest that improvements with Aquablation may be larger than those of nonresecting approaches.

In TURP, ejaculatory dysfunction is very common and may be due to heat-induced damage to the ejaculatory duct.[15] In Aquablation the risk of ejaculatory function was lower, possibly because of intentional avoidance of tissue destruction at the verumontanum as well as use of a heat-free mechanism to remove tissue.

Our study was of high quality, being multicenter, international, blinded, and randomized, with expected symptom and uroflow efficacy levels observed for the control (TURP) group. Surgeon participants were highly experienced in TURP and had far less (and, in many cases, no) experience with Aquablation, suggesting that the learning curve for Aquablation may be brief. Direct evaluation of the Aquablation learning curve in this study is challenging as the number of Aquablation cases per investigator was, at most, 18. The 12-month efficacy results are encouraging but further follow-up of this cohort will shed more light on longer-term outcomes. Another potential limitation is that prostate size was capped at 80 cc. A recent publication of larger (60-150 cc) prostates demonstrated a reasonable safety profile, low hospital length of stay, and high levels of symptom reduction efficacy.[18] Aquablation's use in larger prostates is intriguing but remains to be fully demonstrated.

In summary, our study provides high-quality evidence demonstrating that Aquablation for LUTS due to BPH provides sustained (12-month) symptom-reduction efficacy with a low rate of late adverse events in men with prostates between 30 and 80 cc. Aquablation may be a good alternative for men who wish to maintain their ejaculatory function.

Acknowledgments. The authors would like to acknowledge Ronald P. Kaufman, Jr., Andrew Trainer, Andrew Arther, Gopal Badlani, Mark Plante, Mihir Desai, Leo Doumanian, Alexis E. Te, and Mark DeGuenther for enrollment and treatment of patients for the study.

References

1. Trueman P, Hood SC, Nayak US, et al. Prevalence of lower urinary tract symptoms and self-reported diagnosed "benign prostatic hyperplasia", and their effect on quality of life in a community-based survey of men in the UK. *BJU Int*. 1999;83:410–415.
2. Naslund MJ, Gilsenan AW, Midkiff KD, et al. Prevalence of lower urinary tract symptoms and prostate enlargement in the primary care setting. *Int J Clin Pract*. 2007;61:1437–1445.
3. Madersbacher S, Marberger M. Is transurethral resection of the prostate still justified? *BJU Int*. 1999;83:227–237.
4. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol*. 2011;185:1793–1803.
5. Miano R, De Nunzio C, Asimakopoulos AD, et al. Treatment options for benign prostatic hyperplasia in older men. *Med. Sci. Monit*. 2008;14:RA94–RA102.
6. Rassweiler J, Teber D, Kuntz R, et al. Complications of transurethral resection of the prostate (TURP)—incidence, management, and prevention. *Eur Urol*. 2006;50:969–979; discussion 980.
7. Montorsi F, Moncada I. Safety and tolerability of treatment for BPH. *Eur Urol Suppl*. 2006;5:1004–1012.
8. Emberton M, Neal DE, Black N, et al. The effect of prostatectomy on symptom severity and quality of life. *Br J Urol*. 1996;77:233–247.
9. Gilling P, Barber N, Bidair M, et al. WATER: a double-blind, randomized, controlled trial of Aquablation® vs transurethral resection of the prostate in benign prostatic hyperplasia. *J Urol*. 2018;199:1252–1261.
10. Barry MJ, Fowler FJ, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*. 1992;148:1549–1557; discussion 1564.
11. Gilling P, Reuther R, Kahokehr A, et al. Aquablation - image-guided robot-assisted waterjet ablation of the prostate: initial clinical experience. *BJU Int*. 2016;117:923–929.
12. Aljuri N, Gilling P, Roehrborn C. How I do it: balloon tamponade of prostatic fossa following Aquablation. *Can J Urol*. 2017;24:8937–8940.
13. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
14. Li S, Zeng X-T, Ruan X-L, et al. Holmium laser enucleation versus transurethral resection in patients with benign prostate hyperplasia: an updated systematic review with meta-analysis and trial sequential analysis. *PLoS One*. 2014;9 e101615.
15. Bachmann A, Tubaro A, Barber N, et al. 180-W XPS GreenLight laser vaporisation versus transurethral resection of the prostate for the treatment of benign prostatic obstruction: 6-month safety and efficacy results of a European Multicentre Randomised Trial—the GOLIATH study. *Eur Urol*. 2014;65:931–942.
16. McVary KT, Roehrborn CG. Three-year outcomes of the prospective, randomized controlled Rezūm system study: convective radiofrequency thermal therapy for treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. *Urology*. 2018;111:1–9.
17. Roehrborn CG, Gange SN, Shore ND, et al. The prostatic urethral lift for the treatment of lower urinary tract symptoms associated with prostate enlargement due to benign prostatic hyperplasia: the L.I.F.T. study. *J Urol*. 2013;190:2161–2167.
18. Chughtai B, Thomas D. Pooled Aquablation results for American men with lower urinary tract symptoms due to benign prostatic hyperplasia in large prostates (60—150 cc). *Adv Ther*. 2018;35:832–838.