Five year results of the prospective randomized controlled prostatic urethral L.I.F.T. study

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Introduction: *To report the five year results of a prospective, multi-center, randomized, blinded sham control trial of the Prostatic Urethral Lift (PUL) in men with bothersome lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH).*

Materials and methods: *At 19 centers in North America and Australia, 206 subjects ≥ 50 years old with International Prostate Symptom Score (IPSS) > 12, peak flow rate (Qmax) ≤ 12 mL/s, and prostate volume 30 cc-80 cc were randomized 2:1 to the PUL procedure or blinded sham control. In PUL permanent UroLift implants are placed to hold open the lateral lobes of the prostate to reduce urinary obstruction. After randomized comparison at 3 months and the only opportunity to add more PUL implants, PUL patients were followed to 5 years. LUTS severity (IPSS), quality of life (QOL), BPH Impact Index (BPHII), Qmax, sexual function, and adverse events were assessed throughout follow up.*

Results: *IPSS improvement after PUL was 88% greater than that of sham at 3 months. LUTS and QOL were significantly improved by 2 weeks with return to preoperative physical activity within 8.6 days. Improvement in IPSS, QOL, BPHII, and Qmax were durable through 5 years with improvements of 36%, 50%, 52%, and 44% respectively. No difference was seen between Intent to Treat and Per Protocol populations. Surgical retreatment was 13.6% over 5 years. Adverse events were mild to moderate and transient. Sexual function was stable over 5 years with no de novo, sustained erectile or ejaculatory dysfunction.*

Conclusions: *PUL offers rapid improvement in symptoms, QOL and flow rate that is durable to 5 years. These improvements were achieved with minimal use of a postoperative urinary catheter, rapid return to normal, and preservation of both erectile and ejaculatory function. Symptom improvement was commensurate with patient satisfaction. PUL offers a minimally invasive option in the treatment of LUTS due to BPH.*

Key Words: BPH, minimally invasive, surgery, surgical therapy, sexual function

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Introduction

Chronic lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) can significantly impact quality of life by causing loss of sleep, reduced productivity, impaired sex life, social isolation, and clinical depression.[1] The prevalence of histopathologic BPH increases from 40% among men in their 50s to over 80% among men in their 70s.[2] While many men are managed medically, 25% to 70% are non-compliant or discontinue medicines altogether due to insufficient relief or bothersome side effects that include erectile dysfunction, ejaculatory dysfunction, weakness, fatigue and dizziness.[3,4] Today, the vast majority of these men who are underserved by pharmacologic therapy do not undergo interventional treatment so as to avoid hospital stay, lengthy recovery, sexual dysfunction, stress urinary incontinence, stricture, or bladder neck contracture, all potential side effects associated with BPH surgery whether conducted with unipolar or bipolar electrodes or lasers.[5,6] Symptomatic obstructive BPH may lead to irreversible detrusor damage that may reduce the efficacy of surgery even if eventually performed.[7,8] The question whether long term pharmacological treatment has altered the outcomes of BPH interventions is not clear at this point. The needs of this large population underserved by traditional treatment options have been the focus of developments in less invasive interventions. However, while over one quarter of men on medical therapy discontinue use each year, no more than 3% elect the available surgical or less invasive treatment options.[3,4]

Nearly all less invasive procedures have involved a mechanism of action utilizing thermal energy to effect tissue necrosis and resorption to achieve reduced urinary obstruction. Treatment has been demonstrated to result in reduction in LUTS. However, consistency and durability have been less than anticipated.[5] These thermal ablation therapies have succeeded in creating a category of intervention that can be offered with less anesthesia in the office or outpatient setting. Because a tissue ablation injury model relies on biologic healing, recovery is often not achieved for several weeks, and patient urinary conditions often worsen before they improve. Postoperative edema requires days to weeks of urinary catheter, and patients are often plagued with bothersome irritative symptoms for several weeks.[5] Regardless of the specific heat source, studies have shown that the more energy applied to the prostate, the greater and longer lasting LUTS improvement. However, this can be at the cost of more significant and lasting adverse events due to the longer recovery process from larger amounts of tissue ablated and resorbed. The very strongest microwaves, for instance, showed efficacy that was non-inferior to transurethral resection of the prostate (TURP), but involved weeks of retention, catheterization, and tissue sloughing to attain this.[9] Those administering less energy were associated with fewer adverse effects but also showed no improvement in flow rate over sham control.[10] Not surprisingly, thermal ablation has also been shown to be associated with post therapy incidence of sexual dysfunction such as erectile dysfunction (0%-3%) and ejaculatory dysfunction (5%-15%).[5] While thermal ablation treatments offer a less invasive procedure than surgery, one could argue they do not consistently provide a patient expected minimally invasive and tolerable experience.

The Prostatic Urethral Lift (PUL) procedure was developed to address the shortcomings of surgery, medical therapy, and thermal ablation by creating a more minimally invasive solution that the large population of underserved men discontinuing medical therapy might more readily choose to treat their symptoms. By mechanically opening the prostatic fossa and not requiring a response to injury, relief has been shown to be rapid with mild to moderate perioperative adverse effects (postoperative dysuria, hematuria, pelvic discomfort, and urgency) that typically resolve within 2 to 3 weeks.[11,12] Because implants hold the prostate open during the period of expected immediate normal postoperative edema, urinary catheterization rates have been shown to be as low as 20% for an overall mean duration under 1 day, somewhat lower than the 32% seen in this study.[12] Another important distinction of PUL is that no new onset sustained sexual dysfunction has been reported.[11-17] It appears that PUL has succeeded in providing a truly minimally invasive, out-patient patient experience, and what remains to be answered is the extent to which improvements are durable. In this study we present the 5 year durability data of the largest randomized, controlled study of the PUL procedure.

Materials and methods

Protocol

A prospective, randomized, sham controlled, blinded study of the safety and effectiveness of the PUL procedure was performed across 19 centers in the United States, Canada and Australia. Enrollment criteria included age ≥ 50 years, International Prostate Symptom Score (IPSS) ≥ 13, peak flow rate (Qmax) ≤ 12 mL/s with a 125 mL voided volume and a 30 cc-80 cc volume prostate as

measured by transrectal ultrasound. Exclusion criteria included obstructive median lobe and active urinary tract infection. Two hundred and six (206) subjects were randomized 2:1 to active treatment with the PUL device (n = 140) or a sham procedure with rigid cystoscopy (n = 66). Subjects were required to undergo a washout of 2 weeks for alpha-blocker, 3 months for 5 alpha-reductase inhibitor and 3 days for anticoagulants prior to treatment. The study was performed with approval from institutional review boards, Health Canada, Therapeutic Goods Administration of Australia and the United States FDA (Clinicaltrials.gov: NCT01294150).

Procedures

The PUL procedure is conducted by installing small permanent implants transurethrally under endoscopic guidance to lift apart the obstructing lateral lobes and reduce urethral obstruction. The procedural objective is to create a channel through the anterior aspect of the prostatic fossa. The implant is comprised of a monofilament with a metallic capsular tab on one end and a metallic urethral end-piece on the other.

After rigid cystoscopy, the implant delivery device (UroLift System, NeoTract, Pleasanton, CA, USA), which houses a 2.9 mm telescope, is inserted into a 20F sheath and angled laterally (20-30 degrees) usually at the 10 and 2 o'clock position to compress the anterior third of the obstructive lobe. The delivery device laterally deploys a 19 gauge needle through the lobe. As the needle is withdrawn, the capsular tab of the implant engages the prostatic capsule. The monofilament is then tensioned, cut to the specific width of the compressed lobe, and secured in place by the urethral end-piece. Thus, each implant is customized in length and location in situ based on an individual's prostate anatomy. Because the fibromuscular capsule is less compliant than the periurethral tissue, the capsular tab holds firmly in place while the urethral end-piece holds the lobe apart to expand the urethral lumen. The narrow urethral end-piece invaginates into the urethral wall where epithelialization occurs.

The sham control procedure was conducted in as similar a manner as possible. For all active and control procedures, a surgical barrier was placed so the subject could not see below his waist. The sham procedure consisted of rigid cystoscopy with sounds that mimicked those of PUL, including the surgeon calling for devices and deploying but not inserting a disposable biopsy device.

Study assessments

A double blind was maintained and tested through the 3 month end point with the subject and assessor blinded to randomization. After randomized comparison to sham control, all subjects were unblinded, and 80% (53 of 66) of sham subjects enrolled in a crossover study.[15,18] PUL subjects were followed for 5 years and assessed on symptom response (IPSS), quality of life (IPSS QOL and BPH Impact Index, BPHII), peak flow rate (Qmax), sexual function (International Index of Erectile Function, IIEF, and Male Sexual Health Questionnaire for Ejaculatory Dysfunction, MSHQ-EjD) and adverse events. Analyses were conducted both on Per Protocol (PP) and Intent to Treat (ITT) bases. Subjects who underwent an additional BPH procedure, were taking a BPH medication, or represented a protocol deviation were censored in the PP analysis; for the ITT analysis their last value prior to censoring event was carried forward. An independent clinical events committee adjudicated all adverse events. An independent central reviewer over-read all uroflow waveforms, calculating Qmax using the 2-second rule.[19]

Statistical methods

Randomization was conducted just prior to treatment using permuted blocks of various sizes chosen at random and concealed through a password protected central electronic data program. The study was powered for the primary endpoint assuming a t-test comparison of mean values with 0.05 two-sided type 1 error and 80% statistical power. To evaluate change from baseline for multiple time points a general estimating equation model (GEE) was fit to each output parameter. Change from baseline was the dependent variable; visit and baseline score were used as independent variables. An exchangeable correlation structure and identity link were used. This model was used to calculate p values for each follow up interval compared to baseline. ITT analysis utilized a last observation carried forward (LOCF) imputation method. Imputed ITT values were compared to the non-imputed PP efficacy parameter values using a t-test.

Results

A total of 430 subjects were assessed from which 206 were deemed eligible and enrolled between February and December of 2011. Of those assessed for randomization 23 (5.3%) were excluded for an obstructive median lobe. Subjects were excluded only if it was deemed cystoscopically that lateral lobe distraction would not mitigate obstruction. Randomization assigned 140 subjects to PUL and 66 subjects to sham, Figure 1. In North America, all procedures except one (99.4%) were conducted using local anesthesia. An average of 4.9 implants (range 2 to 11) was delivered with four implants being the

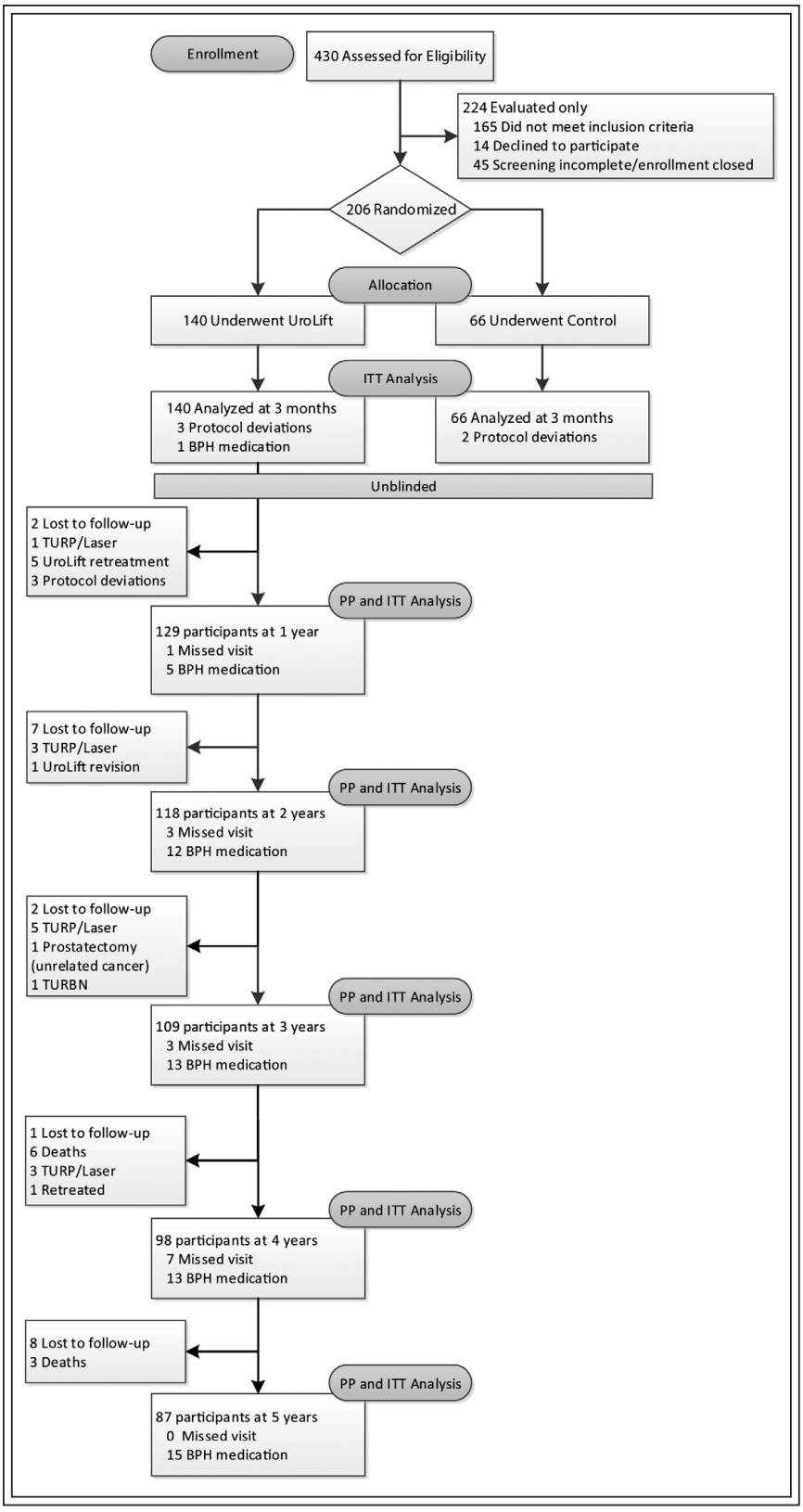

Figure 1. CONSORT diagram of patient enrollment, allocations, treatment and follow up.

most common number (42%), and 85% subjects receiving 6 or less implants. A third of PUL subjects (32%) required catheterization for failed voiding trial resulting in mean catheter duration of 0.9 days averaged over the total cohort. Subjects returned to preoperative activity level by 8.6 ± 7.5 days. Peri-operative adverse events were typically mild to moderate and transient, with the most frequent being hematuria, dysuria, pelvic pain, urgency and urge incontinence. Over the 5 year course of the study, few related adverse events occurred after the initial 3 months, Table 1. There was no reported incidence of new chronic ejaculatory or erectile dysfunction after PUL.

All primary and secondary endpoints were met. Randomized comparison at 3 months showed that PUL was associated with an 88% greater reduction in IPSS compared to sham on an ITT basis (IPSS improvement: PUL -11.1 ± 7.7, sham -5.9 ± 7.7, $p = 0.003$).[9] Improvements in QOL and Qmax were also significantly greater for PUL than for sham (Qmax improvement: PUL 4.28 ± 5.16, sham 1.98 ± 4.88, $p = 0.005$; QOL improvement: PUL 2.2 ± 1.8, sham 1.0 ± 1.5, $p < 0.001$). Mean sexual function measures were not different between groups. After 3 month randomized comparison, ITT PUL results remained durable to 5 years, Figure 2. While there was a modest decrease in IPSS improvement over the 5 years, QOL improvement remained stable. On both ITT and PP bases PUL efficacy remained durable through 5 years, with IPSS, QOL, Qmax, and BPHII remaining improved 35%, 44%, 50%, and 47% (ITT) and 36%, 50%, 44%, and 52% (PP), respectively, Tables 2 and 3. There was no significant difference in any efficacy measure between

TABLE 1. **Adverse events over 5 year course of study**

Time period [months]	**0-3**	**4-12**	**13-24**	**25-36**	**37-48**	**49-60**
Total available subjects	140	139	130	118	108	96
Total subject-months (SM)	413.6	1210.3	1463.8	1324.9	1186.6	1056.3
Related adverse events [total events]	162	15	6	4	2	1
Related adverse events [subjects]	100	12	6	2	2	1
% SM with adverse event per total SM:						
Abdominal pain	0.3%					
Bladder spasm	0.3%	0.09%				
Chills (rigors)				< 0.01%		
Diarrhea	0.2%					
Dizziness	0.2%					
Fever (pyrexia)	0.06%					
Vomiting	0.02%					
Hypotension	0.04%					
Orchitis/epididymo-orchitis	0.3%					
Painful erection	0.2%					
Urinary retention	0.4%					
Urethral stenosis (stricture)	< 0.01%	< 0.01%				
Prostatitis	0.4%	< 0.01%	0.06%			
Urinary tract infection	0.1%	0.03%	0.03%	0.03%		
Pelvic pain	6%	1%				
Hematuria	4%	0.2%	0.3%		0.07%	0.07%
Dysuria	9%	1%	1%	1%		
Urinary urge incontinence	3%	3%	2%	1%	1%	1%
Other	4%	3%	5%	4%	3%	3%

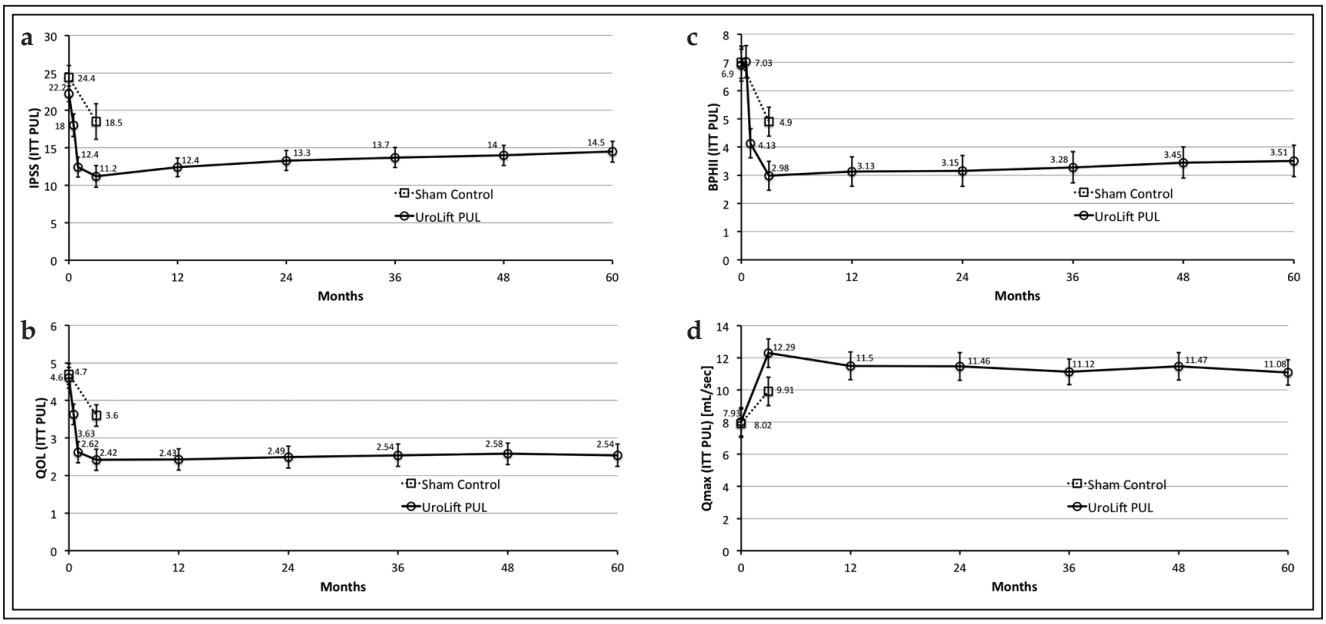

Figure 2. Intent to Treat outcomes for PUL and Sham control for **a)** International Prostate Symptom Score (IPSS); **b)** Quality of Life (QOL); **c)** BPH Impact Index (BPHII); **d)** peak urinary flow rate (Qmax).

PP and ITT analyses. When looking at IPSS QOL, 82% of PUL subjects reported some level of satisfaction with their urinary symptoms at 5 years. Of the 18% who were dissatisfied with their resulting urinary symptoms to some extent (QOL > 3), 10 (77%) entered the study with severe LUTS (IPSS ≥ 20).

At 5 years of follow up, data were available for 104 of 140 PUL subjects (74.3%). Of the 36 not available, 18 (12.9%) subjects were lost to follow up; 9 (6.4%) died of unrelated causes; 9 (6.4%) subjects exited the study for the following reasons: 5 sought treatment for unrelated cancer and 4 exited after undergoing TURP. Surgical retreatment for failure to cure was 13.6% at 5 years with 6 (4.3%) receiving additional PUL implants and 13 (9.3%) undergoing TURP or laser ablation (including the 4 exited subjects). All surgical retreatment was conducted routinely with no adverse effect from the presence of implants. Of the 19 retreated subjects, 18 had severe baseline LUTS (IPSS ≥ 20) and one subject's baseline IPSS was 19. At 5 years 15 (10.7%) subjects were taking an alpha blocker or 5-alpha reductase inhibitor and no patients were taking anticholinergic medication. Analyzing the 12.9% lost to follow up, average IPSS at last follow up was 13.5 ± 9.0 with a matched paired change from baseline of -10.4 ± 8.2 on a mean duration prior to study exit of 28.7 ± 15.9 months. These values were not different from the mean scores of the available cohort.

Genitourinary interventions over 5 years were as follows: one subject required stricture dilation, one underwent transurethral lithotripsy of a ureteric kidney stone, one required cystolitholapaxy for stones not related to implants (this subject later underwent TURP and was counted as retreatment), and 2 subjects underwent radical prostatectomy for unrelated prostate cancer. Both radical prostatectomies were conducted routinely with no interference from implants, and dissection planes remained intact. Ten subjects underwent removal of encrusted implants that had been deployed too proximally such that they

TABLE 2a. **Paired outcome measures after PUL (intent to treat analysis) – 2 weeks to 12 months**

Test		2 weeks	1 month	3 months	6 months	12 months
IPSS	N (paired)	140	140	140	140	140
	Baseline	22.32 ± 5.42	22.32 ± 5.42	22.32 ± 5.42	22.32 ± 5.42	22.32 ± 5.42
	Follow up	18.07 ± 7.76	12.43 ± 6.92	11.26 ± 7.65	11.58 ± 7.45	12.36 ± 7.51
	Change	-4.25	-9.89	-11.06	-10.74	-9.96
	% change	-17.3%	-43.6%	49.4%	-48.0%	-44.2%
	(95% CI)	(-23.0%, -11.6%)	(-48.3%, -39.0%)	(-54.6%, -44.1%)	(-53.2%, -42.7%)	(-49.5%,-38.8%)
	p value	< .0001	< .0001	< .0001	< .0001	< .0001
QOL	N (paired)	140	140	140	140	140
	Baseline	4.62 ± 1.05	4.62 ± 1.05	4.62 ± 1.05	4.62 ± 1.05	4.62 ± 1.05
	Follow up	3.63 ± 1.63	2.62 ± 1.68	2.42 ± 1.72	2.22 ± 1.70	2.43 ± 1.70
	Change	-0.99	-2.00	-2.20	-2.40	-2.19
	% change	-18.0%	-41.7%	-46.2%	-51.2%	-47.4%
	(95% CI)	(-25.3%, -10.6%)	(-48.0%, -35.5%)	(-52.6%, -39.9%)	(-57.1%, -45.2%)	(-53.4%, -41.5%)
	p value	< .0001	< .0001	< .0001	< .0001	< .0001
Qmax	N (paired)			139		139
	Baseline			7.88 ± 2.41		7.88 ± 2.41
	Follow up			11.74 ± 5.29		11.50 ± 5.18
	Change			3.86		3.63
	% change			57.8%		54.5%
	(95% CI)			(44.6%, 71.0%)		(41.4%, 67.5%)
	p value			< .0001		< .0001
BPHII	N (paired)	140	140	140	140	140
	Baseline	6.92 ± 2.79	6.92 ± 2.79	6.92 ± 2.79	6.92 ± 2.79	6.92 ± 2.79
	Follow up	7.03 ± 3.43	4.13 ± 3.14	2.98 ± 3.08	2.76 ± 2.96	3.13 ± 3.12
	Change	0.11	-2.79	-3.94	-4.16	-3.79
	% change	28.3%	-32.3%	-55.3%	-59.2%	-54.1%
	(95% CI)	(8.1%, 48.5%)	(-45.0%, -19.5%)	(-63.1%, -47.5%)	(-65.9%, -52.5%)	(-61.9%,-46.2%)
	p value	0.7360	< .0001	< .0001	< .0001	< .0001

PUL = prostatic urethral lift; IPSS = International Prostate Symptom Score; QOL = quality of life; Qmax = peak flow rate; BPHII = BPH Impact Index

TABLE 2b. **Paired outcome measures after PUL (intent to treat analysis) – 24 months to 60 months**

Test		24 months	36 months	48 months	60 months
IPSS	N (paired)	140	140	140	140
	Baseline	22.32 ± 5.42	22.32 ± 5.42	22.32 ± 5.42	22.32 ± 5.42
	Follow up	13.27 ± 7.98	13.69 ± 8.06	14.04 ± 8.11	14.47 ± 8.37
	Change	-9.05	-8.63	-8.28	-7.85
	% change	-40.0%	-38.3%	-36.7%	-35.0%
	(95% CI)	(-45.8%, -34.3%)	(-44.2%, -32.3%)	(-42.5%, -30.8%)	(-41.0%, -29.0%)
	p value	< .0001	< .0001	< .0001	< .0001
QOL	N (paired)	140	140	140	140
	Baseline	4.62 ± 1.05	4.62 ± 1.05	4.62 ± 1.05	4.62 ± 1.05
	Follow up	2.49 ± 1.74	2.54 ± 1.76	2.58 ± 1.72	2.54 ± 1.76
	Change	-2.13	-2.08	-2.04	-2.08
	% change	-45.8%	-44.2%	-43.5%	-44.4%
	(95% CI)	(-51.9%, -39.7%)	(-50.5%, -37.8%)	(-49.7%, -37.3%)	(-50.5%, -38.4%)
	p value	< .0001	< .0001	< .0001	< .0001
Qmax	N (paired)	139	139	139	139
	Baseline	7.88 ± 2.41	7.88 ± 2.41	7.88 ± 2.41	7.88 ± 2.41
	Follow up	11.46 ± 5.17	11.12 ± 4.71	11.47 ± 5.08	11.08 ± 4.72
	Change	3.58	3.24	3.60	3.21
	% change	54.8%	51.6%	56.7%	49.9%
	(95% CI)	(40.9%, 68.7%)	(38.5%, 64.8%)	(42.9%, 70.4%)	(37.4%, 62.3%)
	p value	< .0001	< .0001	< .0001	< .0001
BPHII	N (paired)	140	140	140	140
	Baseline	6.92 ± 2.79	6.92 ± 2.79	6.92 ± 2.79	6.92 ± 2.79
	Follow up	3.15 ± 3.27	3.28 ± 3.31	3.45 ± 3.30	3.51 ± 3.34
	Change	-3.77	-3.64	-3.47	-3.41
	% change	-52.9%	-49.0%	-47.4%	-46.8%
	(95% CI)	(-61.2%, -44.7%)	(-58.7%, -39.2%)	(-56.5%, -38.4%)	(-55.8%, -37.7%)
	p value	< .0001	< .0001	< .0001	< .0001

PUL = prostatic urethral lift; IPSS = International Prostate Symptom Score; QOL = quality of life; Qmax = peak flow rate; BPHII = BPH Impact Index

protruded into the bladder vesicle. Additionally, three subjects underwent prophylactic removal of implants exposed to the bladder that had not encrusted. These procedures typically only removed the misdeployed implant, but if additional implants were placed or tissue resection was conducted, the procedure was counted in the retreatment numbers reported above. As prior described, independent review of 1 year video cystoscopy revealed that no implant properly deployed within the prostate showed signs of encrustation, but 2.1% of implants were found to be deployed too proximally such that the implant was exposed to standing urine in the bladder.

Sexual function was preserved with no PUL subjects reporting an adverse event of de novo sustained ejaculatory or erectile dysfunction. This measure was a secondary safety endpoint of the FDA study. There was no significant degradation in mean erectile function (IIEF-5) or ejaculatory function (MSHQ-EjD Function) over the course of 5 years, Table 3. Bother due to ejaculatory function improved rapidly and remained modestly improved at 5 years, p = 0.02.

Conclusions

The results of this largest randomized, controlled 5 year study of PUL demonstrate both the clinical advantages of this minimally invasive therapy and definitive 5 year durability, with sustained improvement in symptoms (36% IPSS), quality of life (50% QOL; 52% BPHII) and urinary flow rate (44% Qmax) and an acceptably low surgical retreatment rate of 2%-3% per year. With 82% reporting some level of satisfaction with their urinary symptoms at 5 years, it would appear that this result is sufficient for the vast majority of PUL subjects. With regard to clinical advantages, PUL was shown to be free from serious adverse effects of traditional BPH surgery, such as stress urinary incontinence and transfusion; it is associated with the lowest postoperative catheter requirement of any available BPH procedure; PUL

TABLE 3a. **Paired outcome measures after PUL (per protocol analysis), including sexual function – 2 weeks to 12 months**

Test		2 weeks	1 month	3 months	6 months	12 months
IPSS	N (paired)	135	135	136	133	123
	Baseline	22.33 ± 5.51	22.27 ± 5.49	22.31 ± 5.49	22.21 ± 5.51	22.13 ± 5.56
	Follow up	18.01 ± 7.88	12.28 ± 6.94	11.17 ± 7.68	11.24 ± 7.31	11.52 ± 7.27
	Change	-4.3	-9.99	-11.14	-10.97	-10.61
	% change	-17.5%	-44.1%	-49.7%	-49.0%	-47.4%
	(95% CI)	(-23.4%, -11.6%)	(-48.9%, -39.3%)	(-55.0%, -44.4%)	(-54.3%, -43.7%)	(-52.9%, -41.8%)
	p value	< .0001	< .0001	< .0001	< .0001	< .0001
QOL	N (paired)	136	135	136	133	123
	Baseline	4.62 ± 1.06	4.61 ± 1.06	4.62 ± 1.06	4.60 ± 1.06	4.56 ± 1.01
	Follow up	3.62 ± 1.65	2.59 ± 1.68	2.40 ± 1.72	2.17 ± 1.65	2.25 ± 1.61
	Change	-1.00	-2.02	-2.22	-2.44	-2.31
	% change	-18.0%	-42.2%	-46.7%	-52.2%	-50.6%
	(95% CI)	(-25.6%, -10.5%)	(-48.7%, -35.8%)	(-53.2%, -40.2%)	(-58.2%, -46.3%)	(-56.8%,-44.4%)
	p value	< .0001	< .0001	< .0001	< .0001	< .0001
Qmax	N (paired)			122		102
	Baseline			8.02 ± 2.40		8.04 ± 2.35
	Follow up			12.31 ± 5.28		12.07 ± 5.28
	Change			4.29		4.03
	% change			64.4%		58.5%
	(95% CI)			(49.8%, 79.0%)		(42.8%, 74.1%)
	p value			< .0001		< .0001
BPHII	N (paired)	136	135	136	133	123
	Baseline	6.90 ± 2.82	6.88 ± 2.83	6.90 ± 2.83	6.92 ± 2.82	6.80 ± 2.79
	Follow up	7.01 ± 3.47	4.03 ± 3.07	2.91 ± 3.00	2.66 ± 2.84	2.83 ± 2.91
	Change	0.11	-2.85	-3.99	-4.26	-3.98
	% change	29.2%	-32.8%	-56.0%	-60.1%	-57.3%
	(95% CI)	(8.4%, 49.9%)	(-46.0%, -19.6%)	(-63.9%, -48.1%)	(-66.9%, -53.3%)	(-65.5%,-49.2%)
	p value	0.7725	< .0001	< .0001	< .0001	< .0001
IIEF-5	N (paired)		88	91	94	87
	Baseline		16.28 ± 7.12	16.16 ± 7.02	16.27 ± 7.01	15.99 ± 7.14
	Follow up		17.25 ± 7.63	17.44 ± 7.58	17.33 ± 7.63	16.69 ± 7.76
	Change		0.9	1.27	1.06	0.70
	% change		16.6%	14.4%	11.6%	18.5%
	(95% CI)		(3.5%, 29.8%)	(5.7%, 23.2%)	(2.7%, 20.5%)	(-3.6%, 40.6%)
	p value (GEE)		0.0583	0.0037	0.0104	0.2916
MSHQ-EjD function	N (paired)		88	91	94	87
	Baseline		8.92 ± 3.08	8.67 ± 3.09	8.76 ± 3.23	8.69 ± 3.26
	Follow up		11.22 ± 3.30	10.98 ± 3.16	10.53 ± 3.29	10.25 ± 3.16
	Change		2.30	2.31	1.78	1.56
	% change		36.2%	35.9%	35.9%	27.5%
	(95% CI)		(24.5%, 47.9%)	(25.2%, 46.5%)	(17.0%, 54.7%)	(17.2%, 37.8%)
	p value (GEE)		< .0001	< .0001	< .0001	< .0001
MSHQ-EjD bother	N (paired)		87	91	94	87
	Baseline		2.15 ± 1.65	2.20 ± 1.65	2.19 ± 1.63	2.18 ± 1.69
	Follow up		1.30 ± 1.40	1.13 ± 1.34	1.27 ± 1.30	1.43 ± 1.37
	Change		-0.85	-1.07	-0.93	-0.76
	% change		-33.3%	-47.6%	-40.2%	-28.3%
	(95% CI)		(-50.1%, -16.5%)	(-61.8%, -33.4%)	(-53.6%, -26.8%)	(-45.4%,-11.3%)
	p value (GEE)		< .0001	< .0001	< .0001	< .0001

PUL = prostatic urethral lift; IPSS = International Prostate Symptom Score; QOL = quality of life; Qmax = peak flow rate; BPHII = BPH Impact Index; IIEF-5 = International Index of Erectile Function; MSHQ-EjD = Male Sexual Health Questionnaire for Ejaculatory Dysfunction

TABLE 3b. **Paired outcome measures after PUL (per protocol analysis), including sexual function – 24 months to 60 months**

Test		24 months	36 months	48 months	60 months
IPSS	N (paired)	103	93	78	72
	Baseline	21.82 ± 5.62	21.56 ± 5.88	21.38 ± 5.92	21.47 ± 5.99
	Follow up	12.69 ± 7.85	12.73 ± 7.95	12.58 ± 7.88	13.92 ± 8.44
	Change	-9.13	-8.83	-8.81	-7.56
	% change	-41.4%	-41.1%	-40.6%	-35.9%
	(95% CI)	(-48.1%, -34.6%)	(-48.2%, -34.0%)	(-48.7%, -32.6%)	(-44.4%, -27.3%)
	p value	< .0001	< .0001	< .0001	< .0001
QOL	N (paired)	103	93	78	72
	Baseline	4.52 ± 1.00	4.47 ± 1.01	4.50 ± 0.98	4.51 ± 0.98
	Follow up	2.33 ± 1.64	2.23 ± 1.57	2.08 ± 1.42	2.19 ± 1.54
	Change	-2.19	-2.25	-2.42	-2.32
	% change	-47.4%	-48.8%	-52.0%	-50.3%
	(95% CI)	(-54.6%, -40.1%)	(-56.5%, -41.1%)	(-60.1%, -44.0%)	(-58.4%, -42.2%)
	p value	< .0001	< .0001	< .0001	< .0001
Qmax	N (paired)	86	69	60	52
	Baseline	8.33 ± 2.40	8.32 ± 2.39	8.45 ± 2.38	8.52 ± 2.15
	Follow up	12.53 ± 5.43	11.79 ± 4.81	12.72 ± 5.62	12.00 ± 4.86
	Change	4.21	3.47	4.27	3.48
	% change	58.6%	53.1%	63.4%	44.3%
	(95% CI)	(40.5%, 76.7%)	(32.7%, 73.5%)	(39.2%, 87.7%)	(29.4%, 59.1%)
	p value	< .0001	< .0001	< .0001	< .0001
BPHII	N (paired)	103	93	78	71
	Baseline	6.53 ± 2.88	6.43 ± 2.86	6.41 ± 2.69	6.42 ± 2.61
	Follow up	2.76 ± 2.96	2.65 ± 2.82	2.63 ± 2.56	2.94 ± 2.87
	Change	-3.78	-3.78	-3.78	-3.48
	% change	-54.8%	-53.2%	-55.7%	-51.8%
	(95% CI)	(-64.7%, -44.9%)	(-65.9%, -40.5%)	(-66.4%, -45.0%)	(-63.2%, -40.5%)
	p value	< .0001	< .0001	< .0001	< .0001
IIEF-5	N (paired)	72	66	54	49
	Baseline	15.63 ± 7.04	16.48 ± 6.77	16.87 ± 6.44	16.82 ± 6.22
	Follow up	16.68 ± 7.55	17.02 ± 7.86	17.17 ± 7.07	16.45 ± 7.12
	Change	1.06	0.53	0.30	-0.37
	% change	22.0%	4.0%	7.3%	6.1%
	(95% CI)	(-2.6%, 46.7%)	(-5.6%, 13.6%)	(-7.4%, 22.1%)	(-12.9%, 25.2%)
	p value (GEE)	0.0391	0.3407	0.4724	0.6026
MSHQ-EjD function	N (paired)	72	66	55	49
	Baseline	8.75 ± 3.39	9.17 ± 3.01	9.18 ± 3.01	9.22 ± 2.89
	Follow up	9.83 ± 3.28	9.73 ± 3.47	9.98 ± 3.37	9.53 ± 3.21
	Change	1.08	0.56	0.80	0.31
	% change	30.2%	8.9%	12.3%	9.3%
	(95% CI)	(8.0%, 52.5%)	(-0.6%, 18.3%)	(1.6%, 23.1%)	(-3.8%, 22.5%)
	p value (GEE)	< .0001	0.0122	0.0021	0.0962
MSHQ-EjD bother	N (paired)	72	66	55	49
	Baseline	2.25 ± 1.68	2.15 ± 1.63	2.20 ± 1.67	2.18 ± 1.67
	Follow up	1.63 ± 1.49	1.56 ± 1.45	1.36 ± 1.31	1.90 ± 1.45
	Change	-0.63	-0.59	-0.84	-0.29
	% change	-20.5%	-27.4%	-31.3%	-6.3%
	(95% CI)	(-40.7%, -0.3%)	(-44.3%, -10.5%)	(-49.9%, -12.7%)	(-31.5%, 18.8%)
	p value (GEE)	< .0001	0.0002	< .0001	0.0195

PUL = prostatic urethral lift; IPSS = International Prostate Symptom Score; QOL = quality of life; Qmax = peak flow rate; BPHII = BPH Impact Index; IIEF-5 = International Index of Erectile Function; MSHQ-EjD = Male Sexual Health Questionnaire for Ejaculatory Dysfunction

offers significant improvement in LUTS by 2 weeks, with the typical mild to moderate adverse effects of transurethral access mitigated in a similar timeframe; and finally, PUL is the only BPH therapeutic option, other than tadalafil, shown to be free from iatrogenic lasting sexual dysfunction, erectile or ejaculatory. As it is rare that any prospective study in BPH extends beyond 5 years, we believe this report demonstrates that PUL has reached maturity as a standard of care for BPH.

In any long term follow up analysis, the quality of the study and the percentage of patients available for follow up must be considered. The accuracy of outcomes such as retreatment rates and efficacy is compromised when the percentage of patients available for follow up is low. In the L.I.F.T. study, 74% of subjects were available at 5 years (over 80% of living subjects with a prostate at 5 years), a rate commensurate with high quality studies. The percentage of patients available at 5 years in prospective studies ranges from 28%-73% for TURP,[21-23] 37.6%-77% for PVP laser,[24-26] 39%-83% for TUMT,[21,27] 28%-94% for TUNA,[22,28] and 33%-69% in BPH drug trials.[29,30] Thus, comparisons made between PUL from this study and other BPH treatments must be made with caution as low quality studies can be misleading. A question to be asked in any clinical study is to what extent loss to follow up affects the data. We answer this in the LIFT study by reporting efficacy results both in the traditional PP analysis and using an ITT analysis where last available data is carried forward. No statistical difference in results was seen at 5 years between PP and ITT analyses. Also, analyzing the 12.9% subjects lost to follow up shows that their final IPSS improvement prior to exiting the study was on average substantial (10.4 point improvement over an average of 28 months).

In addition to sustained efficacy, durability has traditionally been assessed by the rate of surgical re-intervention for recurrent BPH symptoms. We report a cumulative rate of 10.7% after 3 years and 13.6% after 5 years for PUL, or about 2-3% per year. In comparison, the rates are 6.1%-17.7% for PVP laser at 5 years[24-26] and 5.8%-7.0% (often quoted as 1% to 2% per year) for TURP at 5 years.[31,32] Surgical retreatment rates for thermal ablation treatments have been reported to be 9%-21% for TUMT at 5 years,[21,27] 14%-15% for TUNA at 5 years.[22,28] However, it should be noted that the majority of studies of thermal ablation procedures show higher retreatment rates over a shorter follow up duration, with TUMT retreatment at 31%-40% at 3 years, TUNA at 20%-36% at 2-3 years.[33,35] Among medical therapies, the rates of progression to surgery have been reported to be 4%-27.7% by 3-5 years with alpha blockers,[29,35,36] 2%-4% by 4-5 years with 5-alpha reductase inhibitors[29,37] and 1%-6% by 4-5 years with combination therapy.[29,38] It should be noted that these surgery rates may underestimate the true failure rates for medical therapy. Often drug patients dissatisfied with medication will change prescriptions, stop and start treatment or discontinue altogether without electing surgery.[3,4,31] This "treatment interruption" rate has been shown to be at least 16% per year,[32] and the drug discontinuation rate after 12 months of treatment is as high as 62%-91%.[3,4,39]

Use of BPH medication after surgical treatment has been poorly reported to date in most clinical studies. However, recent attention has been paid to this in population studies, showing a very high rate of pharmacotherapy after surgery. The incidence of BPH medical treatment after PUL was 3.6% at 1 year and 10.7% at 5 years post-procedure. A comprehensive population study of 2,620,269 BPH patients in France found that among the patients who had BPH surgery (80% with TURP), the incidence of BPH medication treatment was as high as 13.8% at 1 year and 40% at 5 years post-surgery.[31] The authors noted that their study elucidated the gap between scientific knowledge of BPH surgery based on clinical trial reporting and the findings in real-world practice in which medication rates post-surgery are quite high. Similarly, a retrospective study of 6,430 U.S. TURP and laser patients found that the rate of new use of BPH medication was 22% at 3 years post-surgery for both types of patients (20%-25% TURP, 18%-25% laser).[40] Direct comparisons between prospective controlled studies and population studies must be made with caution, and perhaps if similarly rigorous reporting of medication usage could be demanded of prospective studies moving forward, this phenomenon can be better understood. While the need for BPH pharmacotherapy after surgical treatment could be a result of misdiagnosis or inadequate treatment, it could also be interpreted as a result of patients seeking surgical options too late in the disease progression. Because of the morbidity associated with traditional surgical treatments, men may tend to delay surgery at the expense of decreasing bladder function, and medication after surgery is continued in an attempt to address unmitigated bladder issues. One goal of PUL is to provide a less invasive option, such that men may be compelled to elect treatment prior to irreversible bladder dysfunction. Whether PUL elected earlier in the disease process effectively addresses a possible window of curability for imminent bladder dysfunction requires further study.

With regard to technical learning from this study, as discussed in prior work, there was no dependence of PUL efficacy on prostate volume, number of implants or number of implants per prostate volume. For all investigators in North America, the data represent their very first PUL procedures, as there was no run-in to this study. The typical procedure involves four implants and the average number was 4.9 for this study. Encrustation did not occur on any implant properly deployed within the prostate. From this study we learned that implants should be placed 1.5 cm from the bladder neck, as is standard training today in the many institutions offering PUL. If an implant is inadvertently placed too proximally such that it is exposed to the bladder vesicle, it should be removed peri-operatively with endoscopic graspers. PUL was effective independent of baseline flow rate or LUTS within this study range, though, as one would predict, greater IPSS change occurs with greater baseline IPSS score. A follow on study conducted at seven of the clinical sites gave evidence of continued learning curve, and catheterization rate dropped to 20%, return to preoperative activity was reduced to 5 days, and IPSS was reduced to a greater extent at 2 and 4 weeks.[12]

BPH is a quality of life disease, and treatment options focus on improving quality of life. For many men, improving LUTS while inadvertently damaging sexual function, causing incontinence, or exposing them to other safety concerns, may not result in a net positive health outcome. PUL has been demonstrated to be tolerable under local anesthesia in the office setting, to offer rapid recovery and relief typically without the need for post operative catheter, to provide improvements in symptoms, flow and quality of life through 5 years, and to uniquely preserve both ejaculatory and erectile function. Because of these characteristics for many men suffering from BPH, PUL may be a preferred treatment choice.

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References

1. Speakman M, Kirby R, Doyle S, Ioannou C. Burden of male lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) – focus on the UK. *BJU Int* 2015; 115(4):508-519.
2. Berry, SJ, Coffey, DS, Walsh, PC, Ewing, LL. The development of human benign prostatic hyperplasia with age. *J Urol* 1984;132(3): 474-479.
3. Cindolo L, Pirozzi L, Fanizza C et al. Drug adherence and clinical outcomes for patients under pharmacological therapy for lower urinary tract symptoms related to benign prostatic hyperplasia: population-based cohort study. *Eur Urol* 2015;68(3):418-425.
4. Verhamme K, Dieleman J, Bleumink G, Bosch J, Stricker B, Sturkenboom M. Treatment strategies, patterns of drug use and treatment discontinuation in men with LUTS suggestive of benign prostatic hyperplasia: the Triumph project. *Eur Urol* 2003;44(5):539-545.
5. Roehrborn C, McConnell J, Barry M et al. American Urological Association Guideline: Management of benign prostatic hyperplasia (BPH). American Urological Association Education and Research Inc. 2003.
6. Reich O, Gratzke C, Bachmann A et al. Morbidity, mortality and early outcome of transurethral resection of the prostate: a prospective multicenter evaluation of 10,654 patients. *J Urol* 2008; 180(1):246-249.
7. Flanigan RC, Reda DJ, Wasson JH, Anderson RJ, Abdellatif W, Bruskewitz RC. Five-year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. *J Urol* 1998;160(1):12-17.
8. Tubaro A, Carter S, Trucchi A, Punzo G, Petta S, Miano L. Early treatment of benign prostatic hyperplasia. *Drugs Aging* 2003;20(3):185-195.
9. Gravas S, Laguna P, Ehrnebo M, Wagrell L, Mattiasson A, de la Rosette JJ. Seeking evidence that cell kill guided thermotherapy gives results not inferior to those of transurethral resection: results of a pooled analysis of 3 studies of feedback transurethral microwave thermotherapy. *J Urol* 2005;174(3):1002-1006.
10. Albala DM, Fulmer BR, Turk TMT et al. Office-based transurethral microwave therapy using the TherMatrx TMX-2000. *J Endourol* 2002;16(1):57-61.
11. Roehrborn CG, Gange SN, Shore ND et al. Multi-Center randomized controlled blinded study of the prostatic urethral lift for the treatment of LUTS associated with prostate enlargement due to BPH: the L.I.F.T. study. *J Urol* 2013;190(6):2161-2167.
12. Shore N, Freedman S, Gange S et al. Prospective multi-center study elucidating patient experience after prostatic urethral lift. *Can J Urol* 2014;21(1):7094-7101.
13. McVary KT, Gange SN, Shore ND et al. Treatment of LUTS secondary to BPH while preserving sexual function: randomized controlled study of the prostatic urethral lift. *J Sex Med* 2014;11(1): 279-287.
14. Sønksen J, Barber NJ, Speakman M et al. Prospective, randomized, multinational study of prostatic urethral lift versus transurethral resection of the prostate: 12-month results from the BPH6 study. *Eur Urol* 2015;68(4);643-652.
15. Cantwell AL, Bogache WK, Richardson SF et al. Multi-Center prospective crossover study of the prostatic urethral lift for the treatment of LUTS secondary to BPH. *BJU Int* 2013;113(4): 615-622.
16. McNicholas TA, Woo HH, Chin PT et al. Minimally invasive prostatic urethral lift: surgical technique and multinational study. *Eur Urol* 2013;64(2):292-299.
17. Chin PT, Bolton DM, Rashid JG et al. Prostatic urethral lift: Two-year results after treatment for lower urinary symptoms secondary to benign prostatic hyperplasia. *Urology* 2012;79(1):5-11.

18. Rukstalis D, Rashid P, Bogache W et al. 24-month durability after crossover to the prostatic urethral lift from randomized, blinded sham. *BJU Int* 2016;118(Suppl 3):14-22.
19. Grino P, Bruskewitz R, Blaivis J et al. Maximum urinary flow rate by uroflowmetry: automatic or visual interpretation. *J Urol* 1993;149(2):339-341.
20. Roehrborn C, Wilson T, Black L. Quantifying the contribution of symptom improvement to satisfaction of men with moderate to severe benign prostatic hyperplasia: 4-year data from the combat trial. *J Urol* 2012;187(5):1732-1738.
21. Miller PD, Kastner C, Ramsey EW, Parsons K. Cooled thermotherapy for the treatment of benign prostatic hyperplasia: durability of results obtained with the Targis system. *Urology* 2003;61(6):1160-1165.
22. Hill B, Belville W, Bruskewitz R et al. Transurethral needle ablation versus transurethral resection of the prostate for the treatment of symptomatic benign prostatic hyperplasia: 5-year results of a prospective, randomized, multicenter clinical trial. *J Urol* 2004;171 (6 Pt 1):2336-2340.
23. Liu Z, Li YW, Wu WR, Lu Q. Long-term clinical efficacy and safety profile of transurethral resection of prostate versus plasmakinetic resection of the prostate for benign prostatic hyperplasia. *Urology* 2017;103:198-203.
24. Yamada Y, Furusawa J, Sugimura Y, Kuromatsu I. Photoselective vaporization of the prostate: long-term outcomes and safety during 10 years of follow-up. *J Endourol* 2016;30(12):1306-1311.
25. Hai MA. Photoselective vaporization of prostate: five-year outcomes of entire clinic patient population. *Urology* 2009;73(4):807-810.
26. Malde S, Rajagopalan A, Patel N, Simoes A, Choi W, Shrotri N. Potassium-titanyl-phosphate laser photoselective vaporization for benign prostatic hyperplasia: 5-year follow-up from a district general hospital. *J Endourol* 2012;26(7):878-883.
27. Mynderse LA, Roehrborn CG, Partin AW, Preminger GM, Cote EP. Results of a 5-year multicenter trial of a new generation cooled high energy transurethral microwave thermal therapy catheter for benign prostatic hyperplasia. *J Urol* 2011;185(5):1804-1810.
28. Zlotta AR, Giannakopoulos X, Maehlum O, Ostrem T, Schulman CC. Long-term evaluation of transurethral needle ablation of the prostate (TUNA) for treatment of symptomatic benign prostatic hyperplasia: clinical outcome up to five years from three centers. *Eur Urol* 2003;44(1):89-93.
29. 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.
30. Narayan P, Evans CP, Moon T. Long-term safety and efficacy of tamsulosin for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. *J Urol* 2003;170 (2 Pt 1):498-502.
31. Lukacs B, Cornu J-N, Aout M et al. Management of lower urinary tract symptoms related to benign prostatic hyperplasia in real-life practice in France: a comprehensive population study. *Eur Urol* 2013;64(3):493-501.
32. Madersbacher S, Lackner J, Brossner C et al. Reoperation, myocardial infarction and mortality after transurethral and open prostatectomy: a nation-wide, long-term analysis of 23,123 cases. *Eur Urol* 2005;47(4):499-504.
33. Bouza C, Lopez T, Magro A et al. Systematic review and meta-analysis of transurethral needle ablation in symptomatic benign prostatic hyperplasia. *BMC Urol* 2006;6:14.
34. Hoffman RM, Monga M, Elliott SP et al. Microwave thermotherapy for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 2012;9: CD004135.
35. Kawabe K, Homma Y, Kubota K, Sozu T. How frequent are invasive therapies required in patients receiving tamsulosin for benign prostatic hyperplasia? A retrospective long-term study. *Int J Urol* 2006;13(2):127-131.
36. Masumori N, Hashimoto J, Itoh N, Tsukamoto T. Short-term efficacy and long-term compliance/treatment failure of the a1 blocker naftopidil for patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *Scand J Urol Nephrol* 2007;41(5):422-429.
37. McConnell JD, Bruskewitz R, Walsh P et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. *N Engl J Med* 1998;338(9):557-563.
38. Kim CI, Chang HS, Kim BK, Park CH. Long-term results of medical treatment in benign prostatic hyperplasia. *Urology* 2006;68(5): 1015-1019.
39. Issa MM, Lin PJ, Eaddy MT, Shah MB, Davis EA. Comparative analysis of alpha-blocker utilization in combination with 5-alpha reductase inhibitors for enlarged prostate in managed care setting among Medicare-aged men. *Am J Manag Care* 2008;14(5 Suppl 2): S160-S166.
40. Strope SA, Vetter J, Elliott S, Andriole GL, Olsen MA. Use of medical therapy and success of laser surgery and transurethral resection of the prostate for benign prostatic hyperplasia. *Urology* 2015;86(6):1115-1122.