
Three year results of the prostatic urethral L.I.F.T. study

Claus G. Roehrborn, MD,¹ Daniel B. Rukstalis, MD,² Jack Barkin, MD,³ Steven N. Gange, MD,⁴ Neal D. Shore, MD,⁵ Jonathan L. Giddens, MD,⁶ Damien M. Bolton, MD,⁷ Barrett E. Cowan, MD,⁸ Anthony L. Cantwell, MD,⁹ Kevin T. McVary, MD,¹⁰ Alexis E. Te, MD,¹¹ Shahram S. Gholami, MD,¹² William G. Moseley, MD,¹³ Peter T. Chin, MD,¹⁴ William T. Dowling, MD,¹⁵ Sheldon J. Freedman, MD,¹⁶ Peter F. Incze, MD,¹⁷ K. Scott Coffield, MD,¹⁸ Fernando D. Borges, MD,¹⁹ Prem Rashid, MD²⁰

¹University of Texas Southwestern Medical Center, Dallas, Texas, USA / ²Wake Forest Baptist Health, Winston Salem, North Carolina, USA

³Toronto Urology Clinical Study Group, Toronto, Ontario, Canada / ⁴Western Urological Clinic, Salt Lake City, Utah, USA

⁵Carolina Urologic Research Center, Myrtle Beach, South Carolina, USA

⁶Jonathan Giddens Medicine Professional Corporation, Brampton, Ontario, Canada

⁷Austin Health, Heidelberg, Victoria, Australia / ⁸Urology Associates of Denver, Englewood, Colorado, USA

⁹Advanced Urology Institute, Daytona Beach, Florida, USA / ¹⁰Southern Illinois University School of Medicine, Springfield, Illinois, USA

¹¹Weill Cornell Medical Center, New York, New York, USA / ¹²Urology Associates of Silicon Valley, San Jose, California, USA

¹³Genesis Research LLC, San Diego, California, USA / ¹⁴Illawarra Urology, Figtree, NSW, Australia

¹⁵Chesapeake Urology Research Associates, Baltimore, Maryland, USA / ¹⁶Sheldon J. Freedman, M.D., Ltd., Las Vegas, Nevada, USA

¹⁷The Fe/Male Health Centres, Oakville, Ontario, Canada / ¹⁸Scott and White Healthcare, Temple, Texas, USA

¹⁹Pinellas Urology Inc., St. Petersburg, Florida, USA / ²⁰Urology Centre, Port Macquarie, Australia

ROEHRBORN CG, RUKSTALIS DB, BARKIN J, GANGE SN, SHORE ND, GIDDENS JL, BOLTON DM, COWAN BE, CANTWELL AL, MCVARY KT, TE AE, GHOLAMI SS, MOSELEY WG, CHIN PT, DOWLING WT, FREEDMAN SJ, INCZE PF, COFFIELD KS, BORGES FD, RASHID P. Three year results of the prostatic urethral L.I.F.T. study. *Can J Urol* 2015;22(3):7772-7782.

Introduction: To report the three year results of a multi-center, randomized, patient and outcome assessor blinded 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) ≥ 13 , peak flow rate (Qmax) ≤ 12 mL/s, and prostate volume between 30 cc-80 cc were randomized 2:1 to the PUL procedure or sham control. PUL involved placing permanent UroLift implants into the lateral lobes of the prostate to enlarge the urethral lumen. After randomized comparison at 3 months, PUL patients were followed to 3 years. LUTS severity (IPSS), quality of life, Qmax, sexual function,

and adverse events were assessed throughout follow up.

Results: The therapeutic effect of PUL regarding IPSS was 88% greater than sham at 3 months. Average improvements from baseline through 3 years were significant for total IPSS (41.1%), quality of life (48.8%), Qmax (53.1%), and individual IPSS symptoms. Symptomatic improvement was independent of prostate size. There were no de novo, sustained ejaculatory or erectile dysfunction events and all sexual function assessments showed average stability or improvement after PUL. Fifteen of the 140 patients originally randomized to PUL required surgical reintervention for treatment failure within the first 3 years.

Conclusions: PUL offers rapid improvement in voiding and storage symptoms, quality of life and flow rate that is durable to 3 years. Patients demonstrated a level of symptom relief that is associated with significant patient satisfaction. PUL, a minimally invasive procedure, is very effective in treating bothersome LUTS secondary to benign prostatic obstruction (BPO) and is unique in its ability to preserve total sexual function while offering a rapid return to normal physical activities.

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

Accepted for publication May 2015

Address correspondence to Dr. Claus Roehrborn, Department of Urology, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390 USA

Introduction

Chronic lower urinary tract symptoms (LUTS) such as urinary frequency, urinary urgency, and nocturia are

secondary to benign prostatic obstruction (BPO) in 3 out of 4 men by the seventh decade of life.¹ An estimated 20%-25% of men aged 50 years will eventually require surgical intervention for their symptoms.²

Management options for benign prostatic hyperplasia (BPH) LUTS include watchful waiting, pharmacologic treatment, surgery, and minimally invasive therapy. Once a patient advances beyond watchful waiting, medications such as alpha-blockers and 5-alpha reductase inhibitors offer limited symptom relief. Associated side effects such as dizziness, loss of libido, and sexual dysfunction along with the burden of lifelong compliance lead 30% of men to discontinue treatment after the first year.³ The gold standard surgical therapy, transurethral resection of the prostate (TURP), offers a more effective solution with 14.9 International Prostate Symptom Score (IPSS) improvement.⁴ Not surprisingly, TURP is associated with more serious and possibly long lasting complications including incontinence (3%), bleeding requiring transfusion (2.9%), transurethral resection syndrome (1.4%), stricture formation (7%), erectile dysfunction (10%), loss of ejaculatory function (65%), and reoperation rates of 5%-10% within 5 years.^{4,5} Laser-based therapies have reduced the incidence of bleeding, but are associated with morbidity rates similar to TURP.^{4,6-7}

The Prostatic Urethral Lift (PUL) is a minimally invasive, mechanical approach to BPH which relies on non-absorbable suture implants with a metallic anchor at each end to pull the lateral lobes of the prostate apart.⁹⁻¹¹ PUL has been shown to offer rapid and significant relief of LUTS with minimal side effects.⁹⁻¹⁷ It has also been shown to preserve both erectile and ejaculatory function, potentially preserving important aspects of quality of life for patients.¹⁷⁻¹⁹ We report the 3 year results of the L.I.F.T. study, the largest study conducted on PUL to date, and discuss the ability of PUL to address individual aspects of lower urinary tract health.

Materials and methods

Study protocol

The L.I.F.T. study (Luminal Improvement Following Prostatic Tissue Approximation for the Treatment of LUTS secondary to BPH) was a prospective, randomized, controlled, blinded study conducted in the United States, Canada, and Australia. The study was approved by the appropriate institutional review boards and ethics committees (Clinicaltrials.gov: NCT01294150). Inclusion and exclusion criteria included age > 50 years, IPSS \geq 13, peak flow rate \leq 12 mL/s, prostate volume between 30 cc and 80 cc, absence of

obstructive median lobe, and absence of active urinary tract infection, Table 1. Subjects were required to undergo washout of alpha-blockers, 5-alpha-reductase inhibitors, and anticoagulants for the appropriate length of time. After obtaining informed consent, 206 subjects were randomized 2:1 to receive either the active PUL (n = 140) or the control sham procedure (n = 66).

Study procedures

During the active treatment procedure with PUL, small permanent and adjustable UroLift implants were placed under transurethral, endoscopic guidance. After rigid cystoscopy, the implant delivery device was inserted into a 20 Fr sheath and angled laterally to compress the anterior aspect of the obstructive lateral lobe. The implants were placed via a 19 Ga needle in target locations designed to retract and compress the lateral lobes of the prostate and reduce urethral obstruction. The narrow footprint of the metallic end-piece that remains in the urethra was designed to embed into the adenoma and promote epithelialization of the implant. In both active and control cases, a surgical blinding screen was placed to block the patient's view of the procedure and instruments. Control sham procedure involved rigid cystoscopy with simulated active treatment sounds. The outcome assessment was done by a blinded assessor (usually a research coordinator not involved in the original procedure).

Study assessments

After randomized, blinded comparison at 3 months to sham control, PUL subjects were followed for 3 years and assessed on symptom response via IPSS, quality of life (IPSS QoL and BPHII: BPH Impact Index), peak flow rate (Qmax), sexual function (SHIM: Sexual Health Inventory for Men and MSHQ-EjD: Male Sexual Health Questionnaire for Ejaculatory Dysfunction), and adverse events. The seven individual domain responses of the IPSS were analyzed separately to assess for specific lower urinary tract symptom response to treatment. Independent central reviewers evaluated all recorded cystoscopic videos for prostatic urethra health and standardized flow waveform assessment using the two-second rule.²⁰ An independent clinical events committee adjudicated all adverse events. Subjects were censored from per protocol effectiveness analysis if they underwent another procedure for LUTS or were actively taking LUTS medication.

Statistical methods

Randomization was conducted just prior to treatment using permuted blocks of various sizes chosen at random and concealed through a password protected

TABLE 1. Patient selection criteria

Inclusion criteria

- Male gender
- Diagnosis of symptomatic BPH
- Age \geq 50 years
- International Prostate Symptom Score (IPSS) \geq 13
- Peak urine flow rate \leq 12 mL/sec on a voided volume \geq 125 mL
- Prostate volume \geq 30 cc to \leq 80 cc per ultrasound
- Prostate length measurement of \geq 30 mm and \leq 80 mm

Exclusion criteria

- Current urinary retention
- Post void residual (PVR) urine > 250 mL
- Obstructive or protruding median lobe of the prostate
- Active urinary tract infection at time of treatment
- Previous BPH procedure
- Urethral conditions that may prevent insertion and delivery of device system into bladder (i.e. urethral strictures, meatal stenosis, bladder neck contracture)
- Previous pelvic surgery or irradiation
- History of neurogenic or atonic bladder
- Urinary incontinence (i.e. sphincter)
- Biopsy of the prostate within the past 6 weeks
- Life expectancy estimated to be less than 1 year
- History of prostate or bladder cancer
- PSA > 10 ng/mL unless prostate biopsy is negative for cancer
- Current gross hematuria
- Serum creatinine > 1.8 mg/dL or upper-tract disease which compromises renal function
- Known coagulopathies or subject on anticoagulants or antiplatelets other than aspirin \leq 100 mg (unless antiplatelets are withheld minimum 3 days prior to procedure)
- Use of the following medications pre-screening (uroflow, questionnaires)
- Within 4 months of baseline assessment: estrogen, any drug producing androgen suppression, or anabolic steroids
 - Within 3 months of baseline assessment: 5-alpha-reductase inhibitors
 - Within 2 weeks of baseline assessment:
 - alpha-blockers, androgens, gonadotropin releasing, hormonal analogs, anticholinergics or cholinergic medication
 - phenylephrine, pseudoephedrine, or imipramine medications
 - Within 1 week of baseline assessment, unless documented on stable dose for \geq 6 months: beta blockers, antidepressants, anticonvulsants, and antispasmodics
- Cystolithiasis within the prior 3 months
- History of prostatitis requiring treatment (antibiotics) within the last year
- Other co-morbidities that could impact the study results such as:
 - severe cardiac arrhythmias uncontrolled by medications or pacemaker
 - congestive heart failure NYHA III or IV
 - history of uncontrolled diabetes mellitus
 - significant respiratory disease in which hospitalization may be required
 - known immunosuppression (i.e. AIDS, post-transplant, undergoing chemotherapy)
- Desire to maintain fertility post treatment
- Unable or unwilling to complete all required questionnaires and follow up assessments
- Unable or unwilling to sign informed consent form
- Currently enrolled in any other investigational clinical research trial that has not completed the primary endpoint

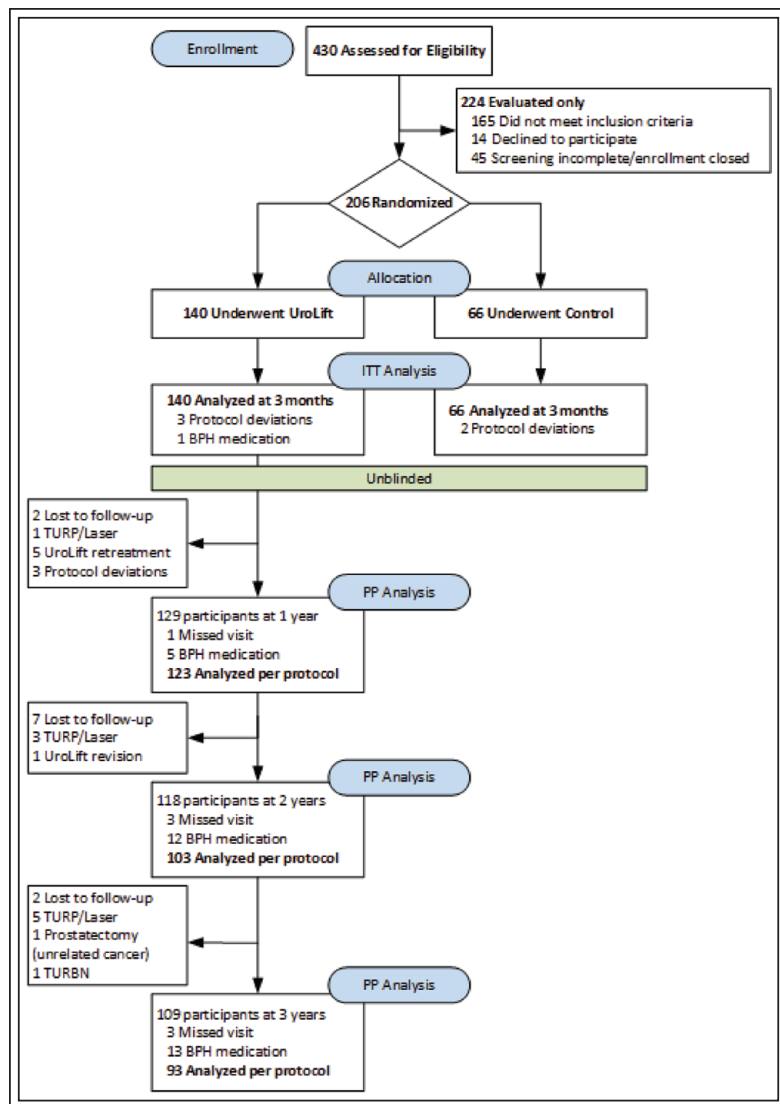


Figure 1. CONSORT diagram of patient enrollment, allocations, treatment and follow up.

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 per protocol change from baseline 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.

Results

Between February and December of 2011, a total of 206 subjects were enrolled, all of whom were deemed eligible for randomization. The randomization algorithm assigned 140 subjects to PUL and 66 subjects to control sham, Figure 1. Fifty-three of the 66 control subjects later elected to undergo PUL, and follow up will be detailed in another report. In the United States, all procedures except one (99.4%) were conducted using local anesthesia. No procedure was abandoned due to subject discomfort. In prostates ranging from 30 cc to 77 cc, two to 11 implants were deployed, Table 2. There was no correlation with number of implants and size of prostate. A portion of PUL subjects (32%) required catheterization for failed voiding trial resulting in mean catheter duration of 0.9 days averaged over the total cohort. On average, subjects returned to preoperative activity level by 8.6 days \pm 7.5 days. Peri-operative adverse events were typically mild and transient, with the most frequent being hematuria, dysuria, pelvic pain, urgency and urge incontinence.

For the intention-to-treat primary endpoint at 3 months, randomized comparison was reported in our previous publication as 88% greater reduction in IPSS after PUL compared to sham (IPSS reduction: PUL 11.1 \pm 7.7, sham

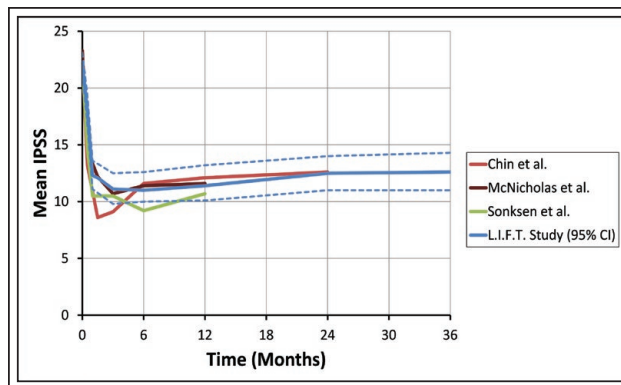


Figure 2. Outcomes after prostatic urethral lift (PUL) from published studies.

TABLE 2. Baseline characteristics and procedure details of per protocol analyzed patients

Characteristics	PUL (n = 137)*	Sham (n = 64)*
	Mean, SD [min-max], (n)	
Age (yrs)	67, 8.5 [49-86], (137)	64, 8.0 [50-84], (64)
Prostate volume (cc)	44.57, 12.47 [30.0-77.1], (137)	41.15, 10.88 [30.0-75.5], (64)
Prostate length (mm)	46.87, 5.75 [33.0-65.0], (137)	46.33, 5.78 [33.0-58.9], (64)
PSA	2.34, 1.98 [0.1-11.0], (137)	2.09, 1.65 [0.3-7.1], (64)
IPSS	22.32, 5.47 [13-35], (137)	24.59, 5.68 [13-33], (64)
Qmax (mL)**	7.88, 2.43 [3.0-13.0], (136)	7.95, 2.37 [2.0-12.0], (64)
PVR (mL)	85.89, 68.99 [0-246], (137)	86.78, 72.96 [0-244], (64)
SHIM	15.87, 7.11 [2-25], (104)	15.98, 7.56 [1-25], (51)
MSHQ-EjD function	8.67, 3.18 [1-15], (104)	8.88, 2.96 [1-15], (51)
MSHQ-EjD bother	2.25, 1.64 [0-5], (104)	2.04, 1.70 [0-5], (51)
Procedure time (min)	66.16, 24.09 [24-162], (137)	46.86, 17.41 [18-100], (63)
PUL implants	5.2, 1.6 [2-11], (137)	n/a
Time to discharge (days)	0.19, 0.39 [0-1], (137)	0.16, 0.41 [0-2], (64)
Return to preoperative activity level (days)	8.79, 7.54 [0-43], (137)	3.08, 4.44 [0-28], (64)

*one site's subjects have been excluded for protocol deviations

**voided volume must be ≥ 125 mL

PUL = prostatic urethral lift; PSA = prostate-specific antigen;

IPSS = International Prostate Symptom Score

Qmax = peak flow rate; PVR = post-void residual; SHIM = Sexual Health Inventory for Men

MSHQ-EjD = Male Sexual Health Questionnaire for Ejaculatory Dysfunction

5.9 ± 7.7 , $p = 0.003$).⁹ For the PUL group, per protocol improvement from baseline in total IPSS at 3 months, 1, 2, and 3 years was 49.7%, 47.4%, 41.4% and 41.1%, respectively, Table 3a. Quality of life measures and Qmax remained significantly improved through 3 years as well, Table 3a. The results of this study in conjunction with comparative data from other published studies indicate a reproducible therapeutic response after PUL, Figure 2.^{10,15,17}

Over the 3 years follow up of 140 PUL subjects, 129 (92.1%) were accounted for and 11 subjects were lost to follow up, Figure 1. Of the 129 available subjects, 93 were included in the effectiveness analysis. Of the 36 subjects who were not included in the 3 year analysis, three had missing data, three were censored for protocol deviations, 13 were censored for alpha-blocker or 5-alpha reductase inhibitors use at time of follow up, and two were censored for unrelated

TABLE 3a. Paired outcome measures after prostatic urethral lift (PUL)

Test/ Procedure		3 months	1 year	2 years	3 years
IPSS	n (paired)	136	123	103	93
	Baseline	22.31 +/-5.49 (21.38, 23.24)	22.13 +/-5.56 (21.14, 23.12)	21.82 +/-5.62 (20.72, 22.91)	21.56 +/-5.88 (20.35, 22.77)
	Follow up	11.17 +/-7.68 (9.87, 12.47)	11.52 +/-7.27 (10.22, 12.82)	12.69 +/-7.85 (11.16, 14.22)	12.73 +/-7.95 (11.09, 14.37)
	Change (95% CI)	-11.14 +/-7.72 (-12.45, -9.83)	-10.61 +/-7.51 (-11.95, -9.27)	-9.13 +/-7.62 (-10.62, -7.64)	-8.83 +/-7.41 (-10.35, -7.30)
	% change (95% CI)	-49.7% +/-31.4% (-55.0%, -44.4%)	-47.4% +/-31.1% (-52.9%, -41.8%)	-41.4% +/-34.3% (-48.1%, -34.6%)	-41.1% +/-34.5% (-48.2%, -34.0%)
	p value (GEE)	< .0001	< .0001	< .0001	< .0001
	QoL	n (paired)	136	123	103
Baseline		4.62 +/-1.06 (4.44, 4.80)	4.56 +/-1.01 (4.38, 4.74)	4.52 +/-1.00 (4.33, 4.72)	4.47 +/-1.01 (4.27, 4.68)
Follow up		2.40 +/-1.72 (2.11, 2.69)	2.25 +/-1.61 (1.97, 2.54)	2.33 +/-1.64 (2.01, 2.65)	2.23 +/-1.57 (1.90, 2.55)
Change (95% CI)		-2.22 +/-1.78 (-2.52, -1.92)	-2.31 +/-1.60 (-2.59, -2.02)	-2.19 +/-1.72 (-2.53, -1.86)	-2.25 +/-1.72 (-2.60, -1.89)
% change (95% CI)		-46.7% +/-38.3% (-53.2%, -40.2%)	-50.6% +/-34.6% (-56.8%, -44.4%)	-47.4% +/-37.0% (-54.6%, -40.1%)	-48.8% +/-37.4% (-56.5%, -41.1%)
p value (GEE)		< .0001	< .0001	< .0001	< .0001
BPHII		n (paired)	136	123	103
	Baseline	6.90 +/-2.83 (6.42, 7.38)	6.80 +/-2.79 (6.31, 7.30)	6.53 +/-2.88 (5.97, 7.10)	6.43 +/-2.86 (5.84, 7.02)
	Follow up	2.91 +/-3.00 (2.40, 3.42)	2.83 +/-2.91 (2.31, 3.35)	2.76 +/-2.96 (2.18, 3.33)	2.65 +/-2.82 (2.07, 3.23)
	Change (95% CI)	-3.99 +/-3.23 (-4.54, -3.45)	-3.98 +/-3.30 (-4.56, -3.39)	-3.78 +/-3.49 (-4.46, -3.09)	-3.78 +/-3.33 (-4.47, -3.10)
	% change (95% CI)	-56.0% +/-3.2% (-63.9%, -48.1%)	-57.3% +/-3.3% (-65.5%, -49.2%)	-54.8% +/-3.5% (-64.7%, -44.9%)	-53.2% +/-3.3% (-65.9%, -40.5%)
	p value (GEE)	< .0001	< .0001	< .0001	< .0001
	Qmax	n (paired)	122	102	86
Baseline		8.02 +/-2.40 (7.59, 8.45)	8.04 +/-2.35 (7.58, 8.50)	8.33 +/-2.40 (7.81, 8.84)	8.32 +/-2.39 (7.75, 8.89)
Follow up		12.31 +/-5.28 (11.36, 13.26)	12.07 +/-5.28 (11.03, 13.11)	12.53 +/-5.43 (11.37, 13.70)	11.79 +/-4.81 (10.64, 12.95)
Change (95% CI)		4.29 +/-5.16 (3.36, 5.21)	4.03 +/-4.96 (3.06, 5.00)	4.21 +/-5.09 (3.12, 5.30)	3.47 +/-5.00 (2.27, 4.67)
% change (95% CI)		64.4% +/-81.6% (49.8%, 79.0%)	58.5% +/-79.8% (42.8%, 74.1%)	58.6% +/-84.2% (40.5%, 76.7%)	53.1% +/-85.1% (32.7%, 73.5%)
p value (GEE)		< .0001	< .0001	< .0001	< .0001

IPSS = International Prostate Symptom Score; QoL = quality of life

BPHII = benign prostatic hyperplasia impact index

Qmax = peak flow rate

TABLE 3b. Paired outcome measures after prostatic urethral lift (PUL)

Test/ Procedure		3 months	1 year	2 years	3 years
PVR	n (paired)	136	120	102	88
	Baseline	85.09 +/-68.60 (73.45, 96.72)	84.54 +/-66.11 (72.59, 96.49)	80.02 +/-60.56 (68.13, 91.91)	80.89 +/-64.56 (67.21, 94.56)
	Follow up	76.07 +/-83.10 (61.98, 90.17)	72.43 +/-99.85 (54.38, 90.48)	89.62 +/-126.82 (64.71, 114.53)	73.33 +/-90.13 (54.23, 92.43)
	Change (95% CI)	-9.01 +/-85.71 (-23.55, 5.52)	-12.11 +/-100.39 (-30.25, 6.04)	9.60 +/-134.06 (-16.73, 35.93)	-7.56 +/-91.64 (-26.97, 11.86)
	% change (95% CI)	43.1% +/-251.6% (-1.8%, 88.0%)	19.5% +/-165.6% (-11.8%, 50.8%)	93.5% +/-412.0% (9.1%, 177.9%)	28.7% +/-225.6% (-21.9%, 79.2%)
	p value (GEE)	0.2184	0.1354	0.5167	0.5778
SHIM	n (paired)	91	87	72	66
	baseline	16.16 +/-7.02 (14.70, 17.63)	15.99 +/-7.14 (14.47, 17.51)	15.63 +/-7.04 (13.97, 17.28)	16.48 +/-6.77 (14.82, 18.15)
	Follow up	17.44 +/-7.58 (15.86, 19.02)	16.69 +/-7.76 (15.04, 18.34)	16.68 +/-7.55 (14.91, 18.46)	17.02 +/-7.86 (15.08, 18.95)
	Change (95% CI)	1.27 +/-4.65 (0.31, 2.24)	0.70 +/-5.12 (-0.39, 1.79)	1.06 +/-4.78 (-0.07, 2.18)	0.53 +/-4.41 (-0.55, 1.62)
	% change	14.4% +/-42.1% (5.7%, 23.2%)	18.5% +/-103.8% (-3.6%, 40.6%)	22.0% +/-105.1% (-2.6%, 46.7%)	4.0% +/-38.9% (-5.6%, 13.6%)
	p value (GEE)	0.0047	0.2989	0.0455	0.3380
MSHQ-EjD	n (paired)	91	87	72	66
	Baseline	8.67 +/-3.09 (8.03, 9.31)	8.69 +/-3.26 (7.99, 9.39)	8.75 +/-3.39 (7.95, 9.55)	9.17 +/-3.01 (8.43, 9.91)
	Follow up	10.98 +/-3.16 (10.32, 11.64)	10.25 +/-3.16 (9.58, 10.93)	9.83 +/-3.28 (9.06, 10.60)	9.73 +/-3.47 (8.87, 10.58)
	Change (95% CI)	2.31 +/-2.58 (1.77, 2.85)	1.56 +/-2.68 (0.99, 2.13)	1.08 +/-2.51 (0.49, 1.67)	0.56 +/-2.48 (-0.05, 1.17)
	% change	35.9% +/-51.2% (25.2%, 46.5%)	27.5% +/-48.4% (17.2%, 37.8%)	30.2% +/-94.8% (8.0%, 52.5%)	8.9% +/-38.5% (-0.6%, 18.3%)
	p value (GEE)	< .0001	< .0001	< .0001	0.0129
MSHQ-Bother	n (paired)	91	87	72	66
	Baseline	2.20 +/-1.65 (1.85, 2.54)	2.18 +/-1.69 (1.82, 2.55)	2.25 +/-1.68 (1.86, 2.64)	2.15 +/-1.63 (1.75, 2.55)
	Follow up	1.13 +/-1.34 (0.85, 1.41)	1.43 +/-1.37 (1.13, 1.72)	1.63 +/-1.49 (1.28, 1.97)	1.56 +/-1.45 (1.20, 1.92)
	Change (95% CI)	-1.07 +/-1.44 (-1.37, -0.77)	-0.76 +/-1.55 (-1.09, -0.43)	-0.63 +/-1.51 (-0.98, -0.27)	-0.59 +/-1.52 (-0.96, -0.22)
	% change (95% CI)	-47.6% +/-57.8% (-61.8%, -33.4%)	-28.3% +/-67.1% (-45.4%, -11.3%)	-20.5% +/-73.3% (-40.7%, -0.3%)	-27.4% +/-58.1% (-44.3%, -10.5%)
	p value (GEE)	< .0001	< .0001	< .0001	0.0002

PVR = post-void residual; SHIM = Sexual Health Inventory for Men; MSHQ-EjD = Male Sexual Health Questionnaire for Ejaculatory Dysfunction; IPSS = International Prostate Symptom Score; QoL = quality of life; BPHII = benign prostatic hyperplasia impact index; Qmax = peak flow rate

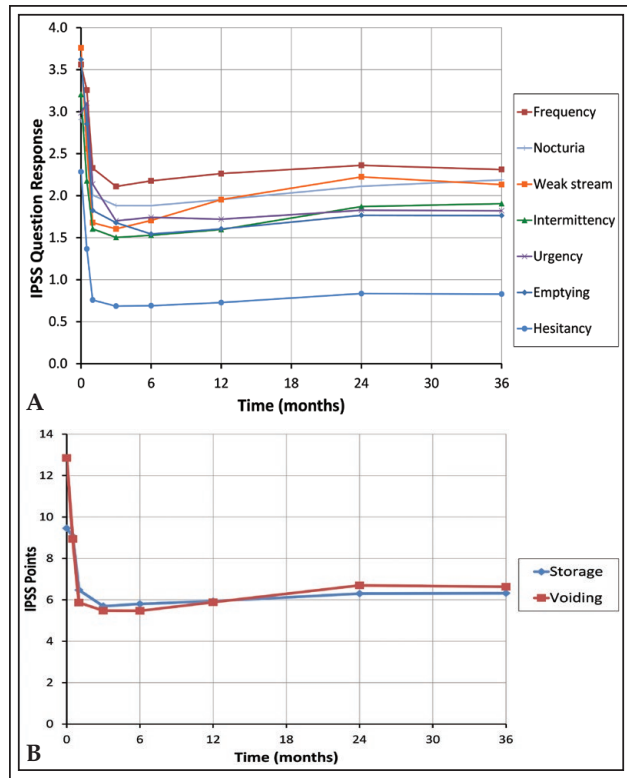


Figure 3. IPSS domains after prostatic urethral lift (PUL), including **A)** seven individual question responses and **B)** obstructive and irritative symptom response.

prostate procedures. The remaining 15 subjects (10.7% of the originally enrolled 140) underwent surgical retreatment for LUTS (six received additional

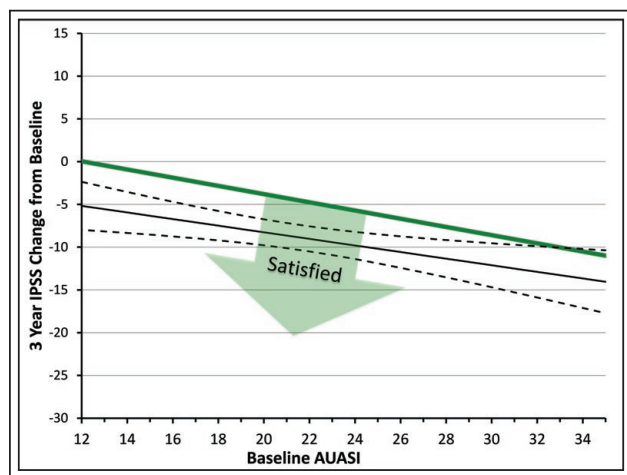


Figure 4. IPSS change at 3 years as a function of baseline score with 95% confidence interval (dotted line). Threshold for patient satisfaction indicated with green line.

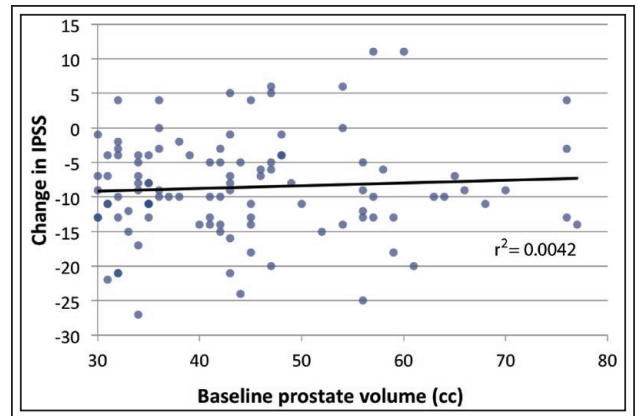


Figure 5. Symptom response at 3 years plotted against baseline prostate volume.

PUL implants and nine underwent TURP or laser vaporization).

Interventions were as follows: one subject required stricture dilation, one required removal of bladder stones not related to implants, two subjects underwent radical prostatectomy for unrelated prostate cancer, and one underwent bladder neck resection during transurethral lithotripsy of a ureteric kidney stone. Ten subjects underwent removal of implants: eight were deployed too proximally such that they protruded into the bladder vesicle and became encrusted and two were removed prophylactically. One of the subjects with encrustation had developed urosepsis which resolved.

Analysis of individual IPSS domains indicated that each aspect of IPSS is significantly and durably improved, Figure 3a. IPSS subgroup analysis showed that both voiding and storage function improve significantly by 4 weeks after PUL and remain so to 3 years ($p < 0.0001$; Figure 3b). IPSS change as a

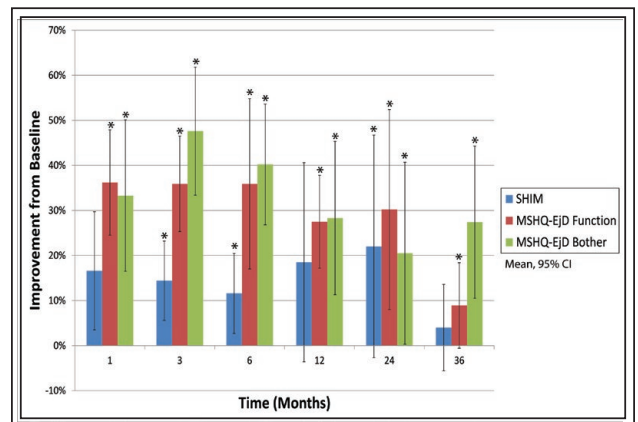


Figure 6. Sexual function questionnaire response after prostatic urethral lift (PUL) * $p < 0.05$.

function of baseline IPSS score is presented in Figure 4 in the context of a patient satisfaction regression line derived from 4844 subjects studied during the CombAT trial.²¹ Theoretically, a patient with a response that falls below the regression line is likely to experience a level of satisfaction with his LUTS treatment.

There were no significant correlations found on linear regression between symptom response at any follow up interval and baseline prostate volume or length. Further, the number of implants placed at time of procedure did not correlate with symptom response at any follow up time point. Additionally, the number of implants per prostate volume and the number of implants per prostate length were calculated for each patient and were found not be correlated with symptom response. Figure 5 shows a representative scatter plot and linear regression for the symptom response at 3 years plotted against baseline prostate volume ($R^2 = < 0.005$, not correlated).

Sexual function was preserved with no reported adverse events for PUL participants of de novo sustained erectile or ejaculatory dysfunction. Participants who underwent PUL procedure had average erectile function as measured by SHIM score above baseline at all follow up time points. In addition, ejaculatory function as measured by average MSHQ-EjD was improved throughout follow up ($p = 0.01$ at 3 years, Table 3b, Figure 6). Both associated with ejaculatory function was also improved significantly at every follow up interval ($p \leq 0.0002$, Table 3b, Figure 6).

Conclusions

The very stable responses in symptom, quality of life and urinary flow improvement from 3 months to 3 years, coupled with a low BPH retreatment rate of 10.7%, demonstrate durability of the PUL. This study offers data from the largest population with the longest term follow up of a randomized trial of the PUL procedure. PUL also demonstrated a freedom from stress urinary incontinence, transfusion and iatrogenic sexual dysfunction commonly associated with other BPH procedures. No other BPH procedure has demonstrated such rapid return to normal activity and improvement in symptoms that lasts through three years. When plotting symptomatic improvement from this randomized study along with that of other published studies, Figure 2, it is clear that results are reproducible among patient populations, protocol structures and operating surgeons.

The seven specific urinary symptoms assessed by the IPSS have been shown to have variable impact on

patient satisfaction and quality of life.²²⁻²³ If a treatment strategy is to address a patient's specific bothersome symptoms, it is important to understand the ability of available therapies to relieve these symptoms. When analyzed individually, the PUL procedure reduced all seven symptoms assessed by the IPSS quickly and durably, Figure 3a. When grouped into obstructive and irritative domains of the IPSS, the results in Figure 3b demonstrate that both voiding and storage symptoms respond to the PUL procedure.

In evaluating BPH treatment alternatives, a critical element of the risk/benefit decision is to determine what level of symptomatic relief is likely associated with patient satisfaction. The CombAT study indicated that satisfaction is dependent on both baseline IPSS score and improvement of symptoms.²¹ In this context, analysis of L.I.F.T. data would predict that PUL treatment would result, in general, with patient satisfaction. The results correlate well with the fact that L.I.F.T. subjects experienced approximately 50% improvement in both QOL and BPHII quality of life instruments.

We sought to find an algorithm for treatment that could predict the optimum prostate size or number of implants to deploy per prostate volume. Prostate volume, prostate length, number of placed implants, and the density of placed implants are not correlated with symptom relief and do not appear to predict response to the procedure. This may be because of differences in tissue compliance as well as anatomic character of individual prostates. Instead of relying on a prescriptive algorithm to determine the necessary number of implants based on volume or length, investigators can visually assess the urethral caliber after each implant is placed and deliver the appropriate number of implants to achieve an anterior channel dependent on the tissue's compliance and response. The number of delivered implants ranged from 2 to 11 in this trial, indicating an ability to tailor the procedure to a patient's specific anatomical characteristics.

This study demonstrated that encrustation can occur with PUL implants, but that this phenomenon is preventable by ensuring that the implants are placed correctly and not exposed inside the bladder neck. With independently adjudicated video cystoscopies at one year, no implant properly deployed within the prostate showed signs of encrustation. When an implant is deployed too proximally such that it protrudes into the bladder vesicle, it can develop encrustation. Therefore, it is important to deploy implants fully within the prostate. In the event that an implant is too close to the bladder neck and protrudes intravesically, it should be removed peri-operatively with grasping forceps.

Sexual function appears to be preserved, as there were no reports of de novo, sustained erectile or ejaculatory dysfunction. The SHIM score remained stable and slightly elevated from baseline at all intervals, indicating preserved erectile function throughout the trial. Ejaculatory function, an aspect of sexual function that has been found to be important to patients,^{19,24} was significantly improved at every interval after PUL. Most medications and all of the invasive options for the management of BPO have been shown to have a negative impact on ejaculatory function. Further, the bother associated with ejaculatory problems showed a similar, statistically significant improvement throughout the study.

The cumulative rate of surgical reintervention for failure to cure by 3 years after PUL was 10.7%. This rate is similar to rates reported after TURP (2.3%-4.3% at 1 year, 5.8%-9.7% at 5 years)²⁵⁻²⁷ and laser vaporization (1.7%-5.3% at 1 year, 6.7% at 2 years, 6.8%-34% at 5 years).²⁸⁻³³ Other minimally invasive therapies such as TUMT (transurethral microwave therapy) and TUNA (transurethral needle ablation) are known to have significantly higher retreatment rates than TURP.⁴ The results of this study suggest that the overall secondary procedure rate after PUL would be considerably less than after TUMT (31%-40% at 3 years) and TUNA (20%-36% at 2-3 years), although a direct comparison is difficult to make due to lack of data.³⁴⁻³⁵

The PUL procedure offers a new solution for patients suffering from BPH. It addresses the need for clinically meaningful relief from LUTS that is superior to medications but without the morbidity and sexual side effects caused by TURP, laser or medical therapy while being a quick, safe, minimally invasive outpatient procedure.

Disclosures

All of the authors were investigators in this study. Dr. Gange is a NXThera investigator. Dr. McVary is a consultant, advisor or investigator for Allergan, Lilly/ICOS, NxThera, Watson Pharmaceuticals, Neotract, NIDDK, GlaxoSmithKline, Astellas, AMS and Sphiris.

Acknowledgements

The authors would like to thank the participants, clinical research coordinators, and supporters of the L.I.F.T. study. Special thanks to Drs. Rodney Anderson, Kyle Anderson, and Rajesh Shinghal for their work on the independent clinical events adjudication committee. The authors would also like

to thank NeoTract, Inc., especially Theodore Lamson, PhD and Jacqueline Nerney Welch, MD, PhD, for their support in the preparation of this manuscript. □

References

1. Wei J, Calhoun E, Jacobsen S. Urologic diseases in America project: benign prostatic hyperplasia. *J Urol* 2005;173(4):1256-1261.
2. Norman R, Nickel J, Fish D, Pickett S. 'Prostate-related symptoms' in Canadian men 50 years of age or older: prevalence and relationships among symptoms. *Br J Urol* 1994;74(5):542-550.
3. 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.
4. 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.
5. 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.
6. Bachmann A, Tubaro A, Barber N et al. A European multicenter randomized noninferiority trial comparing 180 W Greenlight-XPS laser vaporization and transurethral resection of the prostate for the treatment of benign obstruction: 12-month results of the GOLIATH study. *J Urol* 2015;193(2):1-9.
7. McVary K, Roehrborn C, Avins A et al. Update on AUA guideline on the management of benign prostate hyperplasia. *J Urol* 2011; 185(5):1793-1803.
8. Thangasamy I, Chalasani V, Bachmann A, Woo H. Photoselective vaporization of the prostate using 80-W and 120-W laser versus transurethral resection of the prostate for benign prostatic hyperplasia: a systematic review with meta-analysis from 2002 to 2012. *Eur Urol* 2012;62(2):315-323.
9. Roehrborn C, Gange S, Shore N 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.
10. McNicholas T, Woo H, Chin P et al. Minimally invasive prostatic urethral lift: surgical technique and multinational study. *Eur Urol* 2013;64(2):292-299.
11. Barkin J, Giddens J, Incze P, Casey R, Richardson S, Gange S. UroLift system for relief of prostate obstruction under local anesthesia. *Can J Urol* 2012;19(2):6217-6222.
12. Cantwell A, Bogache W, Richardson S 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.
13. 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.
14. Woo H, Chin P, McNicholas T et al. Safety and feasibility of the prostatic urethral lift: a novel minimally invasive treatment for lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). *BJU Int* 2011;108(1):82-88.
15. Chin P, Bolton D, Jack G 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.
16. Roehrborn C, Gange S, Shore N et al. Durability of the prostatic urethral lift: 2-year results of the L.I.F.T. study. *Urology Practice* 2015;2(1):26-32.

17. Sonksen J, Barber N, Speakman M et al. Prospective, randomized, multinational study of the prostatic urethral lift versus transurethral resection of the prostate: 12-month results from the BPH6 study. *Eur Urol* 2015; Published online May 1, 2015.
18. McVary K, Gange S, Shore N 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.
19. Bell J, Laborde E. Update on sexual impact of treatment for benign prostatic hyperplasia. *Curr Urol Rep* 2012;13(6):433-440.
20. 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.
21. 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.
22. Miranda E, Gomes C, Torricelli F et al. Nocturia is the lower urinary tract symptom with greatest impact on quality of life of men from a community setting. *Int Neurourol J* 2014;18(2):86-90.
23. Ushijima S, Ukimura O, Okihara K, Mizutani Y, Kawauchi A, Miki T. Visual analog scale questionnaire to assess quality of life specific to each symptom of the International Prostate Symptom Score. *J Urol* 2006;176(2):665-671.
24. Helgason A, Adolfsson J, Dickman P, Fredrikson M, Arver S, Steineck G. Waning sexual function—the most important disease-specific distress for patients with prostate cancer. *Br J Cancer* 1996; 73(11):1417-1421.
25. Roos NP, Wennberg JE, Malenka DJ et al. Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. *N Engl J Med* 1989; 320(17):1120-1124.
26. 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.
27. Mamoulakis C, Schulze M, Skolarikos A et al. Midterm results from an international multicentre randomised controlled trial comparing bipolar with monopolar transurethral resection of the prostate. *Eur Urol* 2013;63(4):667-676.
28. Tabatabaei S, Choi B, Collins E et al. 120W Greenlight laser prostatectomy – one year data from an ongoing prospective multicentre study (International Greenlight Users Group – IGLU). *J Urol* 2010;184(4): e740.
29. Bouchier-Hayes DM, Anderson P, Van Appledorn S, Bugeja P, Costello A. KTP laser versus transurethral resection: early results of a randomized trial. *J Endourol* 2006;20(8):580-585.
30. Taşçi, A.I., Ölbey Y, Luleci H et al. 120-W GreenLight laser photoselective vaporization of prostate for benign prostatic hyperplasia: midterm outcomes. *Urology* 2011;78 (1):134-140.
31. Ruszat R, Seitz M, Wyler S F et al. GreenLight laser vaporization of the prostate: single-center experience and long-term results after 500 procedures. *Eur Urol* 2008; 54(4): 893-901.
32. Ruszat R, Wyler S F, Seitz M et al. Comparison of potassium-titanyl-phosphate laser vaporization of the prostate and transurethral resection of the prostate: update of a prospective non-randomized two-centre study. *BJU Int* 2008;102(10):1432-1438.
33. Rieken M, Ebinger Mundorff N, Bonkat G, Wyler S, Bachmann A. Complications of laser prostatectomy: a review of recent data. *World J Urol* 2010;28(1):53-62.
34. Bouza C, Lopez T, Magro A, Navalpotro L, Amate J. Systematic review and meta-analysis of transurethral needle ablation in symptomatic benign prostatic hyperplasia. *BMC Urol* 2006;6:14.
35. Hoffman R, Monga M, Elliott S et al. Microwave thermotherapy for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 2012; 9:CD004135.