

# 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

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## ABSTRACT

**Purpose:** We report the 5-year efficacy and safety of transurethral needle ablation of the prostate (TUNA) compared to transurethral resection of the prostate (TURP) for the treatment of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH).

**Materials and Methods:** A total of 121 men 50 years or older with LUTS secondary to BPH a minimum of 3 months in duration were enrolled in this prospective, randomized clinical trial at 7 medical centers across the United States. Of the participants 65 (54%) were randomly selected to receive TUNA and 56 (46%) were selected to receive TURP. International Prostate Symptom Score, quality of life, peak urinary flow rate, post-void residual urinary volume, and prostate size and configuration were evaluated before the procedure and then annually for 5 years after the procedure. Adverse events were also recorded throughout the study.

**Results:** Improvement from baseline for TUNA and TURP retained statistical significance at each interval for International Prostate Symptom Score, quality of life and peak flow rate. Post-void residual volume was statistically significant at all time points for TURP and at year 5 for TUNA. The TURP group reported 41% retrograde ejaculation, while the TUNA group reported none. The incident of erectile dysfunction, incontinence and stricture formation was also greater in TURP than in TUNA cases with significantly fewer adverse events for TUNA than for TURP.

**Conclusions:** The results of this study demonstrate stable treatment outcomes after 5 years of followup and suggest that TUNA is an attractive treatment option for men with LUTS due to BPH.

**KEY WORDS:** prostate, prostatic hyperplasia, transurethral resection of prostate, urinary tract

Benign prostatic hyperplasia (BPH) is nonmalignant growth of the prostate gland that can lead to a constellation of symptoms in the aging male known as lower urinary tract symptoms (LUTS). While the prevalence of BPH varies depending on clinical or histopathological definitions, longitudinal community based studies show that the prevalence of moderate to severe LUTS resulting from BPH increases with age and negatively impacts mental and physical aspects of health.<sup>1</sup> Clinical evidence also demonstrates the progressive nature of this disease, which if left untreated can lead to serious complications such as acute urinary retention, recurrent urinary tract infections and bladder calculi.

Therapeutic interventions ranging from medical management to invasive surgery are available to treat BPH. Transurethral resection of the prostate (TURP), first introduced more than 70 years ago, still remains the gold standard against which current therapies are measured. However, with advances in technology the number of therapeutic options has increased. Medical therapy with  $\alpha$ -receptor blockade or 5 $\alpha$ -reductase inhibition is now often the initial therapy to improve LUTS and it has been shown to be effective.<sup>2–5</sup> In

patients who are unwilling to remain on medication or in whom medical therapy failed minimally invasive treatment modalities have been developed, including transurethral microwave therapy,<sup>6</sup> interstitial laser therapy,<sup>7</sup> water induced thermotherapy<sup>8</sup> and transurethral needle ablation of the prostate (TUNA).<sup>9–11</sup>

TUNA uses radio frequency (RF) energy to heat the prostate adenoma. It has been shown to be efficacious for improving voiding symptoms in men with BPH. We report 5-year treatment outcomes from a multicenter, prospective, randomized trial comparing TUNA to TURP.

## MATERIALS AND METHODS

**Patient selection and evaluation.** To participate in the study men 50 years or older were required to have LUTS secondary to BPH a minimum of 3 months in duration. All patients who participated in this trial provided informed consent. Medical history, physical examination, digital rectal examination, prostate specific antigen (PSA) determination, urinalysis and urine culture were performed. The International Prostate Symptom Score (I-PSS), quality of life score (QOL), sexual function questionnaire, peak urinary flow rate (PFR), post-void residual urine (PVR) as calculated from 3-dimensional transabdominal ultrasound measurements

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obtained immediately after voiding, prostate size and configuration on transrectal ultrasound (TRUS) and cystourethroscopy findings were also evaluated during this trial. Inclusion criteria included an I-PSS of greater than 13, a PFR of 12 ml per second or less with a minimum voided volume of at least 125 ml and a prostate size of between 20 and 75 gm, as determined by TRUS. Exclusion criteria included an active urinary tract infection, urinary retention or PVR greater than 350 cc, abnormal renal function, PSA greater than 10 ng/ml, biopsy proven prostate cancer, an enlarged median lobe, neurogenic bladder and/or sphincter abnormalities, previous nonpharmacological prostate treatment, a prostate gland of less than 34 or greater than 64 mm in transverse diameter, current therapy affecting prostate physiology or another medical conditions that would pose an unacceptable patient risk. If serum PSA decreased within 4 to 10 ng/ml, TRUS guided prostate biopsies were performed to exclude prostate cancer.

Participants were randomized to TUNA or TURP based on a computerized random number generator, such that enrollee volume in each group remained as balanced as possible across each study site. The size of the treatment groups was determined by a standard power calculation. Post-procedure assessment included I-PSS, QOL score, sexual function questionnaire, PFR, PVR and adverse events recorded annually for up to 5 years.

**TUNA.** The TUNA procedure has been previously described.<sup>10,11</sup> In this study the TUNA device consisted of a hand piece similar to a rigid 18Fr cystoscope with a 0-degree optical lens, light source and irrigation system, an RF generator that operated at a frequency of 460 kHz and 2, 18 gauge needle electrodes to deliver RF energy to the prostate. The needles exited the end of the catheter at a 90-degree angle with an acute angle of 40 degrees to each other and they could extend up to 22 mm. Protective polytetrafluoroethylene insulating shields covered the base of the needle electrodes and were positioned to protect the urethral mucosa from heating to prevent sloughing and minimize discomfort. Controls in the handle allowed each needle and its covering to be advanced or retracted independently and the needles could be rotated 180 degrees to reach either lateral lobe of the prostate. The RF signal of 460 kHz generated thermal energy through inductive tissue heating. Water molecules within the prostate cells resist the passage of the electric current, which causes them to vibrate. Friction between cells develops and leads to an increase in tissue temperature. The RF generator incrementally increased the energy output to produce slow and uniform heating, initiating tissue ablation via coagulative necrosis.<sup>12</sup> The area of involvement was limited to approximately 6 mm beyond the needle tip as the RF signal dissipated. Temperatures at the center of the lesion reached 90C to 110C with a gradient decrease of 5C to 15C for 2 to 3 mm, such that peripheral temperatures attained 50C to 54C.<sup>13</sup> Thermal sensors located at the shield and hand piece tip monitored prostate and urethral temperature, respectively. The RF generator was connected to the hand piece and to a rectal temperature probe. The generator regulated the RF energy reaching the prostate by providing simultaneous temperature measurements of the urethra, prostate and rectum. This energy regulation prevented urethral and rectal damage as well as prostate tissue charring. Since the completion of this study, the equipment has been updated with new software that provides more consistent prostate heating and shorter treatment time. A rectal temperature probe is no longer used because rectal temperature does not increase.

Cystoscopy was performed during the pretreatment evaluation to assess visually the prostatic urethra. If a rigid cystoscopy is used, patient ability to tolerate TUNA using local anesthesia can be assessed in advance.<sup>14</sup> TRUS was done to measure prostate transverse diameter. The length of

needle deployment was calculated by subtracting 6 mm (estimated lesion size) from the distance between the urethra and prostatic capsule. The insulating sheaths were then set at 5 or 6 mm to protect the urethra.

Broad-spectrum antibiotic coverage was given 12 hours prior to the procedure. Patients were placed in the dorsal lithotomy position and 30 ml 2% lidocaine jelly were instilled intraurethrally 10 to 15 minutes prior to beginning the procedure. A penile clamp was used to occlude the distal urethra. Under direct vision the TUNA hand piece was introduced into the urethra and the needle electrodes were inserted into the prostate 0.5 to 1.0 cm distal to the bladder neck. RF energy was delivered through the needles and the total power output was manually controlled to achieve preset temperature levels at the needle tip. Each lesion required 5½ minutes of treatment; that is 4 minutes to heat the prostate to 50C to 54C and 1½ minutes with the temperature maintained above 50C. Depending on prostate gland length 1 to 3 treatments were performed on each lateral lobe. At the end of the procedure the instrument was removed, the bladder was emptied and the patient was taken to the recovery area. A catheter was not routinely placed and patients were discharged home with 3 to 5 days on oral anti-inflammatories and antibiotics.

**TURP.** Each TURP was done at one of the reporting centers. It was performed or supervised by a urologist who had completed a minimum of 100 such procedures. The patient received general or spinal anesthesia. Resection was performed using standard techniques and a urethral catheter was left indwelling for 24 to 48 hours postoperatively. Followup after TURP was identical to that for TUNA.

**Statistical methods.** All baseline and followup data were stored elsewhere. Statistical analysis was performed using the Wilcoxon signed rank test for comparison between baseline and followup data with  $p < 0.5$  considered significant.

## RESULTS

A total of 121 patients met trial inclusion/exclusion criteria and were enrolled in the study, of whom 65 (54%) were treated with TUNA and 56 (46%) were treated with TURP. Baseline characteristics in each group were matched for age, symptom score, QOL mean PFR and PVR (table 1). Patients were evaluated yearly for 5 years following the procedure. I-PSS and QOL measured the subjective response, while PFR and PVR measured the objective response to treatment. Table 2 lists treatment group results for the 5-year study period.

**Symptom score.** Mean baseline I-PSS  $\pm$  SE in the TUNA and TURP cohorts was  $24.0 \pm 0.8$  and  $24.1 \pm 0.8$ , respectively (table 1). Following treatment significant improvement from baseline occurred in the 2 cohorts at each yearly interval ( $p < 0.0001$ , table 2). The improvement was greater for TURP than for TUNA (fig. 1). This difference was statistically significant in the first 4 years (table 2). Throughout the study a majority of patients (TUNA 55% to 89% and TURP 68% to 95%) had at least 30% improvement in I-PSS above baseline (table 3).

**QOL score.** The improvement in QOL for TUNA and TURP remained durable throughout the study course (fig. 2). The change at each yearly followup was statistically significant in

TABLE 1. Baseline patient characteristics

Parameter	Mean TUNA $\pm$ SE	Mean TURP $\pm$ SE	p Value
No. pts	65	56	
Age	$66 \pm 1.0$	$66 \pm 1.0$	0.99
I-PSS	$24.0 \pm 0.8$	$24.1 \pm 0.8$	0.91
QOL	$11.8 \pm 0.5$	$12.6 \pm 0.5$	0.24
PFR (ml/sec)	$8.8 \pm 0.3$	$8.8 \pm 0.3$	0.99
PVR (ml)	$91.8 \pm 10.0$	$81.9 \pm 9.3$	0.47

TABLE 2. Five-year TUNA vs TURP results

Parameter	Mean Preop ± SEM	Mean 1 Yr ± SEM	Mean 2 Yrs ± SEM	Mean 3 Yrs ± SEM	Mean 4 Yrs ± SEM	Mean 5 Yrs ± SEM
I-PSS (No. pts):						
TUNA	24.0 ± 0.8 (65)	11.7 ± 1.0 (56)	15.0 ± 1.3 (43)	15.2 ± 1.3 (38)	13.2 ± 1.5 (24)	10.7 ± 1.4 (18)
p Value vs baseline		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TURP	24.1 ± 0.8 (55)	7.8 ± 0.9 (44)	9.5 ± 1.1 (35)	10.1 ± 1.4 (31)	7.6 ± 1.6 (21)	10.8 ± 1.6 (22)
p Value vs baseline		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
p Value TUNA vs TURP		0.0049	0.0028	0.0079	0.0137	0.9813
QOL (No. pts):						
TUNA	11.8 ± 0.5 (64)	4.3 ± 0.5 (55)	6.0 ± 0.7 (43)	5.4 ± 0.7 (40)	5.2 ± 0.9 (22)	3.8 ± 0.7 (18)
p Value vs baseline		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
TURP	12.6 ± 0.5 (56)	3.7 ± 0.7 (45)	3.7 ± 0.7 (33)	4.7 ± 1.0 (32)	3.7 ± 1.0 (21)	4.0 ± 0.8 (22)
p Value vs baseline		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
p Value TUNA vs TURP		0.4814	0.0309	0.5275	0.2316	0.8719
PFR (No. pts):						
TUNA	8.8 ± 0.3 (65)	14.6 ± 1.0 (53)	12.5 ± 0.7 (40)	13.0 ± 1.3 (33)	11.7 ± 1.4 (18)	11.4 ± 1.2 (13)
p Value vs baseline		<0.0001	<0.0001	0.0025	0.0358	0.0162
TURP	8.8 ± 0.3 (56)	21.1 ± 1.3 (43)	21.3 ± 1.4 (33)	19.1 ± 2.0 (26)	18.9 ± 2.5 (17)	18.6 ± 2.3 (15)
p Value vs baseline		<0.0001	<0.0001	<0.0001	0.0006	0.0005
p Value TUNA vs TURP		<0.0001	<0.0001	0.0106	0.0142	0.0143
PVR (No. pts):						
TUNA	91.8 ± 10.0 (65)	80.3 ± 11.0 (52)	74.1 ± 12.6 (40)	78.2 ± 13.7 (32)	138.2 ± 45.7 (19)	60.4 ± 21.8 (13)
p Value vs baseline		0.1161	0.3788	0.102	0.4019	0.0872
TURP	81.9 ± 9.3 (56)	47.1 ± 7.0 (43)	34.6 ± 5.6 (31)	50.7 ± 10.4 (26)	39.5 ± 13.1 (17)	27.4 ± 7.9 (17)
p Value vs baseline		0.0014	0.0005	0.0095	0.0058	0.0031
p Value TUNA vs TURP		0.0173	0.0114	0.1285	0.0564	0.1281

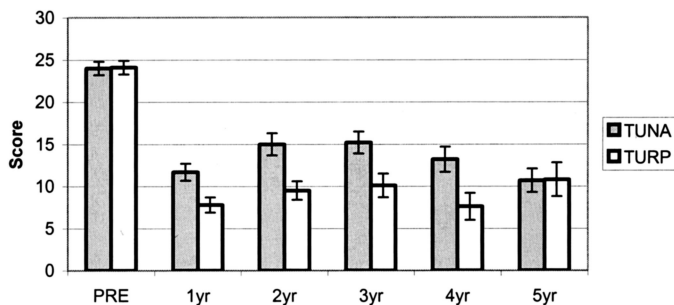


FIG. 1. Five-year TUNA vs TURP I-PSS. PRE, before procedure

the 2 cohorts compared to baseline ( $p < 0.0001$ , table 2). When comparing TUNA to TURP, there was a statistically significant difference in QOL only at year 2 ( $6.0 \pm 0.7$  vs  $3.7 \pm 0.7$ ,  $p = 0.0309$ ). Throughout the study 68% to 84% of the TUNA group and 78% to 87% of the TURP group had at least a 30% improvement in QOL over baseline (table 3).

**PFR.** Mean baseline PFR was  $8.8 \pm 0.3$  per second in each treatment group. The TUNA and TURP groups demonstrated a significant improvement in PFR at each interval compared to baseline (table 2). Patients treated with TURP had a greater improvement in PFR than those treated with TUNA and this difference was statistically significant at each time point (fig. 3). Throughout the 5 years 48% to 62% of TUNA and 67% to 82% of TURP cases showed greater than 30% improvement above baseline in mean PFR (table 3).

**PVR.** Mean baseline PVR was  $91.8 \pm 10.0$  and  $81.9 \pm 9.3$  ml in the TUNA and TURP cohorts, respectively. The TURP cohort had a statistically significant decrease in PVR throughout the study. PVR did not significantly decrease in the TUNA cohort. When comparing TUNA to TURP, the change in PVR for TURP was greater at each time point (table 2).

**Adverse events.** TUNA showed significantly fewer adverse events than TURP ( $p < 0.0001$ , table 3). In the 2 patients with TUNA who reported erectile dysfunction the average onset of dysfunction was 2.6 years after treatment. One patient with TUNA reported stress urinary incontinence and another reported urge urinary incontinence. Nine of 65 men (14%) in the TUNA cohort required further intervention for BPH symptoms and went on to receive additional treatment (TURP). One of 56 men (2%) in the TURP cohort went on to

receive additional treatment (transurethral incision of the bladder neck). In addition, 1 patient with TURP underwent radical prostatectomy due to cancer.

#### DISCUSSION

Multiple treatment options are now available to treat patients with LUTS due to BPH. Medical therapy with  $\alpha$ -adrenoceptor blockade and  $5\alpha$ -reductase inhibition is often the first line treatment approach. These medications have established efficacy profiles and they are well known to most physicians.<sup>15,16</sup> However, not all patients on medication experience significant voiding improvement. Some men have undesirable side effects and prefer other interventions rather than long-term medication. These patients can potentially benefit from a minimally invasive procedure such as TUNA.

Schulman and Zlotta first reported the feasibility of the TUNA procedure in men with LUTS resulting from BPH.<sup>11</sup> They determined that this procedure could be safely performed in the outpatient setting and it was effective for improving symptomatic BPH. Histological evaluation from prior feasibility studies demonstrated that RF ablation of the prostate led to localized and reproducible necrotic lesions.<sup>12</sup> Neurohistochemical analysis showed severe thermal damage to intraprostatic nerve fibers that extended beyond the area of tissue necrosis and it was postulated that the resultant denervation of  $\alpha$ -adrenergic and/or sensory nerves may contribute to clinical improvement.<sup>17</sup>

Short-term results after TUNA indicate that a majority of patients maintain subjective and objective improvement in voiding parameters but long-term data to document the durability of this improvement have been unavailable until this point.<sup>9,18,19</sup> This 5-year, prospective, randomized clinical trial demonstrates the durability of response achieved using RF energy to ablate the prostate in men with symptomatic BPH. At a 5-year followup 55% and 68% average improvement over baseline in I-PSS and QOL were noted with greater than 30% improvement in 89% and 83% of patients, respectively. PFR improved from a baseline of 8.8 to 11.4 ml per second at 5 years for a 29% increase. PVR in the TUNA cohort varied from year to year and the change compared to baseline did not attain statistical significance at any time point, suggesting that TUNA does not alter PVR.

While a gradual decrease in PFR following TUNA was noted during the study, a similar decrease was seen in patients after TURP. This decrease in PVR may have been

TABLE 3. Five-year TUNA vs TURP percent improvement over baseline

% Parameter	% Yr 1		% Yr 2		% Yr 3		% Yr 4		% Yr 5	
	TUNA	TURP	TUNA	TURP	TUNA	TURP	TUNA	TURP	TUNA	TURP
AUA symptom score:										
Greater than 30	71	95	63	83	55	81	67	86	89	68
Greater than 50	50	75	30	63	34	61	42	71	56	50
Greater than 80	21	34	12	26	8	29	13	43	17	23
QOL:										
Greater than 30	84	87	79	82	73	78	68	86	83	82
Greater than 50	71	82	53	70	58	72	41	76	67	64
Greater than 80	35	58	26	48	23	53	18	43	17	36
PFR:										
Greater than 30	62	81	58	82	48	73	56	71	54	67
Greater than 50	47	56	40	70	42	54	39	53	15	53
Greater than 80	30	12	23	12	27	8	33	12	0	7
PVR:										
Greater than 30	46	65	53	61	56	73	37	65	69	88
Greater than 50	42	49	38	55	41	62	21	65	62	71
Greater than 80	15	28	15	26	31	31	16	47	54	47

TABLE 4. Five-year TUNA vs TURP adverse events

Adverse Event	No. TUNA (%)	No. TURP (%)
Retrograde ejaculation	0	23 (41.1)
Erectile dysfunction	2 (3.1)	12 (21.4)
Urinary incontinence	2 (3.1)	12 (21.4)
Stricture formation/scar tissue	1 (1.5)	4 (7.1)
Re-treatment	9 (13.8)	1 (1.8)

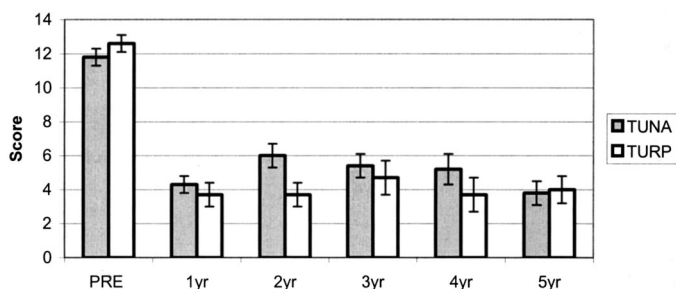


FIG. 2. Five-year TUNA vs TURP QOL. PRE, before procedure

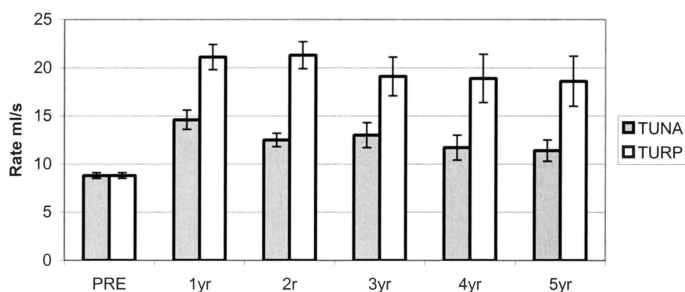


FIG. 3. Five-year TUNA vs TURP PFR. PRE, before procedure

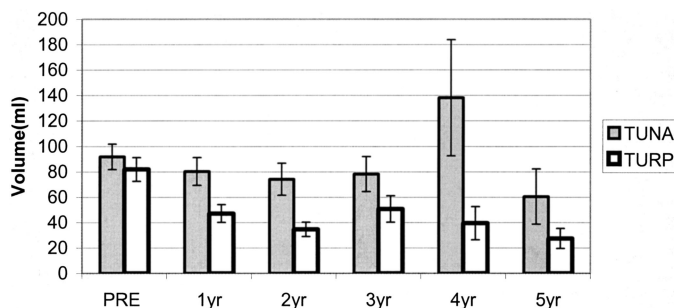


FIG. 4. Five-year TUNA vs TURP PVR. PRE, before procedure

indicative of BPH regrowth and progression rather than treatment failure. A gradual worsening in I-PSS and QOL was also noted during the first 3 years with improvement then seen in years 4 and 5. Late improvement at these time points was most likely a result of decreasing patient numbers and it did not indicate new improvement.

Patients undergoing TURP experienced a greater number of adverse events compared to those with TUNA. The incidence of erectile dysfunction following TUNA (3.1%) was within the reported 2.6% annual incidence of erectile dysfunction in 40 to 69-year-old men<sup>20</sup> and it was significantly less than the 21.4% incidence of impotence after TURP. Two patients in the TUNA cohort reported urinary incontinence. One man had stress urinary incontinence during treatment for metastatic lung cancer 30 months after TUNA and the

other had urge incontinence, a sign of bladder dysfunction and not sphincteric dysfunction, 1 month after TUNA. The incontinence rate in the TURP group exceeded the published incidence in current literature. This was likely due to the questionnaire used to report incontinence in this study. Any episode of urgency or stress incontinence occurring at any time during the study was recorded as incontinence for that patient. This likely led to falsely elevated incontinence rates. The 1-year data on this cohort of patients indicates a 3.6% incidence of incontinence and it more accurately reflects incontinence as a result of the procedure.<sup>9</sup> Nine of 65 of TUNA cases (14%) required further intervention for BPH symptoms and went on to TURP.

When comparing the treatment results of TUNA and TURP, TURP results remained superior throughout the study course (table 2). It is not surprising that TURP delivered better results than TUNA. TURP is a more invasive treatment, in which the majority of adenomatous tissue is directly excised, resulting in the superior relief of bladder outlet obstruction. However, the trade-off of greater improvement in the evaluated parameters associated with TURP was a greater risk of side effects.

The equipment used in this study was recently updated to a more technologically advanced and user-friendly version. The power generator is now computer driven and it adjusts power output automatically based on tissue temperature and impedance. As a result, tissue heating occurs more rapidly and evenly, and it can be done in a shorter time (3 minutes per site). The updated hand piece has temperature sensors at the needle tip instead of at the insulating sheaths. These sensors demonstrate consistent heating to 100C to 110C at the core of each lesion. The optics of the hand piece have also been improved, so that direct visualization of needle placement is now possible.

CONCLUSIONS

TUNA is a minimally invasive treatment option for LUTS secondary to BPH that can be performed safely and with good

durability of improvement at up to 5 years of followup. While improvement in the TURP arm was superior to that in the TUNA arm, TUNA had a lower risk of adverse events. In appropriately selected patients who have bothersome voiding symptoms due to BPH TUNA is an attractive treatment option.

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