



TITLE: TRANSURETHRAL MICROWAVE THERMOTHERAPY FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

AUTHOR: Leah Karliner, MD, MAS
Assistant Professor of Medicine
Division of General Internal Medicine
Department of Medicine
University of California San Francisco

PUBLISHER: California Technology Assessment Forum

DATE OF PUBLICATION: 10/28/2009

PLACE OF PUBLICATION: San Francisco, CA

DRAFT



TRANSURETHRAL MICROWAVE THERMOTHERAPY FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum is requested to review the scientific evidence for the use of Transurethral Microwave Thermotherapy for the Treatment of Benign Prostatic Hyperplasia, with a particular question of difference in efficacy dependent on prostate size.

BACKGROUND

Benign prostatic hyperplasia (BPH) and resultant lower urinary tract symptoms are very common, with 60% of 60-69 year old US men reporting at least one symptom (nocturia, incomplete emptying or hesitancy), and 75% of men 70 years or older reporting at least one symptom.¹ In a primary care clinical setting, 30% of men over 50 report moderate to severe symptoms, with two-thirds of these men reporting being bothered by their symptoms.² Oral medication with alpha1-blockers or 5alpha-reductase inhibition are considered first line treatment of bothersome symptoms.³ For those men at highest risk of symptomatic progression (large prostate, poor peak flow rate, high post-void residual), dual therapy with both classes of medication may be indicated.⁴ Not all men achieve adequate response to medical treatment for BPH, however, and many go on to have a more invasive treatment. The most common surgical treatment to which all other invasive treatments are compared is transurethral resection of the prostate or TURP. While TURP is considered very effectively for rapid symptom improvement and for its persistent effects, it requires hospitalization, carries the risks of anesthesia, bleeding, urethral scarring and erectile dysfunction (ED).⁵ Thus, there has been an effort to develop minimally invasive interventions to treat symptomatic BPH. The most prominent of these is Transurethral Microwave Thermotherapy or TUMT.

TUMT is an outpatient procedure requiring topical anesthesia, oral analgesics and rarely sedation. It involves the positioning of a microwave antenna within the prostate after introduction via a urinary catheter. Early (low energy) TUMT heated intraprostatic temperatures to 40-45°C. More

recent practice is to use high energy TUMT which heats the prostate above 45°C to temperatures up to 70°C, while at the same time using urethral cooling to keep the urethral temperature below 45°C.⁶ The Cochrane Collaboration published a systematic review on the topic in 2009 and concluded that TUMT was a reasonable alternative to TURP and alpha-blockade, however TURP was more clinically effective.⁷ We undertook a similar review of the evidence, paying particular attention to reported prostate size in the trials.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

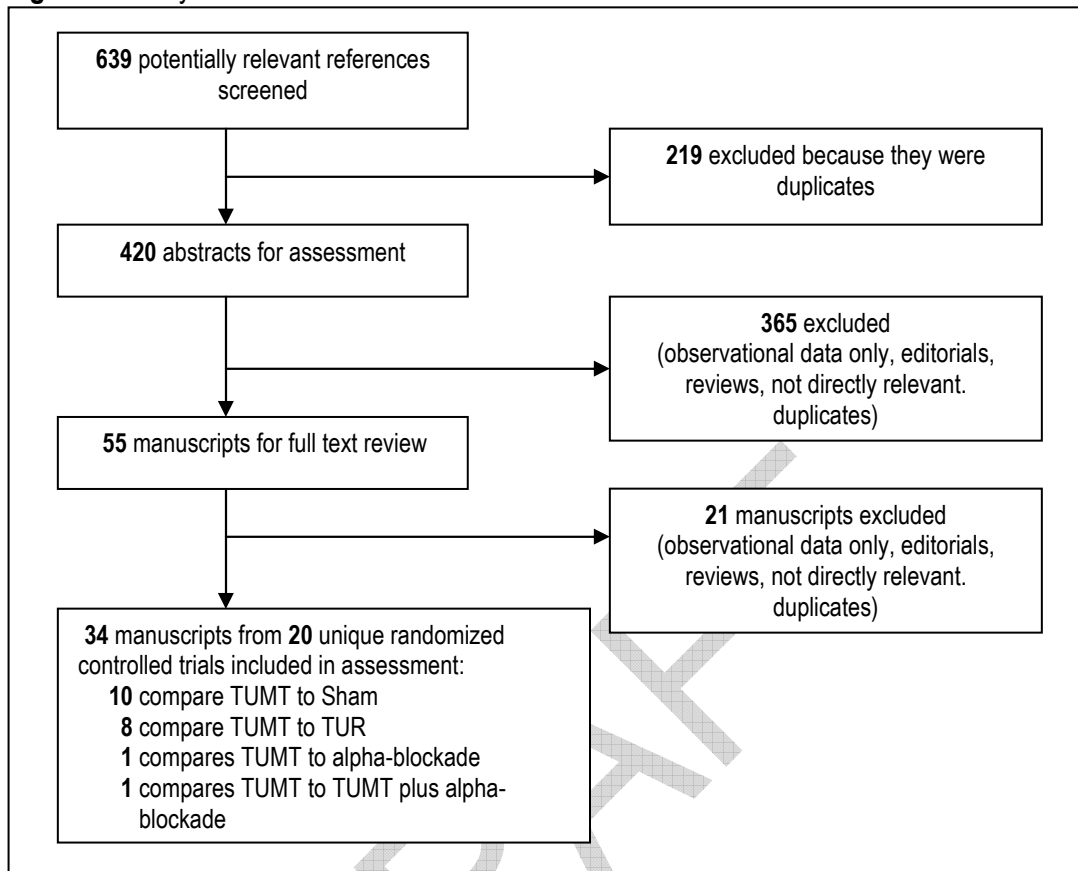
There are many manufacturers of devices for this technology. All have received approval for marketing through the FDA Premarket Approval (PMA) process.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline, Embase, and Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched for relevant references through August 2009. (See appendix for search terms) Of 420 potentially relevant citations, we found 34 papers from 20 unique randomized controlled studies (RCT) to include in this assessment. (See Figure below for study selection details) Of these 20 studies, 10 were RCTs of TUMT versus a sham control,⁸⁻²⁴ eight were RCTs of TUMT versus transurethral resection of the prostate (TURP),²⁵⁻³⁸ one was an RCT of TUMT versus alpha-blockade,^{39, 40} and one was an RCT of TUMT versus TUMT plus alpha-reductase inhibition.⁴¹

Figure 1: Study Selection



Level of Evidence: 1, 2
TA Criterion 2 is met.

TA Criterion 3: The technology must improve net health outcomes.

TUMT vs. Sham Control (Table 1)

All ten of the RCTs comparing TUMT to a sham control - in which the patients receiving the sham intervention underwent instrumentation similar to the actual intervention without the application of microwave thermotherapy – were small. Most reported results at three to six months after the intervention. One reported five-year follow-up; however this was on a very small subset of the original participants and an overall extremely small number of patients (n=15).²² Among the ten studies, eight different thermotherapy devices were used. Although not all of the studies stated prostate size/volume as an inclusion or exclusion criterion, those that did had varying criteria,

including prostates between 30-80grams,^{8,9} 30-100mL,¹⁰ 25-100mL,²¹⁻²³ ≤50g,¹⁴ ≤100g,¹⁸ or simply excluding those patients with enlarged or predominantly enlarged median lobes.^{15-17, 19, 20, 24} On the whole it does appear that the included patients had moderately severe obstructive symptoms based on low peak flow rates and high scores on symptom scales, but not so severe as to cause post-void residual volumes greater than 350mL. Not all studies listed their exclusion criteria; however, among those that did, there was apparent uniformity in excluding patients with prostate cancer, prostatitis, urethral stricture, intravesical pathology such as stones or mass, neurogenic bladder dysfunction, active urinary tract infection, prior prostate surgery, coagulopathy, metallic implant or cardiac pacemaker, or a short prostatic urethra (<25mm).

In all ten studies the sham group showed significant improvement from baseline in both obstructive symptoms, as measured on a variety of different validated symptom scales, as well as on urodynamic measures (usually peak flow rate) when studied. All but three of the studies^{10, 19, 24} demonstrated significantly greater improvement in obstructive symptoms for the TUMT group than for the sham group. However, differences in improvement of urodynamics varied across studies. In one of the higher quality studies which recruited from multiple centers that had 12-month follow-up, reported their loss-to follow-up rate, and conservatively treated those lost to follow-up as “non-responders”, there was no difference in peak flow rate improvement between TUMT and sham treated patients.^{8,9} However, in another reasonably high quality study which used double blinding – neither patients nor physicians evaluating the outcomes were aware of study assignment – investigators reported a substantially higher proportion of the TUMT group with a significant increase in peak flow rate compared to the sham group (58% vs. 27%; $p<.01$).¹³ Of the three negative studies, one had unclear inclusion criteria for obstruction,²⁴ another did not present the baseline data by treatment group and thus it is not possible to assess the adequacy of randomization.¹⁹ The third negative study was reasonably large (n=200 overall, although the number in each group is unclear), was only single blinded (patients).¹⁰

Table 1. Published Randomized Controlled Trials of TUMT vs. Sham Control. N=10 Unique Studies

Study	Participants / prostate weight or volume / other inclusion criteria	Device / max tissue temperature	Results	Quality Comments (single or multi-center, randomization, blinding, follow-up)
Abbou 1994, 1995	TUMT n=66; Sham n=31 >age 50 Prostate 30-80g Voiding difficulty ≥3 months	Thermex II Prostcare BSD-50 / 45°C	TUMT 50% decrease Madsen score vs. Sham 17% decrease (p<.01) No difference in Peak flow rate change (14% vs. 17%).	Recruitment from 7 centers; single treatment center. TUMT group had somewhat lower Madsen Score and residual volume at baseline. 12-month follow-up. Withdrawals (17% TUMT; 38% sham) all treated as non-responders.
Albala 2002	N=200; “randomized 2:1 TUMT:Sham” Age 50-80 Prostate volume 30-100mL AUA symptom score >13 Bother score > 11 Peak flow rate <12mL/s	TherMatrix TMx-2000 / 50-55°C	TUMT AUA symptom score decreased from 22.5 to 12.4 vs. Sham from 22.8 to 17 at 3 months (“p>.05”; actual p-value not given)	Treatment in 7 offices. Patients blinded. After 3 months allowed cross-over to treatment group. Follow-up for treatment group only for 12 months.
Bdesha 1993, 1994	42 randomized, 2 lost to follow-up. TUMT n=22; Sham n=18 WHO symptom score >14 Residual volume ≥50 or peak flow rate <15mL/s Large glands (>40mm) excluded	Leo Microthermer / 42-45°C	TUMT group 82% responded vs. Sham 17% (p<.001)	Single center. Patients, investigator and evaluators blinded. 3-month follow-up.
Blute 1996	TUMT N=78; Sham N=37 Madsen symptom score >8 Residual volume 100-200mL Peak flow rate <10 Prostate length 3.5-5cm	Prostatron / temperature not given	TUMT 58% increase in peak flow vs. Sham 27% (p<.01) TUMT 55% decrease in Madsen score vs. Sham 28% (p<.001)	Patients and evaluating physicians blinded. 3-month follow-up. Too much loss to follow-up for 12-month outcomes.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

			TUMT 3.2% increase in residual volume vs. Sham 3.7% (p>.05)	
Brehmer 1999	N=44: TUMT30min =14 TUMT 60min=16 Sham=14 Peak flow rate <12mL/s Prostate weight ≤50g	ECP / 46°C	ICS symptom questionnaire no significant difference between groups. Improvement in both TUMT groups (compared with sham) in flow rate, daytime and nocturnal frequency.	Patients blinded; no mention of evaluator or investigator blinding. Single site; underpowered study. 4-month follow-up
Larson 1998	Randomized 3:1 TUMT N=125 Sham N=44 AUA symptom score ≥ 9 Peak flow rate ≤12mL/s No enlarged median lobe Prostate weight ≤100g	Urologix Targis / 44.5°C	TUMT AUA symptom scores 50% decrease at 6 months compared with sham 32% decrease (p<.01). Decrease in symptoms not significantly related to prostate volume. Percent decrease in symptoms similar for those with moderate and severe symptoms at baseline.	Multi-center recruitment and treatment – 5 centers. Double blinded. Mean prostate volume 17% greater in sham group at baseline, but AUA symptom scores not different. 6-month follow-up
Nawrocki 1997	TUMT N=38 Sham N=40 No treatment N=42 Peak flow rate <15mL/s Residual volume <350mL No enlarged middle lobe; no other mention prostate size	Prostasoft v. 2 / temp not stated	Change in minimal urethral opening pressure and in AUA symptom score not significantly different between TUMT and sham; both interventions better than no treatment.	Single site. Double blinded for two active & sham treatment groups. No standard table 1 to evaluate adequacy of randomization. 6-month follow-up.
Roehrborn 1998 Trachtenberg 1998 Tan 2005	TUMT N=147 Sham N=73 Age ≥55 AUA symptom score ≥13 Peak flow rate ≤12mL/s Prostate volume 25-100mL	Dornier Urowave / 50°C	Both groups had equally improved AUA symptom score and peak flow rates at 1 month, with further improvement at 3 months, remaining steady at 6 months for TUMT group compared to Sham (p<.05).	Multicenter trial. Double blinded. Randomization adequate. 5-year follow-up report (Tan et al 2005) is on very small subset (N=15) of original sample from a single site.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

Venn 1995	TUMT N=48 Sham N=48 Madsen score >8 "Urodynamic evidence of bladder outlet obstruction" "Predominantly lateral lobe enlargement"	Microwave Engineering Designs / 46°C	No significant difference found between treatment and sham groups on Madsen score reduction or peak flow rate at 3 or 6 months.	Single center. Single blinded. Unclear inclusion criteria. 6-month considerable differential loss to follow-up (42/48 TUMT; 20/48 Sham).
Ogden 1993 de la Rosette 1994 de Wildt 1996 Francisca 1997	TUMT N=47 Sham =46 Age >45 Madsen score > 8 Peak flow rate <15mL/s Residual volume <350mL No prominent isolated middle lobe	Neither device nor max temp stated	TUMT group with higher proportion >50% decrease in Madsen score at 3 months (62% vs. 18%; p=.002); >50% increase in peak flow rate (36% vs. 11%; p<.002); >50% decrease in post-void residual volume (49% vs. 22%; p=.002).	Two- centers. Individual results reported in Ogden & de la Rosette / Francisca; combine results reported in de Wildt. Randomization adequate. After 3-months allowed crossover of sham patients to TUMT group, so cannot make comparison after 3-months.

AUA
WHO
ICS

American Urologic Association
World Health Organization
International Continence Society

TUMT vs. TURP (Table 2)

All of the eight trials of TUMT vs. TURP were relatively small with fewer than 100 people in each group. Most were single site, with the exception of two of the more recent studies.^{34, 36-38, 42} Understandably, none of the patients were blinded to surgical assignment; however, none of the studies appear to have blinded investigators evaluating or adjudicating outcomes either. While exact inclusion criteria differed from study to study, they all included men with high symptom scores, impaired peak flow rates, moderate post-void residual volumes, medium length prostatic urethras, and varying size prostate glands. Three studies included men with any prostate volume above 30mL,^{31-33, 36} three limited to between 30-100mL,^{25, 29, 30, 34, 37, 38} and two did not state prostate size as an inclusion or exclusion criteria.^{26-28, 35} None specified a large median lobe as an absolute exclusion criterion. All studies used either the Prostatron/Prostasoft or the ProstaLund devices.

All eight studies found both TUMT and TURP to be effective at achieving clinically and statistically significantly reduced symptom scores and – with the exception of one smaller study which found no peak flow rate improvement in the TURP group²⁵ – increased peak flow rates compared to baseline. On the whole, TURP achieved lower symptom scores and higher peak flow rates than TUMT; these differences persisted at six and 12 month follow-up. For example in one of the larger trials conducted in the Netherlands with the Prostatron device by Floratos et al, the TUMT group achieved an average increase in peak flow rate from 9.2mL/s at baseline to 15.1mL/s at 12-months, compared with an increase from 7.8mL/s to 24.5mL/s in the TURP group. This effect declined somewhat for the TUMT group at 24 and 36 months to 14.5 and 11.9mL/s respectively, while it did not decline in the TURP group (23.0 and 24.7mL/s). Likewise, both groups improved in their symptom scores (mean IPSS), with a decrease for the TUMT group from 20 to 8, 9, and 12 at 12, 24 and 36 months respectively and a greater and more persistent decrease for the TURP group from 20 to 3, 4 and 3. At three years post-treatment 14 (18%) of the TUMT group had undergone another treatment for BPH, for the most part related to treatment failure; whereas, eight (12%) of the TURP group had undergone another treatment such as TURP or laser therapy, for the most part related to a complication of TURP such as ureteral stricture or bladder neck sclerosis.³¹

While the details of the results differ across studies, this study by Floratos et al is representative of the results of the TUMT vs. TURP RCT's taken together – TUMT provides symptomatic and urinary flow improvement for men with moderately severe obstructive symptoms, however not as great or as long-lasting as TURP. This seems to be similar for the Prostatron and ProstaLund devices, with the larger of the two ProstaLund device studies by Wagrell et al reporting a five-year retreatment rate of 10% for the TUMT group (both medical and surgical treatments for BPH), and of 4% for the TURP group (alpha-blockade and urethral stricture treatment).^{34, 37, 38}

DRAFT



CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

Table 2. Published Randomized Controlled Trials of TUMT vs. TURP. N=8 Unique Studies

Study	Participants / prostate weight or volume / other inclusion criteria	Device / max tissue temperature	Results	Quality Comments (single or multi-center, randomization, blinding, follow-up)
Ahmed 1997	TUMT N=30 TURP N=30 Groups matched for age Age ≥ 55 years AUA symptom score ≥12 Peak flow rate <15mL/s Residual volume<300mL Prostate Volume 25-100mL Excluded patients with prior drug treatment for BPH	Prostasoft v2.5 60 minute session/ rectal temp 43.5°C	Both groups with significant and equal decrease in AUA symptom score; TUMT 18.5 to 5.3; TURP 18.4 to 5.2). TURP with significant improvement in peak flow rate (9.5 to 14.6; p=.001); TUMT with no improvement (10.1 to 9.1; p>.05). TURP with significant improvement in post void residual volume (109.1 to 32.5; p<.001); TUMT with insignificant increase (94.4 to 104.9; p>.05).	Single site. No apparent blinding. No loss to follow-up. 6-month follow-up.
D'Ancona 1997, 1998	TUMT N=31 TURP N=21 Age ≥45 years Prostate volume 30-100mL Prostate length 25-50mm Madsen score ≥8 Peak flow rate ≤15mL/s Residual volume≤300mL	Posatron v.2.5 / max temp not given / mean energy applied 152kJ	Both groups had improvement in symptom scores and peak flow rate at three months which then stabilized at 6-months without further change at 1 year and slight increase at 2.5 years, with TURP group consistently doing a little better than TUMT group. TURP group 78% had 50% improvement in symptom scores vs.68% of TUMT group (no p-value given); similarly 100% TURP group had improvement in uroflowmetry vs. 68% TUMT group (no p-value given).	Single site. No apparent blinding. Randomization adequate. At 12-month follow-up TUMT group 27/31; TURP group 27/21. At 2.5 year follow-up TUMT group 17/31; TURP group 12/21. In TUMT group, 2 had undergone TURP at 6-month f/u and 4 more had undergone TURP at 2.5 year follow-up.
Dahlstrand 1993, 1994, 1995	TUMT N=39 TURP N=44	Prostatron / 44.5°C	TUMT and TURP groups with equal and significant reduction in Madsen symptom score and residual volume at	Single site. Randomization blinded but no other mention of blinding.



CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

	<p>Age ≥45 years Prostate volume not stated Prostate length 35-50mm Madsen score >8 Peak flow rate <15mL/s Residual volume ≤350mL</p>		<p>8 weeks, with significantly more improvement in the TURP group at 3, 6, 12 and 24 months.</p> <p>TUMT and TURP groups both with significant improvement in peak flow rate at all time periods; TURP group with significantly greater improvement than TUMT group at all time periods.</p>	<p>Minimal loss to follow-up over 2 years.</p>
<p>Francisca 1999, 2000</p>	<p>TUMT N=74 TURP N=73</p> <p>Age ≥45 years Prostate volume ≥30mL Prostatic urethra length ≥25mm Madsen score ≥8 Peak flow rate <15mL/s Residual volume ≤350mL</p>	<p>Prostasoft 2.5 / rectal temp 43.5°C</p>	<p>Madsen score improved for both groups, but more for TURP compared to TUMT at 1 year (87% improvement vs. 63%; no p-value given). Peak flow rate results were similarly improved for both groups, but more for TURP.</p> <p>Both groups experienced improvement in QOL overall, with no significant difference in the total score between groups. TURP group improved significantly more on both general and specific perception of urinary difficulties scale (p<.01 for both).</p> <p>TUMT group with more ejaculation associated with orgasm at 3 and 12 months compared with TURP group (67% vs. 37% at 12 months; p=.006). TUMT group more satisfied with sexual functioning at 3 months than TURP group (55% very satisfied vs. 26%; p=.02)</p>	<p>Single site. No mention of blinding. Randomization adequate.</p> <p>Excluded patients in both groups with poor outcomes: in TUMT group 8 patients excluded, 3 of whom had adverse outcomes & received surgical treatment; in TURP group 17 patients excluded, 2 of whom had adverse outcomes & received further treatment.</p> <p>Not clear that QOL questionnaire had been validated previously; although reliability data is given for this study.</p>



CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

<p>Floratos 2001</p>	<p>TUMT N=78 TURP N=66</p> <p>Age ≥45 years Prostate volume ≥30mL Prostatic urethra length ≥25mm Madsen score ≥8 Peak flow rate <15mL/s Residual volume ≤350mL</p>	<p>Prostatron / temp not stated, but average energy delivered 140kJ</p>	<p>Both groups with significant improvement on I-PSS, QOL, peak flow rate, with more improvement in the TURP group on all parameters at 1, 2, and 3 years. Additionally, while some effect was maintained for 3 years in both groups, improvement in the TURP group was more persistent. No p-values were given for comparison between groups.</p>	<p>Single site. No mention of blinding. Randomization adequate.</p> <p><u>During 36 month follow-up</u> TUMT group: 14 underwent another treatment usually related to treatment failure, 7 lost to follow-up; TURP group 8 underwent another treatment usually related to a complication of TURP, 11 lost to follow-up</p>
<p>Nielsen 2002</p>	<p>TUMT N=46 TURP or TUIP N=24 (ILC N=48)</p> <p>Age ≥50 years Prostate volume not stated Prostatic urethra length ≥25mm I-PSS ≥7 Peak flow rate ≤12mL/s Residual volume ≤350mL</p>	<p>Prostasoft v2.0 and v2.5 / temp not stated</p>	<p>All groups had significant improvement on I-PSS at 1, 3, and 6 months, with significantly more improvement in TURP group at 1 and 3 months and equal improvement at 6 months.</p> <p>All groups had significant improvement in peak flow rate, with the TURP group achieving the highest flow rates, significantly higher than TUMT group at 6 months.</p>	<p>Single site. No mention of blinding. Randomization adequate. Intention to treat analysis; one patient randomized to TUMT inadvertently had a TURP; one patient randomized to TURP declined surgery. 2 patients randomized to TURP were excluded due to diagnosis of prostate cancer. 6-month follow-up.</p>



CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

<p>Schlein 2006</p>	<p>TUMT N=61 TURP or prostate enucleation N=59</p> <p>Age ≥45 years Prostate volume >30mL Prostatic urethra length ≥35mm Residual volume ≤300mL Indwelling catheter /intermittent catheterization for ≥1 month</p>	<p>ProstaLund CoreTherm /</p>	<p>The majority of both groups were catheter free at 3 months with no significant change at 6 months (TUMT 79% vs. TURP 88% at 6-months; p=.2).</p> <p>Mean IPSS scores for both groups were in the mild symptom range at 3 and 6 months, with scores for the TURP group being significantly lower than the TUMT group; however no baseline scores are given and improvement from baseline is not reported.</p>	<p>Multisite. No mention of blinding. No traditional Table 1 to assess randomization adequacy. 12 of the TUMT patients had prostate volumes >100mL at study entry. 6-month follow-up.</p>
<p>Wagrell 2002, 2004</p>	<p>TUMT N=100 TURP N=46</p> <p>Age ≥45 years Prostate volume 30-100mL Peak flow rate <13mL/s Residual volume ≤300mL I-PSS ≥13</p>	<p>ProstaLund CoreTherm/ 55°C</p>	<p>Both groups improved significantly, with an increase in peak flow rate and decrease in IPSS score at 3 months; these improvements persisted at 12 months. There was no statistical difference between the two groups.</p> <p>For those remaining in the study at 2, 3 and 5 years: Peak flow rate improvement persisted at 2, 3, and 5 years for both groups. The TURP had slightly higher rates, but the difference was not statistically significant at any time point (at 5-years TUMT 11.4mL/s vs. TURP 13.6mL/s; p=0.2) Results were similar for decrease in IPSS.</p> <p>Retreatment: at 5-years, 10% of the</p>	<p>Multisite. No mention of blinding Randomization adequate.</p> <p>Utilized a wash-out period of 6-weeks for alpha-43cptom blockers or finasteride.</p> <p>Dropout: 154 initially randomized; 5 TURP group and 3 TUMT group withdrew prior to treatment 2-year results reflect 79/100 TUMT and 39/46 TURP groups. 3-year results reflect 69/100 TUMT and 36/46 TURP groups. 5-year results reflect 62/100TUMT and 34/46 TURP groups.</p> <p>Standard procedure of indwelling catheter x 14 days after TUMT & 3-7 days after TURP Individualized treatment time based on temperature and estimated coagulation necrosis.</p>



CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

			TUMT group had undergone additional BPH treatment – medical & surgical; 4% of the TURP group had undergone additional treatment including 1 alpha-blocker and 1 urethral stricture treatment.	
--	--	--	---	--

QOL
I-PSS

Quality of life
International Prostate Symptom Scoree

DRAFT

Adverse Events in the TUMT vs. TURP trials (Table 3)

A review of the adverse events in the TUMT vs. TURP RCTs demonstrates that both the early and late adverse effects are greater with TURP. In particular, there is higher risk with TURP of blood loss, hematuria, urethral stricture, meatal stenosis, bladder neck sclerosis and sexual side effects including retrograde ejaculation and erectile dysfunction. There is little to no report of these side effects occurring anew after the procedure in the TUMT group. There is very little report of incontinence in either group. TUMT, on the other hand, seems to confer more early risk of urinary tract infection, irritative voiding symptoms and longer-post-procedure indwelling catheter times. All studies gave prophylactic antibiotics at the time of the procedure and for variable lengths of time post-procedure for the TUMT groups.

Table 3. Adverse events reported in the TUMT vs. TURP RCTs.

Study	TURP adverse events	TUMT adverse events
Ahmed 1997	Blood transfusions in 4 patients; 4-week indwelling catheters 2 patients; severe UTI 1 patient; mild UTI 2 patients; meatal narrowing 2 patients; bladder neck stenosis 1 patient. Sexual dysfunction: 4/19 sexually active men with ED; 12/19 with retrograde ejaculation.	Immediate post-procedure worsening of symptoms & dysuria; blood stained urethral discharge & constipation x 24 hours. All self-cath – 3 required indwelling catheters; severe UTI 1 patient Sexual dysfunction: 4/18 sexually active men with retrograde ejaculation. No ED.
D’Ancona 1997, 1998	Average hospital admission days = 4. Indwelling catheter 4-5 days 4% UTI 19% Irritative voiding symptoms 14% hematuria requiring treatment No mention of sexual side effects	No hospital admissions Indwelling catheter 6-35 days 16% UTI 29% Irritative voiding symptoms 0 hematuria requiring treatment No mention of sexual side effects
Dahlstrand 1993, 1994, 1995	3 patients with post-operative bleeding requiring re-operation 4 patients with UTI 3 patients with dysuria 2 patients with urethral strictures 2 patients with meatal stenoses 4 new cases of retrograde ejaculation; no ED	5 patients with UTI 5 patients with dysuria No new cases of retrograde ejaculation; no ED
Francisca 1999, 2000	2 patients with urethral stricture requiring urethrotomy Sexual side effects in results Table 2 No peri-procedure events reported	2 patients with persistent urinary retention treated with further surgery 1 patient with urethral stricture requiring urethrotomy Sexual side effects in results Table 2 No peri-procedure events reported

Floratos 2001	2 deaths of “unrelated cause” 3 patients with bladder neck sclerosis 2 urethral strictures 1 stress urinary incontinence No periprocedure events reported	2 deaths of “unrelated cause” No periprocedure events reported
Nielsen 2002	<u>Early</u> 2 (9%) patients had blood loss requiring transfusion 3 (14%) patients had UTI “re-retention” in 1 (5%) of patients No persistent retention after treatment <u>Late</u> 1 (5%) patient with urethral stricture 1 (5%) patient with stress incontinence Sexual 7 (50%) patients with retrograde ejaculation 1 (14%) sexually active patient with ED	<u>Early</u> No blood transfusions 14 (30%) had UTI “re-retention” in 3 (7%) of patients Persistent retention in 1 (2%) of patients <u>Late</u> No urethral stricture No stress incontinence Sexual 6 (22%) patients with retrograde ejaculation 2 (9%) sexually active patients with ED
Schlein 2006	Overall 22% with UTI 1 patient with serious UTI 1 patient with hematuria 1 patient with bleeding 1 patient with bladder neck sclerosis 1 patient with stroke	Overall 33% with UTI 1 patient with hematuria
Wagrell 2002, 2004	Serious 4 patients with hematuria 1 patient with UTI 1 patient with TURP syndrome 1 patient with urosepsis 1 patient with clot retention Mild 13% with micturition urgency 13% with urinary retention 20% with UTI 39% with hematuria 11% with impotence 13% with transient incontinence	Serious 1 patient with hematuria 1 patient with urine retention Mild 37% with micturition urgency 19% with urinary retention 18% with UTI 13% with hematuria 6% with impotence 3% with transient incontinence

UTI Urinary tract infection

TUMT and Alpha-blockade/Alpha-reductase inhibition

A single trial has compared TUMT (N=51) to medical management (N=52) with an alpha-blocker medicine.^{39, 40} Inclusion criteria were similar that that in the TUMT vs. TURP trials. This study used the Targis device and compared it to oral medication treatment with 5-10mg of terazosin and found that while the initial response (first two weeks) was greater for alpha-blockade, there was equal

response at six weeks, and the improvement was greater for TUMT by 12 weeks. TUMT achieved at least 50% improvement in symptom score (IPSS) and peak flow rate for a much greater proportion of patients than did alpha-blockade at six months (for IPSS 78.4% vs. 32.7%; for peak flow rate 64.7% vs. 9.6%; $p < .0005$ for both comparisons). This difference appeared to be sustained at 18 months. The same authors conducted a trial comparing TUMT to TUMT plus alpha-reductase inhibition with tamsulosin to evaluate whether alpha-blockade could accelerate the improvements resulting from TUMT.⁴¹ This study of 81 patients found that addition of prophylactic tamsulosin 0.4mg/day two weeks prior to TUMT and continuing for six weeks after TUMT improved symptom scores (IPSS) but not peak flow rates at two and six weeks post-procedure. Both groups achieved equal improvement at 12 weeks. The symptomatic improvement for the TUMT plus tamsulosin group was already present at the time of the TUMT procedure, indicating that it was likely independent of and not additive to the effect of TUMT.

TA Criterion 3 is met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

As noted above in the discussion of the TUMT vs. TURP trials, compared to the gold-standard of TURP, TUMT is somewhat less effective with somewhat less sustained improvements. However, TUMT also is an outpatient procedure that does not require parenteral anesthesia and which poses fewer serious short-term risks and long-term adverse side-effects than TURP. Thus, the benefits TUMT does attain are done so with less risk.

TA Criterion 4 is met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

While most of the studies conducted to date have been at single centers, there have been many observational studies and RCTs conducted throughout the United States and Europe (primary the Netherlands) in outpatient surgical centers. It appears that this procedure, while like any procedure requires training, is relatively simple and many of the operative dependent issues (e.g. maximum temperature applied) are controlled by software in the newer devices.

TA Criterion 5 is met.

CONCLUSION

In summary, while somewhat inconsistent in inclusion criteria, outcome measures and quality, the bulk of the studies comparing TUMT to sham-TUMT demonstrate clinical improvement at three and six months for men with moderately severe obstruction due to BPH that is above and beyond a placebo effect. In addition, the studies comparing TUMT to TURP demonstrate that TUMT provides symptomatic and urinary flow improvement for men with moderately severe obstructive symptoms, however not as great or as long-lasting as TURP. This seems to be similar for the two devices used in these trials (Prostatron and ProstaLund). However, TUMT also is an outpatient procedure that does not require parenteral anesthesia and which poses fewer serious short-term risks and long-term adverse side-effects than TURP. Thus, the benefits TUMT does attain are done so with less risk. There is some additional data indicating that prophylactic alpha-blockade prior to TUMT and in the early post-procedure period provides improved symptomatic relief in the first few months after TUMT when irritative bladder symptoms and need for catheterization are most common. It remains unclear if TUMT is equally effective for men with very large prostates (larger than 100mL or 100g) as for men with smaller prostates. While some of the trials of TUMT vs. TURP may have included a small number of men with very large prostates, they were underpowered to examine this issue, and none of the trials with sham TUMT included this group.

DRAFT RECOMMENDATION

It is recommended that transurethral microwave thermotherapy *meets* CTAF criteria 1-5 for safety, effectiveness and improvement in health outcomes for the treatment of benign prostatic



hyperplasia in men with moderately severe obstructive symptoms and prostate volume of 30-100mL, with no history of prostate procedures, and without prostate cancer, .

October 28, 2009

This is the first assessment of this technology to be reviewed by CTAF

DRAFT

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center has not conducted a formal assessment of this technology.

Centers for Medicare and Medicaid Services (CMS)

No specific National Coverage Decision regarding this technology was found in a search of the CMS web site.

California Urological Association (CUA)

The CUA has provided an opinion regarding the use of this technology. A representative is not available to attend the meeting.

American Urological Association (AUA)

The AUA is in the process of updating its guideline and expects publication in 2010.

ABBREVIATIONS USED IN THIS REVIEW

BPH	Benign prostatic hypertrophy
ED	Erectile dysfunction
TUMT	Transurethral microwave thermotherapy
FDA	Food and Drug Administration
PMA	Pre-market approval
DARE	Database of Abstracts of Reviews of Effects
RCT	Randomized controlled trial
TURP	Transurethral resection of the prostate
AUA	American Urologic Association
WHO	World Health Organization
ICS	International Continence Society
QOL	Quality of Life
I-PSS	International prostate symptom score
UTI	Urinary tract infection

APPENDIX: Search strategy

PubMed:

Search	Most Recent Queries	Time	Result
#16	Search #10 OR #15	19:09:26	295
#15	Search #11 AND #13 AND (in process[sb] OR publisher[sb] OR pubmednotmedline[sb]) AND eng[la]	19:09:03	21
#13	Search microwave* OR thermotherap* OR tumt OR microwave thermal* OR minimally invasiv*	19:08:08	43849
#11	Search prostatic hyperplas*[ti] OR prostatic hypertroph*[ti] OR bph[ti]	19:06:06	5246
#10	Search #8 NOT #9	19:03:24	274
#9	Search #8 Limits: Animals	19:03:06	24
#8	Search #5 OR #6 AND ENG [LA]	19:01:34	298
#7	Search #5 OR #6	19:01:23	302
#6	Search #3 AND TREATMENT OUTCOME[MH] AND FOLLOW-UP STUDIES[MH]	19:01:14	51
#5	Search #3 AND #4	19:00:32	285
#4	Search Limits: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Comparative Study, Consensus Development Conference, Consensus Development Conference, NIH, Controlled Clinical Trial, Evaluation Studies, Multicenter Study, Research Support, N I H, Extramural, Research Support, N I H, Intramural, Research Support, Non U S Gov't, Research Support, U S Gov't, Non P H S, Research Support, U S Gov't, P H S, Technical Report, English	19:00:12	5820465
#3	Search #1 AND #2	18:40:04	709
#2	Search hyperthermia, induced[mh] OR microwaves[mh] OR diathermy[mh] OR thermotherapy[tiab] OR tumt[tiab] OR microwave thermal* OR (minimally invasive* AND (microwave OR microwaves OR thermotherap* OR thermal))	18:39:51	28414
#1	Search prostatic hyperplasia/therapy OR prostatic hyperplasia[majr]	18:37:26	12430

Embase

Search Queries

Access the EMBASE.com [Info site](#) if you have questions about this message or other features of this service. Please do not reply to this email.

No. Query	Results
#16 #13 OR #14 OR #15	245
#15 #10 OR #11 AND (random*:ab,ti OR systematic:ab,ti)	110
#14 #10 OR #11 AND 'treatment outcome'/exp AND ('clinical	139

	study'/exp OR 'major clinical study'/exp OR 'controlled study'/exp)	
#13	#10 OR #11 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)	115
#12	#10 OR #11	585
#11	#8 NOT #9	574
#10	#3 AND #6 AND [english]/lim AND [animals]/lim AND [humans]/lim	11
#9	#3 AND #6 AND [english]/lim AND [animals]/lim	30
#8	#3 AND #6 AND [english]/lim	604
#7	#3 AND #6	804
#6	#4 OR #5	21267
#5	'microwave radiation'/de OR 'microwave radiation' OR 'thermotherapy'/de OR 'thermotherapy' OR 'tumt'/de OR tumt OR 'microwave thermal' OR ('minimally invasive' AND (microwave* OR thermotherap* OR thermal))	21267
#4	'transurethral microwave thermotherapy'/exp	289
#3	#1 OR #2	15441
#2	'prostate hypertrophy'/exp/mj	14283
#1	'prostate hypertrophy'/exp/dm_su,dm_th,dm_dm	6080

EMBASE.com provides access to more than 23 million validated biomedical and pharmacological records from EMBASE and MEDLINE

Cochrane Library

#1 ([prostatic hyperplasia or prostatic hypertrophy or bph](#)) and ([microwave or microwaves or thermotherap* or tumt or \(microwave and thermal\)](#)) 104 [edit](#) [delete](#)

REFERENCES

1. Platz EA, Smit E, Curhan GC, Nyberg LM, Giovannucci E. Prevalence of and racial/ethnic variation in lower urinary tract symptoms and noncancer prostate surgery in U.S. men. *Urology*. Jun 2002;59(6):877-883.
2. Collins MF, Friedman RH, Ash A, Hall R, Moskowitz MA. Underdetection of clinical benign prostatic hyperplasia in a general medical practice. *J Gen Intern Med*. Sep 1996;11(9):513-518.
3. O'Leary MP. Lower urinary tract symptoms/benign prostatic hyperplasia: maintaining symptom control and reducing complications. *Urology*. Sep 2003;62(3 Suppl 1):15-23.
4. Trachtenberg J. Treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in relation to the patient's risk profile for progression. *BJU Int*. Jun 2005;95 Suppl 4:6-11.
5. AUA. *Benign Prostatic Hyperplasia (BPH): A Patient's Guide*: American Urological Association.
6. Rubenstein J, McVary KT. Transurethral Microwave Thermotherapy of the Prostate (TUMT). *eMedicine*; 2008.
7. Hoffman RM, Monga M, Elliot SP, Macdonald R, Wilt TJ. Microwave thermotherapy for benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2007(4):CD004135.
8. Abbou CC, Colombel M, Payan C, et al. The efficacy of microwave induced hyperthermia in the treatment of BPH: the Paris public hospitals' experience. *Prog Clin Biol Res*. 1994;386:449-453.
9. Abbou CC, Payan C, Viens-Bitker C, et al. Transrectal and transurethral hyperthermia versus sham treatment in benign prostatic hyperplasia: a double-blind randomized multicentre clinical trial. The French BPH Hyperthermia. *Br J Urol*. Nov 1995;76(5):619-624.
10. Albala DM, Fulmer BR, Turk TM, et al. Office-based transurethral microwave thermotherapy using the TherMatrx TMx-2000. *J Endourol*. Feb 2002;16(1):57-61.
11. Bdesha AS, Bunce CJ, Kelleher JP, Snell ME, Vukusic J, Witherow RO. Transurethral microwave treatment for benign prostatic hypertrophy: a randomised controlled clinical trial. *BMJ*. May 15 1993;306(6888):1293-1296.
12. Bdesha AS, Bunce CJ, Snell ME, Witherow RO. A sham controlled trial of transurethral microwave therapy with subsequent treatment of the control group. *J Urol*. Aug 1994;152(2 Pt 1):453-458.
13. Blute ML, Patterson DE, Segura JW, Tomera KM, Hellerstein DK. Transurethral microwave thermotherapy v sham treatment: double-blind randomized study. *J Endourol*. Dec 1996;10(6):565-573.
14. Brehmer M, Wiksell H, Kinn A. Sham treatment compared with 30 or 60 min of thermotherapy for benign prostatic hyperplasia: a randomized study. *BJU Int*. Aug 1999;84(3):292-296.
15. De la Rosette JJMCH, De Wildt MJAM, Alivizatos G, Froeling FMJA, Debruyne FMJ, Blute ML. Transurethral microwavethermotherapy(TUMT) in benign prostatic hyperplasia: Placebo versus TUMT. *Urology*. 1994;44(1):58-63.
16. De Wildt MJ, Hubregtse M, Ogden C, Carter SS, Debruyne FM, De la Rosette JJ. A 12-month study of the placebo effect in transurethral microwave thermotherapy. *Br J Urol*. Feb 1996;77(2):221-227.
17. Francisca EA, d'Ancona FC, Hendriks JC, Kiemeney LA, Debruyne FM, de la Rosette JJ. Quality of life assessment in patients treated with lower energy thermotherapy (Prostasoft 2.0): results of a randomized transurethral microwave thermotherapy versus sham study. *J Urol*. Nov 1997;158(5):1839-1844.
18. Larson TR, Blute ML, Bruskewitz RC, Mayer RD, Ugarte RR, Utz WJ. A high-efficiency microwave thermoablation system for the treatment of benign prostatic hyperplasia: results of a randomized,

- sham-controlled, prospective, double-blind, multicenter clinical trial. *Urology*. May 1998;51(5):731-742.
19. Nawrocki JD, Bell TJ, Lawrence WT, Ward JP. A randomized controlled trial of transurethral microwave thermotherapy. *Br J Urol*. Mar 1997;79(3):389-393.
 20. Ogden CW, Reddy P, Johnson H, Ramsay JW, Carter SS. Sham versus transurethral microwave thermotherapy in patients with symptoms of benign prostatic bladder outflow obstruction. *Lancet*. Jan 2 1993;341(8836):14-17.
 21. Roehrborn CG, Preminger G, Newhall P, et al. Microwave thermotherapy for benign prostatic hyperplasia with the Dornier Urowave: results of a randomized, double-blind, multicenter, sham-controlled trial. *Urology*. Jan 1998;51(1):19-28.
 22. Tan AH, Nott L, Hardie WR, Chin JL, Denstedt JD, Razvi H. Long-term results of microwave thermotherapy for symptomatic benign prostatic hyperplasia. *J Endourol*. Dec 2005;19(10):1191-1195.
 23. Trachtenberg J, Roehrborn CG. Updated results of a randomized, double-blind, multicenter sham-controlled trial of microwave thermotherapy with the Dornier Urowave in patients with symptomatic benign prostatic hyperplasia. Urowave Investigators Group. *World J Urol*. 1998;16(2):102-108.
 24. Venn SN, Montgomery BS, Sheppard SA, et al. Microwave hyperthermia in benign prostatic hypertrophy: a controlled clinical trial. *Br J Urol*. Jul 1995;76(1):73-76.
 25. Ahmed M, Bell T, Lawrence WT, Ward JP, Watson GM. Transurethral microwave thermotherapy (Prostatron version 2.5) compared with transurethral resection of the prostate for the treatment of benign prostatic hyperplasia: a randomized, controlled, parallel study. *Br J Urol*. Feb 1997;79(2):181-185.
 26. Dahlstrand C, Geirsson G, Fall M, Pettersson S. Transurethral microwave thermotherapy versus transurethral resection for benign prostatic hyperplasia: preliminary results of a randomized study. *Eur Urol*. 1993;23(2):292-298.
 27. Dahlstrand C, Walden M, Geirsson G, Pettersson S. Transurethral microwave thermotherapy versus transurethral resection for symptomatic benign prostatic obstruction: a prospective randomized study with a 2-year follow-up. *Br J Urol*. Nov 1995;76(5):614-618.
 28. Dahlstrand C, Walden M, Geirsson G, Sommar S, Pettersson S. Transurethral microwave thermotherapy versus transurethral resection for BPH. *Prog Clin Biol Res*. 1994;386:455-461.
 29. D'Ancona FC, Francisca EA, Witjes WP, Welling L, Debruyne FM, de la Rosette JJ. High energy thermotherapy versus transurethral resection in the treatment of benign prostatic hyperplasia: results of a prospective randomized study with 1 year of followup. *J Urol*. Jul 1997;158(1):120-125.
 30. D'Ancona FC, Francisca EA, Witjes WP, Welling L, Debruyne FM, De La Rosette JJ. Transurethral resection of the prostate vs high-energy thermotherapy of the prostate in patients with benign prostatic hyperplasia: long-term results. *Br J Urol*. Feb 1998;81(2):259-264.
 31. Floratos DL, Kiemeny LA, Rossi C, Kortmann BB, Debruyne FM, de La Rosette JJ. Long-term followup of randomized transurethral microwave thermotherapy versus transurethral prostatic resection study. *J Urol*. May 2001;165(5):1533-1538.
 32. Francisca EA, d'Ancona FC, Hendriks JC, Kiemeny LA, Debruyne FM, de La Rosette JJ. A randomized study comparing high-energy TUMT to TURP: quality-of-life results. *Eur Urol*. Nov 2000;38(5):569-575.
 33. Francisca EA, d'Ancona FC, Meuleman EJ, Debruyne FM, de la Rosette JJ. Sexual function following high energy microwave thermotherapy: results of a randomized controlled study comparing transurethral microwave thermotherapy to transurethral prostatic resection. *J Urol*. Feb 1999;161(2):486-490.

34. Mattiasson A, Wagrell L, Schelin S, et al. Five-year follow-up of feedback microwave thermotherapy versus TURP for clinical BPH: a prospective randomized multicenter study. *Urology*. Jan 2007;69(1):91-96; discussion 96-97.
35. Norby B, Nielsen HV, Frimodt-Moller PC. Transurethral interstitial laser coagulation of the prostate and transurethral microwave thermotherapy vs transurethral resection or incision of the prostate: results of a randomized, controlled study in patients with symptomatic benign prostatic hyperplasia. *BJU Int*. Dec 2002;90(9):853-862.
36. Schelin S, Geertsen U, Walter S, et al. Feedback microwave thermotherapy versus TURP/prostate enucleation surgery in patients with benign prostatic hyperplasia and persistent urinary retention: a prospective, randomized, controlled, multicenter study. *Urology*. Oct 2006;68(4):795-799.
37. Wagrell L, Schelin S, Nordling J, et al. Feedback microwave thermotherapy versus TURP for clinical BPH--a randomized controlled multicenter study. *Urology*. Aug 2002;60(2):292-299.
38. Wagrell L, Schelin S, Nordling J, et al. Three-year follow-up of feedback microwave thermotherapy versus TURP for clinical BPH: a prospective randomized multicenter study. *Urology*. Oct 2004;64(4):698-702.
39. Djavan B, Roehrborn CG, Shariat S, Ghawidel K, Marberger M. Prospective randomized comparison of high energy transurethral microwave thermotherapy versus alpha-blocker treatment of patients with benign prostatic hyperplasia. *J Urol*. Jan 1999;161(1):139-143.
40. Djavan B, Seitz C, Roehrborn CG, et al. Targeted transurethral microwave thermotherapy versus alpha-blockade in benign prostatic hyperplasia: outcomes at 18 months. *Urology*. Jan 2001;57(1):66-70.
41. Djavan B, Shariat S, Fakhari M, et al. Neoadjuvant and adjuvant alpha-blockade improves early results of high-energy transurethral microwave thermotherapy for lower urinary tract symptoms of benign prostatic hyperplasia: a randomized, prospective clinical trial. *Urology*. Feb 1999;53(2):251-259.
42. Sall M, Bruskewitz RC. Prostatic urethral strictures after transurethral microwave thermal therapy for benign prostatic hyperplasia. *Urology*. Dec 1997;50(6):983-985.