TransUrethral Microwave Thermotherapy:

An evolving technology in the treatment of benign prostatic enlargement

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An evolving technology in the treatment of benign prostatic enlargement

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van de Medische Wetenschappen

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INTRODUCTION AND OUTLINE OF THESIS

INTRODUCTION

Benign prostatic hyperplasia is a nonmalignant enlargement of the prostate that is due to excessive growth of both the glandular and stromal elements of the prostate gland. This is a very common condition in men over 40 years of age of all races and cultures and it may lead to troublesome lower urinary tract symptoms that usually result in referral to a urological clinic.[1]

Previously, the therapeutic options for symptomatic benign prostatic enlargement mainly consisted of surgical resection of the prostate. The transurethral surgical approach (TURP) has dominated prostatic surgery because of the high success rate and low morbidity obtained in the hands of experienced urologists. Although it is an effective treatment for most men, it is by no means perfect. Approximately 20-25 percent of patients that underwent surgery do not have satisfactory long-term outcome with a reoperation rate up to about 15% over an 8 year observation period.[2,3] Furthermore, there is some morbidity of this surgical intervention. The necessity for general or spinal anesthesia, possible blood transfusion (5- 10%) and infection, involves risks with a mortality rate that still amounts to about 1%.[4,5] Some degree of urinary incontinence is reported in 2-4% and the incidence of urethral strictures even amounts to 2-20% of patients.[6,7]

Due to the aging population, the costs induced by the treatment of BPH represent a substantial part of health expenses in most countries.[8] Because of these problems as well as the desire of many men to avoid surgery whenever possible, the management of symptomatic BPH is in transition. It now also includes medical management that essentially is palliative and reversible at the end of the treatment,[9-11] and several procedural and minimally invasive procedures that aim at the definite removal of tissue.[12-16] Efforts to dilate the prostatic tract by either balloon or stents have either been abandoned, or reserved for the unfit patient.[17,18]

The application of heat in prostatic disease has been advocated over a century.[19] Heat is a physical agent whose biologic effects depend on the intensity,

duration and means of application. The majority of the interventional nonsurgical modalities that have emerged the last decade, apply the thermal energy to the prostate adenoma by either the rectal or urethral route. Different heat applicators have been used, varying from laser-devices to high intensity focused ultrasound and radiofrequency. Presently, the major drawback of these options still is the necessity for anesthesia. The use of microwave as a heat source, has been extensively investigated. Pioneer microwave research efforts in the early 1980's were focused on the use of hyperthermia by applying microwave heat rectally or urethrally. It eventually became apparent that with hyperthermia the aimed temperature of 45°C or less, wasn't effective and higher temperatures were required. This led to development of transurethral microwave thermotherapy that was designed to apply microwave energy deep within lateral prostatic lobes, whilst simultaneously cooling the urethral mucosa thus enabling an outpatient based anesthesia-free procedure.[16]

The rational behind microwave thermotherapy

Microwaves comprise the 300-3000 MHz range of the appropriate electromagnetic spectrum. The entire spectrum of electromagnetic waves (X-rays, visible light, infrared) can interact with living matter, but the mechanisms of interactions are not the same on the entire frequency range. The interaction with microwaves results in the heating of biological tissue.

As microwaves propagate through biological tissue, energy is transferred to heat via electromagnetic field oscillation of free charges (electrons and ions) and by polarization of small molecules (mainly H_2O). The resulting molecular kinetic energy raises the temperature of the tissue and causes heating. The penetration of microwaves is greater in low-water content tissue (fat) than in high-water content tissue (muscle). Moreover, the higher the frequency, the less the penetration. Consequently, the depth of the penetration is dependent on the frequency and the

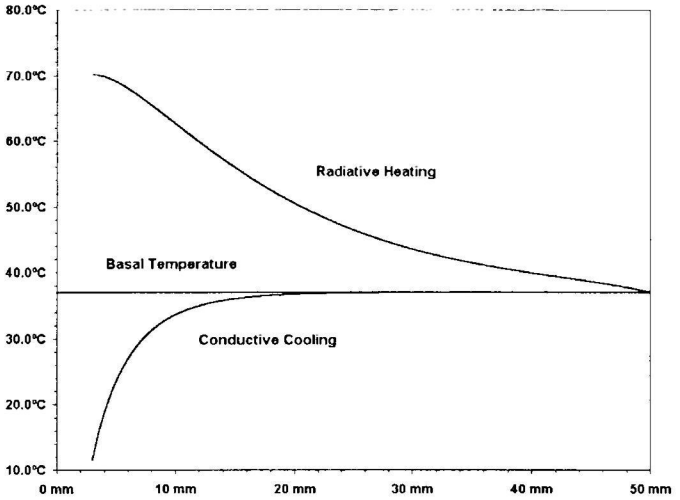
predominant type of targeted tissues, and at any time given frequency, penetration also varies with the temperature. Unfortunately, the waves are refracted, reflected, and dispersed when met with tissue inhomogeneities. Furthermore, tissue temperatures in a microwave field depend, not only on the energy extracted, but also on the thermal conduction and convection related to tissue perfusion.

With thermotherapy the transurethral route was chosen to deliver the microwave energy through a flexible applicator. A frequency of 1296 MHz was chosen, since the isothermic field shows a concentric heat distribution more or less following the anatomical borders of the transition zone of the prostate and not reaching the maximum temperature in the rectal mucosa. The goal of heating is to destroy tissue by achieving temperatures that exceed the cytotoxic threshold and induces cell death. The cytotoxic thermal threshold for prostatic adenomatous tissue is 45°C for 30 minutes.[16] However, the threshold depends on the cell type and thus when heterogenous tissue is treated, not all cells within the treated area will die. Furthermore, small capillaries are thrombosed, whereas larger vessels are spared because they are cooled by blood flow.

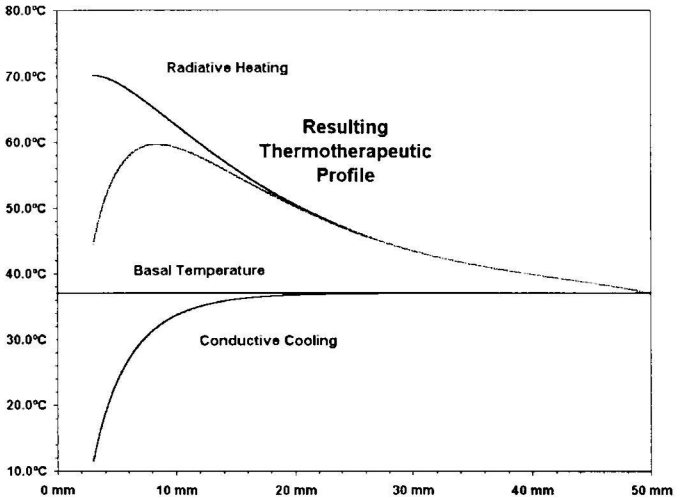
In order to destroy intraprostatic tissue at a depth of 10 to 15 mm from the urethra, the required power would raise the temperature at the urethral level to 75° to 80° C (figure 1A). Therefore, to avoid heating of the urethral mucosa, which is rich in pain receptors, the urethral temperature should be no more than 45°C, which is the thermal pain threshold, the urethra is cooled. Whereas microwave heating is depending on radiation penetrating tissue, cooling is based on conductivity which has a limited action. These two principles, radiative heating and conductive cooling, result in a temperature curve with a steep ascending slope and a progressive 'descending' slope (figure 1B). In this manner, deep within the prostate temperatures exceed the cell toxicity threshold with consequent tissue destruction, whereas the urethral mucosa remains spared. And in this way, the urethral temperatures maintain below the thermal pain threshold which enables the treatment to be performed without the need for anesthesia.

Figure 1. *Transurethral microwave therapy (TUMT) concept (x axis: distance in cm from antenna in the urethra; y-axis: temperature in °C. A) Microwave heating pattern shows the energy needed to induce deep tissue necrosis would raise temperature to 70-80°C in the urethra. B) Combination of deep radiative heating and superficial conductive heating leads to an asymmetrical temperature profile, with a steep ascending slope and a progressive descending slope.*

A



B



(Graphs courtesy of Vincent Cabane)

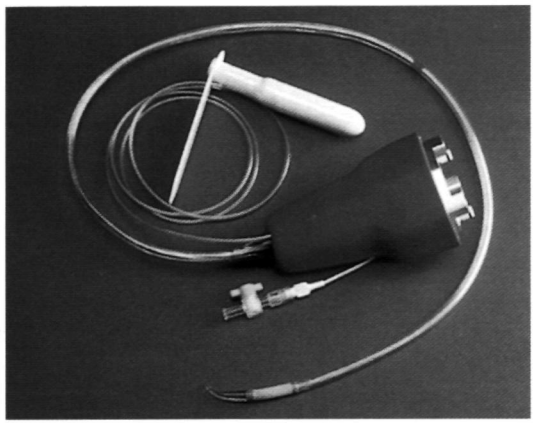
Figure 2. *The Prostatron device with treatment couch and control module*

Material and methods

The Prostatron device

The Prostatron is an integrated unit consisting of a microwave generator, a urethral cooling system, a fiberoptic temperature-monitoring system and a treatment couch (figure 2). The Prostatron is controlled by a dedicated computer software system (Prostasoft version 2.0: lower energy protocol; version 2.5: high energy protocol) operated from the separate control module. The device is used in conjunction with a disposable transurethral applicator and rectal thermometry probe (figure 3). The microwave antenna is mounted within a flexible 20F urethral applicator with a Foley balloon self-retaining device. The treatment applicator contains two channels for the circulation of the coolant. The tip of the thermosensor is positioned beneath the surface of the catheter to measure the applicator surface temperature at the hottest point of the microwave field. The antenna is positioned

Figure 3. *Microwave transurethral catheter delivery system with rectal temperature probe*



in a precise relation to the Foley balloon so that the predictable microwave field can treat the greatest volume of the prostate without compromising the external sphincter.

The integral thermometry system is of the optical fiber type, designed to measure temperature accurately within a microwave field, and is consistently accurate to 0.1°C. In addition to the urethral thermosensor, three further fibers are mounted on a rectal probe to monitor the temperature of the anterior rectal wall. The rectal thermosensors are placed at 80, 90, and 100 mm from the anal verge, positions which have been shown to indicate the maximum rectal wall temperature most reliably during treatment.

The cooling system is comprised of both a refrigeration and a heating unit providing precise control of applicator temperature during treatment. The coolant is circulated at a constant rate, although the temperature can be varied from 20° to 40°C. The microprocessor controls the power output of the Prostatron in response to preset parameters of achieved temperature within the rectal and urethral thermosensors. Multiple safety devices are incorporated to prevent the excessive or misplaced delivery of energy, and the treatment remains under the physician's control at all times. The treatment profile with temperature readings

from all four sensors (1 urethral and 3 rectal) and energy output is displayed on a video monitor and recorded by a computer for subsequent analysis.

The technique

The patient is placed on the treatment couch in supine position. After disinfecting the penis and applying lidocaine jelly transurethrally, the bladder is emptied with a 14 Ch Lofric catheter and refilled with 50 ml of saline. The sterilized treatment catheter is then inserted and the balloon inflated with 20 ml of saline and the catheter is withdrawn until the balloon is gently resting at the bladder neck. With the patient positioned in the left lateral position, the rectal temperature probe is then inserted with the temperature sensors directed towards the prostate.

After checking the catheter's correct position by abdominal ultrasound, the catheter module is connected to the Prostatron and the machine is switched on. After calibration of the temperature sensors, the physician starts the microwave power application at 20 W. The power level is increased every 2 minutes to a maximum of 60 W with Prostasoft 2.0 and 70 W with Prostasoft 2.5. The coolant temperature is kept at 20°C until the maximum power is achieved or after 20 minutes. Thereafter, the coolant temperature is increased to a maximum of 44.5°C. If the temperature in the urethral applicator sensor exceeds 44.5°C, the microwave power is stopped until it cools to 44°C. The rectal alarm is set at 42.5°C with Prostasoft 2.0 and at 43.5°C with Prostasoft 2.5. The treatment is continued for 60 minutes from the start of the microwave application. At the conclusion of the treatment, the urethral and rectal probes are removed. With the Prostasoft 2.0 protocol, patients were asked to remain in the department until satisfactory voiding had been established. In case of urinary retention or with the Prostasoft 2.5 protocol, patients received a transurethral catheter and were set up with a leg-bag and discharged home. Depending on the protocol, patients were usually seen for outpatient control one week after treatment.

The first TUMT treatments were performed in 1990. At that time the most commonly used symptom score was the Madsen-Iversen symptom score.[20] In an attempt to standardize the preoperative evaluation of patients with no absolute indication for surgery, Madsen and Iversen developed a point system in which the various symptoms and objective findings are graded according to severity. This physician guided questionnaire grades the quality of the urinary stream, straining to void, hesitancy, intermittency, sensation of bladder emptying, stress incontinence or postmicturition dribbling, and symptoms of urgency, frequency and nocturia. The symptoms are graded on a scale of 0-4 and scores are tabulated (Table 1). The total score can vary between 0 - 25 points. A Madsen-Iversen score of 8 or more has been the entry level for all the studies.

Table 1 *Madsen-Iversen Symptom score sheet*

Symptom	0	1	2	3	4
Stream	Normal	Variable	-	Weak	Dribbling
Voiding	No strain	-	Abdominal strain	-	-
Hesitancy	None	-	-	Yes	-
Intermittency	None	-	-	Yes	-
Bladder emptying	Do not know or complete	Variable	Incomplete	Single retention	Repeated retention
Incontinence	None	-	Yes (including terminal dribbling)	-	-
Urge	None	Mild	Moderate	Severe	-
Nocturia	0 - 1	2	3 - 4	> 4	-
Diuria	q > 3h	q 2-3h	q 1-2h	q < 1h	-

OUTLINE OF THESIS

All treatments for lower urinary tract symptoms and benign prostatic enlargement contain possible 'placebo' effects. In **chapter 1**, the results of a randomized placebo controlled study of transurethral microwave thermotherapy (TUMT) versus Sham are presented. It reports on three months data of one center, and the combined data at 1 year follow-up of two European centers.

The clinical results of transurethral microwave thermotherapy show a clear separation between patients who respond favorably to TUMT in both subjective and objective parameters and patients who do not respond at all. **Chapter 2** reports on a multi center international study that enlightens the differences in treatment outcome between responders and nonresponders to thermotherapy. In seventeen centers, 292 patients were included in the study retrospectively. The baseline clinical variables were correlated with variables derived from the treatment profiles.

The durability and long-term followup results of thermotherapy are presented in **chapter 3**. A total of 305 patients who underwent TUMT at two different centers, was analyzed retrospectively. Improvement in subjective and objective variables are noted over a three-year followup period. Furthermore, the fate of the patients in case of retreatment by either medical therapy or invasive intervention and possible side-effects on short and long term are also discussed.

Although symptomatic improvement after TUMT is very comparable to that achieved with a surgical resection of the prostate, the objective improvement was less pronounced. **Chapter 4** reports on the initial results of a phase II study in patients treated with high energy thermotherapy. Both multi center data on 116 patients, and one year followup data on 85 patients are presented. Not only the common study variables as symptom scores and uroflowmetry variables, but also urodynamics with pressure-flow study variables are used in these two studies.

Significant urodynamic changes after lower energy thermotherapy have

been reported in earlier studies. On the other hand the reduction of bladder outlet obstruction was not comparable to that achieved after a surgical resection of the prostate. **Chapter 5** documents the urodynamic changes of pressure-flow study parameters after high energy thermotherapy. Data of 120 patients are analyzed. Furthermore, possible selection criteria to enhance treatment outcome are identified.

Finally, in **chapter 6** the current status of thermotherapy in the complete armamentarium of treatment options for patients with lower urinary tract symptoms and benign prostatic enlargement is reviewed.

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Chapter 1

TUMT VERSUS SHAM

Based on:

JJMCH de la Rosette, MJAM de Wildt, G Alivizatos, FMJA Froeling and FMJ Debruyne.

Transurethral Microwave Thermotherapy (TUMT) in benign prostatic hyperplasia: Placebo versus TUMT.
*Urology, **40**: 58-63,1994*

MJAM de Wildt, M Hubregtse, CW Ogden, SStC Carter, FMJ Debruyne and JJMCH de la Rosette.

A 12-month study of the placebo effect in transurethral microwave thermotherapy.
British Journal of Urology, 77: 221-227, 1996

PLACEBO VERSUS TUMT

SUMMARY

A prospective, randomized placebo-controlled study was designed to exclude a placebo response in transurethral microwave thermotherapy (TUMT). During a sham procedure, the microwave applicator was installed in the urethra as in the real TUMT treatment and a complete procedure was simulated by the microwave delivery system (Prostatron). Any patient who entered this study had the option to request a second real TUMT treatment if, 3 months after the initial procedure his condition had not improved. A total of 48 patients were available for evaluation at 3 months and 28 at 6 months. The TUMT group had an average decrease of 7.3 points (from 13.2 to 5.9) in the Madsen symptom score, an average increase in flowrate of 3.4 ml/s (9.6 to 13.0), and an increase in voiding percentage of 9.6% (81.7 to 91.3). All improvements were statistically significant. In the sham group, the average Madsen score decreased from 12.1 to 8.2 points, the average flowrate decreased from 9.7 to 9.5 ml/s, and the voiding percentage increased from 80.8% to 84.3%. Only the change in symptom score was significant. In both groups, observations at the 3-month follow-up were similar to those after 6 and 12 months. Patients who had TUMT after sham treatment showed similar significant changes in symptom score and peak flow as observed in the original TUMT group. Patients who did not respond favorably to a first TUMT did not experience improvement after a second TUMT. A placebo effect, although minimal, exists. This placebo response, however, accounts for little of the observed benefit of TUMT.

INTRODUCTION

It is estimated that eventually one third of all men will require treatment for relief of symptoms due to benign prostatic hyperplasia (BPH) .[1] Surgical treatment of the prostate is effective and relatively safe. Hospitalization and anesthesia are necessary. Although the mortality rate is low, [2] morbidity is considerable, [3-6] and has prompted a search for a less morbid but equally effective treatment.[7,8]
Several minimally invasive treatments for patients with complaints related to BPH have recently been introduced.[9-11] The application of heat to the prostate has been believed to be beneficial since the earliest days of medicine. Many ingenious methods of heating the prostate have been described since the mid-19th century.[12] Only limited success was obtained because of the superficial nature of prostatic heating obtained by conduction from the urethral or rectal surface. Transurethral microwave thermotherapy (TUMT) uses a combination of transurethrally administered radiating heat energy and conductive cooling administered via the urethra. This treatment results in high-power microwave application deep in the lateral lobes, leading to irreversible cell damage of prostatic tissue without damaging the urethra. Early results of TUMT seem very promising, although a placebo effect has not yet been excluded.[13] We conducted a randomized, double-blind, placebo-controlled study In this article we will describe the results of a TUMT-sham study.

MATERIAL AND METHODS

From June 1991 to December 1992, 50 men aged 50 to 79 years (average, 63.6) with symptoms of BPH were randomized to receive TUMT or sham treatment. The major inclusion and exclusion criteria for treatment are shown in Table 1. For this study we used the Prostasoft 2.0 version. Screening included a general history,

complete physical examination, estimations of full blood count, urea, creatinine, urine microscopy, and culture. Urine cytology and prostate-specific antigen (PSA) levels were always measured in order to exclude coexisting malignancy The severity of symptoms was scored according to the Madsen FDA symptom score.[14] Uroflowmetry (peak flow Qmax) was performed twice with a minimum voided volume of 100 ml. Residual urine was measured with transabdominal ultrasound. We also computed the voiding percentage ([voided volume/bladder volume] x 100), as a measure of voiding efficiency A transrectal ultrasound of the prostate (TRUS) was performed to measure the volume of the prostate (stepwise measurement according to Hastak et al.,[15] and to determine the prostate configuration. Flexible urethrocystoscopy was used to verify patency of the urethra, and also to look for an enlargement of the middle lobe and for signs of malignancy. A minimum prostatic urethra length of 3 5 cm was required in order to be able to give treatment without risk of damage to the urethral sphincter by the microwave energy. All patients with an abnormal rectal examination, PSA values more than 10 ng/ml (Hybritech), and/or abnormal TRUS underwent biopsy.

Table 1 *Inclusion and exclusion criteria for TUMT treatment*

Inclusion Criteria	Exclusion Criteria
Prostate volume $\geq$ 30 cm^3	Prostatic carcinoma
Length of prostatic urethra $\geq$ 35	Bacterial prostatitis
Age > 45 years	Urethral stricture
Duration of symptoms > 3 months	Neurogenic bladder dysfunction
Madsen symptom score $\geq$ 8 points	Urinary tract infection
Peak uroflow $\leq$ 15 ml/s	Use of drugs influencing bladder
	History of TURP or TUIP
	Diabetes mellitus
	Isolated enlargement of the middle lobe
	Bladder residual urine > 250 ml

Patients were randomized after informed consent had been obtained. The procedure for the real TUMT treatment has been described extensively elsewhere.[13,16] If the patient was randomized to receive sham treatment, the same procedure was performed, but no microwave energy was applied. A customized sham program was run on the computer to give a simulated treatment display on the visual display unit.

At the end of the outpatient session, patients were asked to remain in the department until satisfactory voiding had been established. In the event of urinary retention a urethral catheter was inserted for 1 week. Patients were seen 1, 6, 12, 26, and 52 weeks after treatment. If the patients did not experience improvement at 3 months, a second real TUMT was administered if requested.

Statistical analysis within each group was done with the Student's t-test ($\alpha = 0.05$) while the Wilcoxon's signed rank test ($\alpha = 0.05$) was used for comparison between the groups. For evaluation of the correlation between uroflow and symptom score, the Spearman test was used.

RESULTS

The average age of the TUMT group was 64 years (range, 50 to 79) and for the sham group 63 years (range, 52 to 78). The average prostate volume, as measured with TRUS, was 51 cm^3 for the TUMT as well as the sham group. Fifteen patients received a second TUMT procedure: 11 patients in the SHAM group and 4 patients in the TUMT group.

There was no statistical difference between the two groups for any given parameter at baseline (Table 2). Forty-eight patients were available at 12 weeks for assessment and 28 at 24 weeks. One patient was lost to follow-up and 1 patient was treated by TURP.

Table 2 *Baseline characteristics*

	Mean ± SD	
	TUMT (n=25)	Sham (n=25)
Age (yr)	64.1 ± 6.0	62.7 ± 5.9
Madsen score	13 2 ± 3 4	12.1 ± 2.9
Prostatic volume	51.1 ± 15.4	51.0 ± 18.8
Voided volume (ml)	270 ± 124	260 ± 124
Residual urine (ml)	56.4 ± 37 7	64.6 ± 51 2
Voiding%	81 7 ± 12.3	80.8 ± 12.7
PSA (ng/ml)	5 4 ± 4.5	4.5 ± 3.5

A statistical analysis of the difference between the two groups can only be made at 12 weeks, because, thereafter, patients in either group were offered retreatment with definitive TUMT. The number of patients in the retreatment groups is too small for analysis before 1 year.

Table 3 shows the subjective and objective changes after treatment. For the TUMT group, a significant reduction in Madsen symptom score was shown from the average of 13.2 to 5.9 after 12 weeks (P = 0.0001), to 3.2 after 26 weeks and 3.3 after 52 weeks. At 1 year follow-up, 92% still had a reduction in the severity of symptoms of more than 50%. In the sham group, the reduction of the symptoms was less pronounced, with changes from 12.1 at the onset to 8.2 after 12 weeks, 6.8 after 26 weeks, and 9.1 after 52 weeks. Statistical evaluation after 12 weeks shows a significant reduction of symptom score (p = 0.001). After I year, 38% in the sham group still had a reduction of more than 50% in the severity of symptoms. Uroflowmetric results showed no improvement in the sham group, but in the TUMT group the average improvement after 3 months was 3.4 ml/s, which is statistically significant (p = 0.004). The voiding percentage improved in both groups, but this improvement was statistically significant (p = 0.004) only in the

TUMT group.

Comparison between the sham and the TUMT group after 12 weeks showed a statistically significant difference with regard to symptom score improvement ($p = 0.025$) and peak flow ($p = 0.019$), in favor of the TUMT group. The patients who had a TUMT treatment after sham showed similar results compared to the initial TUMT group (Table 4). However, in the four patients who had a second real TUMT after their first one, no improvement

Table 3. *Main follow-up indices after sham treatment or TUMT*

		Week				
		0	6	12	26	52
Sham	n	25	23	24	11	7
Qmax	mean	9.7	10.0	9 5	10 1	11.3
	p		0 61	0 73		
Symptom	mean	12.1	7.7	8 2	6.8	9.1
	p	0.0001	0 0010			
Voiding%	mean	80.8	84.6	84.3	87.6	90.0
	p	0 06	0 07			
TUMT	n	25	24	24	17	12
Qmax	mean	9.6	11 9	13 0	15.3	14 0
	p	0.015	0.004			
Symptom	mean	13 2	6 2	5.9	3 2	3.3
	p	0.0001	0 0001			
Voiding%	mean	81 7	88.7	91 3	93.0	86.7
	p	0.07	0.004			

was seen. The average prostate volume, as measured with TRUS, was 51 cm^3 before treatment, in the TUMT group and the sham group. No relation was found between the prostate volume and the obtained subjective and objective results.

As shown in Table 2, PSA serum concentrations were normal before treatment When measured 1 week after treatment, there was an elevation of the average PSA value to more than 25 ng/ml (range, 1 0 to 93.0). After 3 months, the PSA level returned to normal (Figs. 1 and 2)

Table 4 *Main follow-up indices of TUMT after prior sham (sham-TUMT) and TUMT after prior TUMT (TUMT-TUMT) treatment*

		Week				
		0	6	12	26	52
Sham-TUMT	n	11	11	11	8	0
Qmax	mean	8 9	13 1	14 8	15 1	-
	p		0 0019	0 003		
Symptom	mean	12 9	6 5	5 6	6 4	-
	p		0 0003	0 0019		
Voiding%	mean	82 4	83 5	84 7	88 9	-
	p		0 85	0 58		
TUMT-TUMT	n	4	4	4	3	1
Qmax	mean	8 4	9 3	7 2	8 3	8 0
Symptom	mean	13 0	6 5	7 8	8 7	9 0
Voiding%	mean	89 7	93 9	84 8	80 0	80 8

The predominant complication in the TUMT group was immediate post-treatment retention of urine in 20%. In the sham group all but one patient passed urine freely before leaving the department. Patients with retention were treated with a transurethral catheter for 1 week. All patients were free of a catheter by 6 weeks. Most patients had some hematuria for up to 3 days; there was, however, no difference between the groups.

Figure 1. *Changes in PSA level after sham treatment and TUMT*

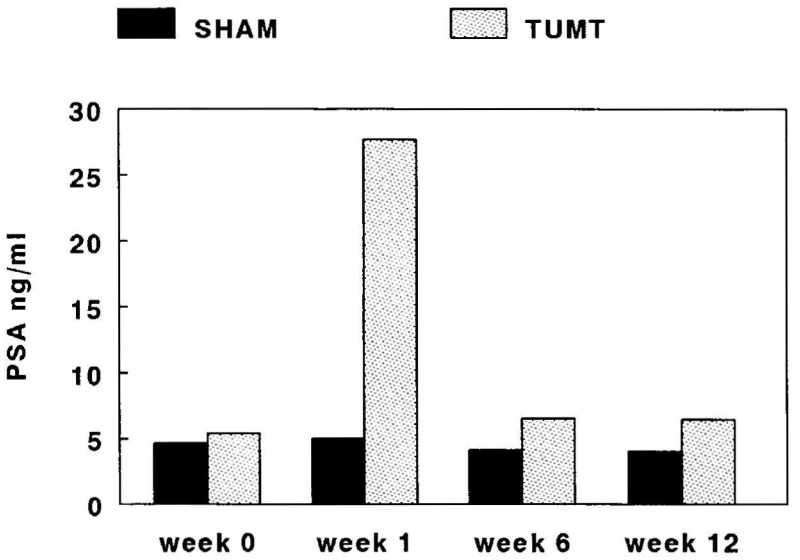
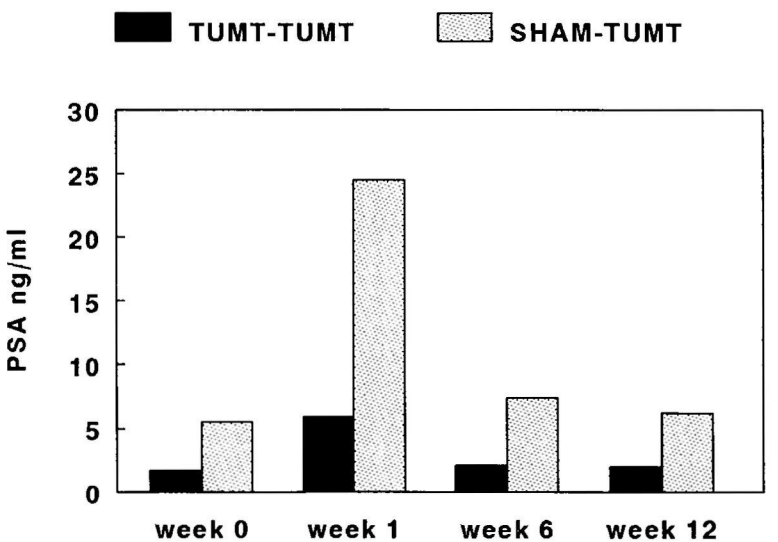


Figure 2. *Changes in PSA level after second TUMT*



DISCUSSION

Very promising changes in objective and subjective parameters after TUMT treatment were presented by Devonec to the American Urological Association (AUA) in 1990.[11] Other studies have shown a significant and sustained response.[13,21-23] However, symptoms in patients with BPH frequently improve without any explicit underlying mechanism of explanation.[18,19] There also may be an important placebo effect in device treatments, as has been shown in pharmacologic studies.[20] It is also well known that catheterization in itself may have a (temporary) beneficial effect on prostatic symptoms.[24] It has been suggested that this catheterization in itself may contribute substantially to the TUMT effect. The objective of this study was to evaluate the effect of TUMT using therapeutic temperatures within the prostate, and to compare the effects with a simulated TUMT treatment (sham).

Several controlled studies have been undertaken to describe the (placebo) effect of TUMT treatment.[11,16,21] In our study there was, as in the study of Ogden et al,[25] a significant increase in flowrate and reduction of symptom scores in the TUMT group, as well as a marked increase in the voiding percentage. However, in our study, the sham group also had a significant change in average symptom score without significant changes in peak flowrate or voiding percentage. The results of flowrate changes are compared to the changes in symptom score for each individual and shown in Figure 3. In contrast to the results of Ogden et al.,[25] a considerable placebo effect is seen in this study for the subjective parameters. Also, on an individual basis, an improvement in peak flowrate may be seen in the sham group. Overall, however, there is a more significant improvement of changes in peak flowrate and symptom score in the TUMT group. The value of the voiding percentage seems to be of more importance than the individual values of voided volume or postmicturition residual urine, and represents the index of voiding efficacy.[26] For patients receiving TUMT treatment, it is clear that the efficiency

of bladder emptying has improved, resulting in a decrease in frequency of micturition. The decrease in frequency of micturition will be reflected in the decrease in the symptom score. After sham treatment, the voiding percentage improves, although not significantly. Although there was a statistically significant improvement in symptom scores in both the TUMT and the sham patients, comparison between the two groups showed a statistically significant difference in favor of the TUMT group. Thus, TUMT gives a small placebo effect reflected in the subjective parameters.

To our surprise, only a minor but not statistically significant correlation (Spearman correlation coefficient 0.38, $p = 0.07$) could be found between the improvement of the subjective and objective parameters for the TUMT group (Fig. 3). In the sham group there was no correlation (Spearman correlation coefficient -0.04, $p = 0.86$). We do not have any clear explanation for this finding. Perhaps the items of the Madsen symptom score do not correlate that well with the objective parameters. This may result in a patient with a good subjective improvement but without a significant objective result and vice versa.

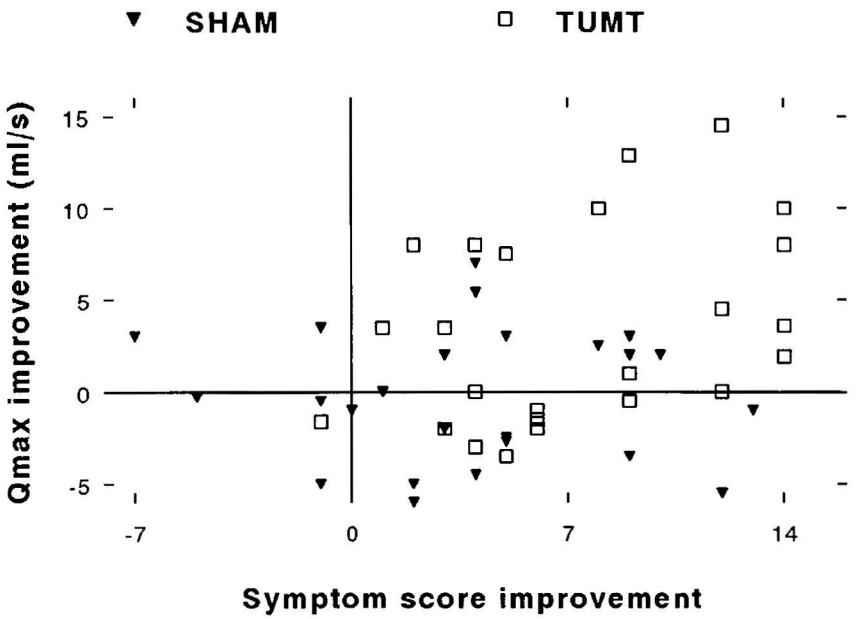
In comparing the results of treatment after 1 year of follow-up, 92% of the patients in the TUMT group, compared with 38% of the remaining patients in the sham group, still had a reduction in the severity of symptoms of more than 50%. Almost half of the patients treated with sham, however, opted for a second treatment compared with only 4 of the 25 patients in the TUMT group. Because of this second TUMT treatment a selection in both groups was made after 3 months. This results in a subgroup of patients with a "better" effect after sham treatment. Because of this selection, the results of these remaining patients in the sham group should improve. The general trend, however, remains unchanged and the 38% of patients with a reduction of severity of symptoms of more than 50% is, therefore, overestimated. Reduction of prostate volume by TUMT, if present at all, is limited. No significant reduction has been shown in earlier reports,[16] and it is interesting to note that although rather bigger prostates have been treated in this

study the results are similar.[25] We noticed a marked change in PSA level after TUMT, which has not been seen in the sham group (Fig. 1). The change in PSA value may be an indication of the effect of the treatment on prostatic tissue, since a second TUMT after an earlier sham treatment shows the same change in PSA levels as seen in the initial TUMT group (Fig. 2). In the four patients who had a second TUMT after TUMT, in both sessions almost no changes in PSA levels were noticed. Thus, there might be a correlation between the success of treatment and the detection of any PSA elevation after TUMT. It is apparent from the sham study that elevation of PSA and the incidence of post-treatment retention are uniquely associated with the application of microwave power and presumably consequent prostatic heating. It is possible that failure of TUMT in certain persons may be related to the morphologic characteristics of the prostate. A further histologic study of the prostate before treatment is needed to understand the relationship between tissue morphology and both a successful clinical outcome and post-treatment elevation of the PSA level. Until now there has been no report of such a correlation.

CONCLUSION

After TUMT there was a significant improvement in the objective (peak flowrate and voiding percentage) and subjective (symptom score) parameters. A subjective improvement is also noticed after sham treatment, but this was significantly less than after TUMT. There was no significant improvement seen in objective parameters after sham treatment. We may conclude that a minimal placebo effect exists. However, it accounts for little of the observed benefit of TUMT.

Figure 3. *Correlation between improvement in peak flow and improvement in symptom score at 12 weeks after TUMT or sham treatment.*



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A 12 MONTH STUDY OF THE PLACEBO EFFECT

SUMMARY

To determine the placebo effect of transurethral microwave thermotherapy (TUMT) in the treatment of benign prostatic enlargement (BPE), a prospective, randomized sham-controlled study in 93 patients (mean age 65 years, range 50-88) was conducted at two centres comparing TUMT or sham treatment. Patients randomized to receive a sham treatment underwent the same initial procedure as for TUMT, but the complete procedure simulated on the visual display with no application of microwave energy. If the patients condition had not improved after 3 months, a second genuine TUMT treatment was given at the patient's request. After 3 months there were significant clinical and statistical differences in efficacy between the groups: 62% and 18% of patients had a > 50% improvement in symptom score in the treated and sham groups, respectively (p=0.001). The corresponding changes in flow rate were 36% and 11% (p=0.002), respectively. After 1 year, 63 patients were divided into those that had TUMT initially and those that had sham initially but subsequently had TUMT and those whose sham procedure had led to sufficient clinical improvement to require no further treatment. The two treatment groups had a significant improvement over the sham group. The benefit from TUMT cannot be due to a placebo effect alone.

INTRODUCTION

Several minimally invasive treatments for patients with symptomatic benign prostatic enlargement (BPE) have been introduced recently. Some rely on mechanical disruption or distraction of the prostatic urethra, e.g. balloon dilatation or stenting ,[1-3] but prostatic heating appears to be the most promising alternative. Heat can be delivered selectively to the prostate using different sources, e.g. high intensity focused ultrasound (HIFU), radiofrequency (transurethral needle ablation, TUNA), endoscopic lasers and microwave devices.[4-8] So far, the microwave techniques have been the most extensively investigated. There are two basic concepts; one is hyperthermia, where the prostatic temperature is not allowed to exceed 45°C and the other is thermotherapy where the target temperature is greater than 45°C.[9-12] Initially, research was concentrated on the use of hyperthermia delivered with either a transurethral or transrectal applicator. Hyperthermia was evaluated against sham treatment in a multicentre study in which five different machines (three transrectal and two transurethral) were tested[13] and which concluded that transrectal hyperthermia was probably ineffective in the treatment of BPE, and thus should not be recommended.[14]

Recently, many researchers have used higher temperature microwave treatments or thermotherapy. The treatments deliver high power microwave energy deep within the lateral prostatic lobes, causing irreversible cell damage to prostatic tissue without damaging the urethra. Results of transurethral microwave thermotherapy (TUMT) are very promising, although the degree and significance of the placebo effect remains controversial.[15] Reports from two other groups have suggested that the response to TUMT is significantly greater than due to any effect of placebo or instrumentation.[16-17] A recent report by Nawrocki et al. casts doubt on the validity of these conclusions.[18]

In this paper we present the long term results of a randomized placebo controlled study conducted in two centres. Moreover, we give an overview of the

published placebo controlled studies on TUMT and discuss the extent of the placebo effect in TUMT in treatment of symptomatic bladder outlet obstruction due to BPE.

PATIENTS AND METHODS

From June 1991 to December 1992, ninety three men (mean age 65 years, range 50 - 88) were recruited into the study. For entry into the study all patients had to be older than 45 and complaining of symptoms of bladder outlet obstruction for more than three months, have a Madsen symptom score of greater than 8 and two free flow rates of 15 ml/s or less on two voids of greater than 150 ml. The presence of BPE was confirmed by transrectal ultrasonography (TRUS), the measurement of prostate specific antigen and, where necessary, by prostatic biopsy. Exclusion criteria were: Prostate cancer, prostatitis, urethral stricture, intravesical pathology (stones, neoplasm), neurogenic bladder dysfunction, urinary tract infection, isolated enlargement of the middle lobe, a residual urine volume of 300 ml or more, use of drugs influencing bladder or prostate function, previous transurethral resection of the prostate (TURP), a metallic pelvic implant, disorders of blood flow or coagulation, diabetes mellitus and mental incapacity or inability to give informed consent.

The assessment before treatment consisted of a general history and complete physical examination. Serum creatinine, urea, and electrolytes and full blood count were measured, and urine was sent for microbiological and cytological analysis. The severity of symptoms was expressed in a Madsen symptom score.[19] Flow rates were corrected for artefacts by two independent observers (M. H. and M. de W.) using the 2-second method[20], with no knowledge of the patient's treatment. The voided volume was correlated with the post-void residual volume (PVR) to give a 'voiding fraction', using formula: voiding fraction=voided volume/(voided

volume + PVR).[21] TRUS was performed to measure the dimensions and configuration of the prostate and prostatic volume calculated using the formula of Stamey and Terris.[22]

The procedures for TUMT treatment have been described previously.[8] When a patient was randomized for the placebo (Sham) treatment, the whole procedure was simulated but without applying microwave energy. During both active and SHAM procedures, a real-time treatment profile was displayed on the computer screen and explained to the patient. The sequence of temperature calibration and checks were identical in both groups. At the end of the session patients were asked to remain in the department until satisfactory voiding had been established. In case of retention, a urethral catheter was placed for one week. The baseline tests were repeated at 1, 12 and 52 weeks after treatment. As far as possible the patient and the investigator were kept unaware as to the treatment administered. When a patient noticed no improvement after three months, whether he had previously received a sham or active treatment, a second genuine TUMT was performed on request.

Statistical analysis within each group was done with the Student t test (with significance defined as $p < 0.05$) while the Wilcoxon signed rank test and the Kruskal-Wallis test were used for comparisons between groups. The Chi-squared test was used to assess the significance of the differences in response rates between the groups.

RESULTS

There were no statistical differences between either the Sham or TUMT group (Table 1). Patients from the London centre were sigificantly older, had more symptoms particularly obstructive ones, and a greater residual urine volume than those at Nijmegen.

Table 1. *Differences in baseline variables between the centres and in each treatment*

	Age (yrs)	Prostate vol. (ml)	Madsen score	Peak-flow (ml/s)	PVR* (ml)	Voided fraction(%)
Centre						
Charing Cross						
Mean	67.2	46 3	14.2	9.1	132 5	67 3
SD	8.1	18.1	3.2	2.4	72.8	15.8
Nijmegen						
Mean	63.4	50 8	12 6	9.6	55.2	83 0
SD	6 0	18.2	3.2	2.7	46 8	12 8
p-value	0.016	0 116	0.036	0.269	<0.00	< 0 001
Treatment (no Pat.)						
Sham (46)						
Mean	63.9	49.0	12 9	9.6	84.7	77.3
SD	6.0	20 0	3.1	2.7	66.1	15.7
TUMT(47)						
Mean	66.3	48.6	13.7	9.2	93 9	74.9
SD	8 1	16 6	3.4	2.5	75.4	16.6
TUMT after Sham (27)						
Mean	65.8	52.0	13.6	9.0	110.0	70.6
SD	6.1	23.9	2.8	3 3	80.4	17.8
p-value	0.197	0.503	0.435	0.385	0.259	0.938

* PVR, Post Void Residual

There were marginal differences between the entry study groups and those that had a re-treatment TUMT after Sham. Eighty-eight patients were available for assessment at 3 months and 63 at 1 year. The fate of the other patients is given in Table 2. The period of follow-up for each group is given as the time after the last treatment session, whether first or second TUMT or SHAM, rather than from the beginning of the study.

Table 2. The number of patients in all groups and the treatments and losses during follow-up

		Number of patients (months)		
Follow-up	Baseline	3	6	12
Sham	46	43	18	13
Lost to follow-up		2	2	1
Second TUMT			23	4
Other*		1		
TUMT	47	45	36	33
TURP		2	1	1
Lost to follow-up			3	2
Second TUMT			4	
Death†			1	
TUMT after Sham	27	26	23	15
Lost to follow-up			3	6
Laser		1		
Other‡				1
Death†				1
TUMT after TUMT	4	4	4	2
Lost to follow-up				2

* Technical failure. † Not treatment related. ‡ α1-blocker treatment

The 46 patients who received Sham treatment experienced a significant improvement in symptoms at 3 months, with the initial Madsen score of 12.9 ± 3.1 decreasing to 10.4 ± 4.7. However, there was no significant change in the peak flow rate (Table 3). Thirteen patients were sufficiently content with their symptoms that no further intervention was required by 1 year, representing the best possible outcome of the Sham treatment or the maximum placebo effect. Only the symptom score had improved significantly from baseline. The main

complication was the rate of retention. After the genuine TUMT treatment, 10 patients (21%) needed a transurethral catheter, whereas in the Sham group only one patient was unable to pass urine freely.

Following either TUMT or TUMT after Sham, there is a statistically significant improvement in both Madsen score and flow rate over baseline, at both 3 months and one year. Comparison with the SHAM group at 3 months showed a significant difference in outcome for each of the variables. At 1 year, the patients treated by TUMT continued to have a statistically significant improvement over the remaining patients from the Sham group in both Madsen score and flow rate. There were no significant differences at 1 year for PVR or voiding fraction amongst the three groups.

Stratification of the three groups by the outcome at 3 months, defined by the criteria for success suggested in the Food and Drug Administration (FDA) guidelines is shown in Table 4. There were more successful patients among those receiving TUMT than among those receiving Sham when assessed by both Madsen score and peak flow rate, but the difference was not as striking using the change in PVR as a criterion of success.

DISCUSSION

The placebo phenomenon is difficult to define and the terminology in treatments using devices is still a matter of debate. Traditionally, placebo trials are associated with drug studies and the benefits which a patient may experience while taking a placebo are often assumed to result only from the psychological improvement obtained by contact with those involved in the trial, or better education in health matters. However there may also be improvement due to the natural resolution of the disease process or as a result of the interventions required during the study. Placebo studies do not address fully the problem that the natural history of disease is necessarily brief, because there are ethical constraints against withholding

Table 3. *Main follow-up indices in the sham, TUMT and TUMT after sham groups at baseline, 12 and 52 weeks*

	Baseline		Follow-up at 12 weeks			Follow-up at 52 weeks		
	Mean	95%CI	Mean	95%CI	p-value	Mean	95%CI	p-value
Madsen score								
Sham	12 9	11 9, 13 9	10 4	8 9,11 8	0 003	8 2	5 5, 11 0	0 011
TUMT	13 7	12 7,14 7	4 7	3 6,5 9	<0 001	4 2	3 0,5 3	<0 001
TUMT after Sham	13 6	12 4,14 8	5 4	3 6,7.2	<0 001	7 0	3 8,10 2	0 005
Peak flow (ml/s)								
Sham	9 6	8 8,10 4	9 7	8 7,10 7	0 846	10 5	7 9,13 1	0 657
TUMT	9 2	8 4,9 9	13 4	11 7,15 3	<0 001	13 4	11 6,15 1	<0 001
TUMT after Sham	9 0	7 6,10 4	13 4	11 1,15 7	<0 001	12 8	9 8,5 8	0 033
PVR* (ml)								
Sham	84 7	64 0,105 1	104 1	74 7,133	0 428	56 3	16 9,95 7	0 433
TUMT	93 9	71 8,116 0	34 2	19 4,46 8	<0 001	49 7	33 0,66 3	0 002
TUMT after Sham	110 0	76 9,143 2	67.1	37 7,91 1	0 012	57 3	23 4,91.1	0 133
Voided fraction (%)								
Sham	77 3	72 4,82 1	75 4	69 6,81 3	0 936	83 5	73 8,93 2	0 814
TUMT	74 9	70 1,79 8	89 5	85 2,93 7	<0 001	84 5	79 3,89.7	<0 001
TUMT after Sham	70 6	63 3,77 8	81 0	73 8,88 2	0 015	84 5	77 1,92 0	0 116

*PVR, Post-void residual

treatment for a prolonged period. The spontaneous changes occurring with time in any disease process are best observed by comparing an active treatment to an arm with no treatment arm, randomly and prospectively. A spontaneous improvement in a patient's condition may seem to occur as the result of the study, e.g. an improved urine flow after more experience or from repeated catherization in studies of BPE. In device-based therapies, the intervention required to prevent the patient knowing wich treatment has been received may have a previously unsuspected therapeutic benefit, e.g. the insertion of a urethral applicator during thermotherapy. One of the critical issues for the evaluation of devices for the

Table 4 *The proportional improvement in the main indices at 3 months of follow-up percentages are based on intention to treat*

	Improvement from baseline parameter (%)							
	< 25%		> 25% < 50%		> 50%		> 75%	
Madsen score								
Sham	26	58%	11	24%	8	18%	4	9%
TUMT	10	21%	8	17%	29	62% p=0 002	14	30%
TUMT after Sham	9	33%	5	19%	13	48% p<0 001	9	33%
Peak flow (ml/s)								
Sham	31	69%	9	20%	5	11%	4	9%
TUMT	23	49%	7	15%	17	36% p<0.002	12	26%
TUMT after Sham	13	48%	2	7%	12	44% p<0 001	7	26%
PVR* (ml)								
Sham	31	69%	4	9%	10	22%	8	18%
TUMT	18	38%	6	13%	23	49% p=0.002	21	45%
TUMT after Sham	14	52%	6	22%	7	26% p=0 449	5	19%

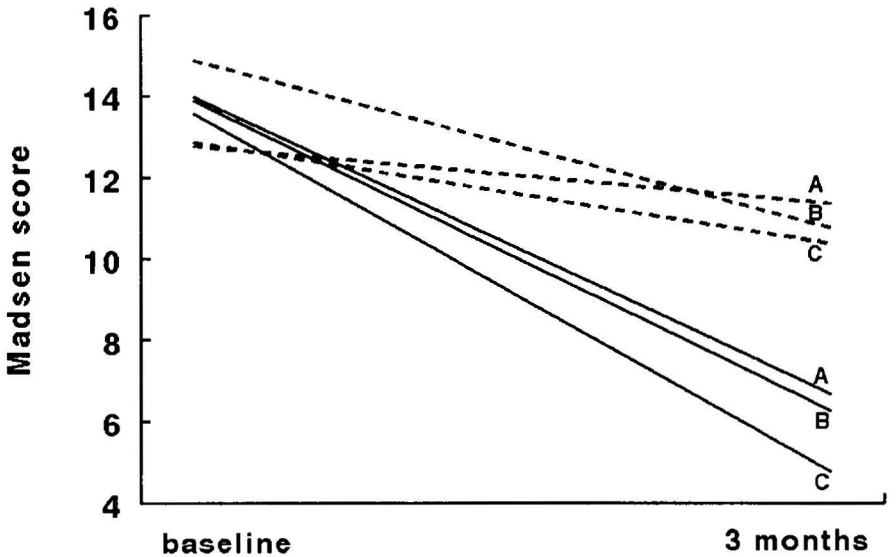
*PVR, Post Void Residual

treatment of symptomatic BPE is whether the placebo response seen with drug studies can be expected with any treatment, be it a device or even surgery.

The results from the present study suggest that there was indeed a significant placebo/instrumental response in patients undergoing sham treatment. The two other comparisons of TUMT and sham treatment,[16 17] also showed similar changes in Madsen score in both the TUMT and sham arms (Fig. 1a). There are some differences in the peak flow rate changes, in that the study by Perrin and

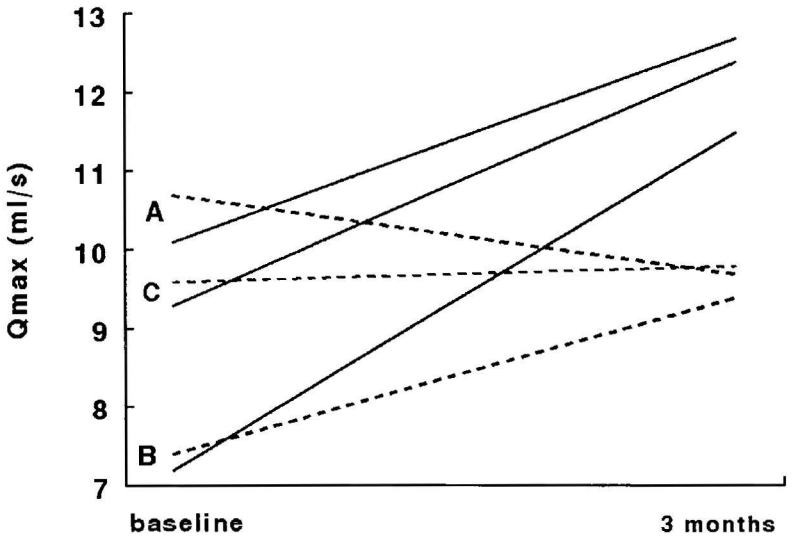
Devonec[17] showed a small decline in peak flow at 3 months and the study by Blute et al.,[16] demonstrated a larger improvement than in the present study (Fig 1b). The study of Bdesha et al., using a transurethral microwave device without cooling differs from other studies in that they found a 16% improvement in symptoms and a deterioration in peak flow rate and PVR in the sham arm.[23] This result is comparable to the 19% symptomatic improvement in the current study. One of the best controlled drug studies in patients with symptomatic BPE is that by the International Finasteride study group,[24] which had a placebo arm followed for up to 1 year and comprising 154 patients. The mean change in symptom score was a decrease in symptom score of 2.6 points from a baseline of 19.2 (13.5%) on a modified Boyarski score with a maximum of 36. The increase in flow rate was minimal with an improvement of only 0.4 ml/s from a baseline of 8.6 ml/s in the placebo-treated patients. Jardin et al. reviewed the placebo response in studies of alpha- blocking agents and reported a change in flow rate from -2.7 to +2.3 ml/s.[25] The placebo response found in TUMT studies is greater than that in many drug studies. Previous studies comparing TUMT to sham agree that there is a greater benefit from thermotherapy.[16,17] Both the centres participating in the present study reported results at three month individually; there was a significant difference between the outcome of sham and TUMT.[26,27] However, the study based in London demonstrated little effect of placebo because a few patients in the sham-treated arm deteriorated significantly during the 3-months follow-up, thereby skewing the data. By pooling the data from the two studies, which were carried out according to the same protocol, the evidence for a placebo effect is strengthened. Only one study has concluded that the majority of the effect of TUMT is due to a placebo response, but the results lack credibility as they were from a non-randomized, unblinded study.[15] Both the study of thermotherapy by Bdesha et al.,[17] and the French multicentre study of hyperthermia devices,[14] showed no difference in flowrate changes between sham and treatment, but it is presumed that this is due to the small increase in flow rate seen with transurethral microwave energy

Figure 1a. *Changes in mean Madsen symptom score.*
Dotted line, Sham. Black line, TUMT A=[13], B=[16],C=Present study



application at lower power and without simultaneous cooling of the applicator.[13,23] The similarity of improvement of symptom score in a non-irrigated method of thermotherapy, e.g. by Bdesha et al.[23] with that in the present study is interesting. To date, there is only one paper reporting subsequent treatment of those receiving sham treatment, and a 1- year follow-up which showed similar results to the present study.[28] However, that study comprised few patients and the microwave therapy was more in the range of hyperthermia than in that of thermal therapy. A study of a three-way randomization between sham, TUMT and watchful waiting (WW) comprising 120 patients in total,[15] reported that the WW group showed no clinically relevant deterioration or improvement. The sham-treated group had a symptomatic improvement of 45% comparable to TUMT (50%). There was little clinically relevant improvement of objective variables in the TUMT group and no relevant improvement in the sham-treated group. However, in that study, the

Figure 1b. *Changes in mean peak flow rate (ml/s).*
Dotted line, Sham. Black line, TUMT. A=[13], B=[16], C=Present study



patients were selected if they had severe obstruction, as defined by pressure-flow studies and may not represent a similar population to that in the present study (P Nawrocki - personal communication). There is evidence to suggest that TUMT has a much less effect on patients with more severe obstruction.[29]

The conclusion from these comparisons of TUMT and sham treatment must be that there is an effect of heat on bladder outlet function in the older man and that only a small part of the clinical benefit can be accounted for by the effect of placebo or instrumentation. This conclusion is further supported by the analysis of those patients who have transferred from sham to TUMT treatment. Presumably, these men are not susceptible to a placebo effect and yet the changes after treatment are still very significant albeit a little less than occurred in the original treatment group. The difference in outcome between TUMT and TUMT after sham probably results from the exclusion of those responding to the placebo

and thus may be considered to represent the therapeutic effect of TUMT.

The most cogent argument for a greater benefit from TUMT than from sham treatment is that from the analysis of the rates of response based on the percentage intention-to-treat. The FDA proposed that response should be examined as a percentage change in each individual criteria, as well as in combination; this gives an agreed framework by which to compare the outcome following what are often very different treatments.[30] After sham treatment, only 11% of men have >50% of change in peak flow rate, compared to 36% of men after TUMT. The difference is more striking when comparing the effect on symptom score, with only 18% of patients receiving sham treatment attaining a satisfactory improvement (i.e. > 50%) as opposed to 62% of those receiving TUMT.

The present study shows that the difference between sham treatment and TUMT persisted for at least 1 year. Only 10 of the 74 patients who were treated by TUMT required any further intervention within one year and of those, only 4 required TURP, the others being treated by either repeated TUMT or other minimal invasive therapy.

We feel strongly that the evidence for a beneficial effect of heating at 'thermotherapy' temperatures is conclusive and that further randomized sham studies would be unethical. The burden of these types of investigation upon the patient is substantial and should not needlessly be repeated. Now the most important question is how the improvement in voiding is obtained in the absence of any significant loss of prostatic volume. It is clear that the mechanism of action of TUMT is substantially different to the reduction in volume and the formation of a cavity that is obtained with TURP and thus provides an exciting opportunity to provide a genuinely novel treatment for patients with symptomatic BPE.
TUMT using this heating level (Prostasoft version 2.0) is particularly suitable for treatment of earlier and less severe disease in the younger man who wishes to avoid disturbance of sexual function or in the elderly with many comorbid conditions preventing safe resection. It is also important that a proportion of

patients respond more to TUMT than do others, possibly because the required threshold temperature of 45° C is not achieved [71] Furthermore, sophisticated methods to select patients are required to make better use of the advantages of this minimally invasive therapy

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Chapter 2

RESPONDERS AND NONRESPONDERS TO THERMOTHERAPY

Based on

MJAM de Wildt, A Tubaro, K Hofner, SStC Carter, JJMCH de la Rosette, M Devonec

Responders and nonresponders to transurethral microwave thermotherapy a multicenter retrospective analysis

J Urol ***154*** *1775-1778, 1995*

SUMMARY

We attempted to identify any parameter could possibly lead to a successful treatment outcome after transurethral microwave thermotherapy Clinical parameters and treatment profiles of 292 patients were analyzed in a retrospective multicenter manner Responders and nonresponders were identified according to a given definition No statistically significant differences in baseline characteristics were found Responders showed a 76% symptomatic improvement rate to 27% in nonresponders, and an 82% improvement rate in peakflow to a 5% decrease in nonresponders Responders also showed an significantly greater increase in posttreatment PSA level and a significantly greater amount of energy released during treatment No baseline clinical parameter is capable of predicting treatment outcome

Microwave heating of the prostate is a fascinating approach to the treatment of voiding disturbances in patients with benign prostatic hyperplasia (BPH).[1,2,3] There are 2 basic concepts: hyperthermia in which the prostatic temperature is not allowed to exceed 45°C, and thermotherapy in which the target temperature is greater than 45°C.[4,5] A recent multicenter study showed that hyperthermia seems likely to be ineffective in the treatment of BPH and thus not to be recommended.[6]

Thermotherapy applies high power microwave energy deep within the lateral prostatic lobes. The results of transurethral microwave thermotherapy are promising. It is presumed that clinical benefit is achieved by a small decrease in adenoma volume and the destruction of certain specific cell types that have some part in the development of bladder outlet obstruction. The clinical improvement has been shown not to be due to a placebo effect or the result of the associated urethral instrumentation in randomized trials of transurethral microwave thermotherapy versus a Sham procedure.[3,7] However, the criteria currently used for inclusion do not prevent a high variability in terms of clinical response to transurethral microwave thermotherapy, and treatment outcome is difficult to forecast in the individual patient.

Clinical experience has shown that significant improvement of subjective and objective parameters of disease severity is achieved in a subgroup of treated patients.[3,5,8] Patient parameters at entry and treatment parameters have been investigated in different series for possible correlation with treatment outcome. For patient selection, the specific type and grade of obstruction at screening was correlated significantly with the response rate in a multicenter European study.[9] Analysis of different treatment parameters that are currently monitored during microwave treatment to date has failed to identify any difference between treatments leading to successful outcome and those producing no change for the individual patient. More recently, analysis of patients undergoing invasive

thermometry of the prostate during treatment suggested a significant correlation between the amount of heat induced within the gland and flow rate improvement.[10]

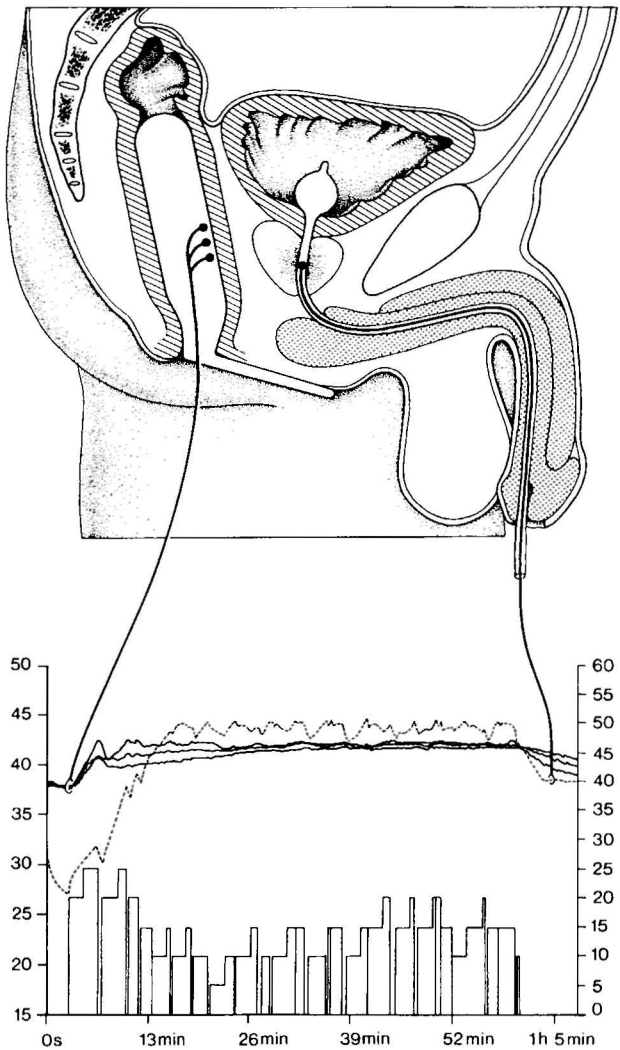
We investigated further patient treatment profiles to identify any parameter that could possibly lead to a successful treatment outcome. Digital records of the microwave treatments from a large series of patients undergoing microwave therapy at 17 different prostate centers worldwide constitute the material for the study.

PATIENTS AND METHODS

Data from BPH patients undergoing microwave thermotherapy at 17 different hospitals were collected. The same instrument and treatment software were used at the various centers, and treatments were performed according to a common study protocol. Treatment was given on an ambulatory basis and has been described in detail previously.[11] A representation of a treatment session, the position of catheter and rectal probe, and a treatment profile are demonstrated in figure 1. During the transurethral microwave thermotherapy the microwave energy is emitted to the prostate resulting in heat. To prevent damage to urethral mucosa or rectal wall, 1 thermal sensor is positioned in the treatment device and 3 sensors in the rectal probe to check the urethral and rectal wall temperature. When the maximum allowed temperature is detected by one of 1 these sensors an alarm automatically interrupts the treatment. Therapy is resumed when the temperature decreases to a certain level.

Screening consisted of a patient history with the Madsen-Iversen symptom score, physical examination with digital rectal examination of the prostate, hematology and blood chemistry studies, including prostate specific antigen (PSA) measurements, electro-cardiography, chest X-ray, kidney and bladder ultrasound imaging or excretory urography, transrectal ultrasound of the prostate, uroflow-

Figure 1. *Position of 3 rectal temperature sensors and urethral sensor in catheter. Curves represent temperature readings of each sensor. Dotted line is urethral curve and 3 continues lines are rectal temperature curves. Graph boxes represent amount of energy generated (watts)*



metry (twice) with measurements of post-void residual volume using ultrasound. All patients studied were candidates for transurethral resection of the prostate and had a Madsen-Iversen symptom score of 8 or more, a maximum flow-rate of 15 ml/s or less and post-void residual of 250 ml or less. Patients were excluded from the trial in case of an obstructive prostatic middle lobe, complications of BPH, suspicion of prostate cancer, presence of any condition that could interfere with bladder dynamics and patient compliance to the protocol.

Each center was asked to provide case record forms and copies of the treatment computer files of at least 10 responders and 10 nonresponders to microwave thermotherapy. Responders were identified by a Madsen-Iversen symptom score of 3 or less, or 50% or greater decrease at month 6, a maximum flow rate of 15 ml/s or more, or 50 % or greater improvement and a post-void residual of 50 ml or less or 50 % or greater improvement at 6 months. Nonresponders were identified by a Madsen-Iversen symptom score of 8 or more, or 50 % or less improvement, a maximum flow rate of 10 ml/s or less, or 20% or less improvement and a post-void residual of 200 ml or more or 50% or less decrease at 6 months. At each center data were derived from consecutive series of patients satisfying the described criteria.

Follow up visits, including symptom evaluation by Madsen-Iversen symptom score, flow rate measurements by free flow uroflowmetry and residual urine measurement by ultrasound, were scheduled at 1, 3 and 6 months after treatment. Blood samples were collected in selected sites at day 1, week 1, and 12 weeks after thermotherapy. Quality data control included survey of the received case record forms and treatment files. Only patients with complete data bases were considered evaluable for analysis. Data collected from case record forms and retrieved from treatment files were entered in a computer and analyzed by a statistical program.

RESULTS

Of 292 patients evaluable 136 were responders and 156 were nonresponders. Analysis of patient parameters at screening showed no significant difference among responders and nonresponders (Table 1).

Table 1. *Patient characteristics*

	Mean ± SD	
	Responders	Nonresponders
Age (yrs)	66.8 ± 7.9	66.4 ± 8.3
Prostate volume (cm^3)	45.0 ± 18.0	44.0 ± 18.0
Madsen score	13.7 ± 4.0	13.3 ± 4.3
Maximum flow rate (ml/s)	8.8 ± 3.7	8.3 ± 3.3
Post-void residual vol. (ml)	96.0 ± 158.0	78.0 ± 80.0
PSA (ng/ml)	4.1 ± 4.3	4.2 ± 3.3

Changes in Madsen-Iversen symptom score, maximum flow rate and post-void residual are presented in figure 2. Responders showed an average improvement of 76% for Madsen-Iversen symptom score and an increase in maximum flow-rate of 82%, with a decrease of 37% of post-void residual volume (Table 2). Non-responders had an average decrease of 27% for symptom score, an actual decrease in flow-rate of 5% and only a decrease of 14% for post-void residual volume.

Screening plasma levels of PSA were found to be comparable among the 2 groups. Heat produced by microwave thermotherapy in the prostate gland is responsible for the observed increase of PSA. Interestingly, at week 1 significantly higher values were measured in responders (+371 %), when compared with nonresponders (+176 %). PSA values at 3 months were again comparable between the two groups and did not differ significantly from baseline (Figure 3).

Different parameters derived from digital records of the microwave treatments

Table 2. *Values at baseline and at 6 months.*

	Mean ± SD	
	Baseline	6 Months
Responders		
Madsen score	13.7 ± 4.0	3.2 ± 3.3
Maximum flow rate (ml/s)	8.8 ± 3.7	16.0 ± 5.7
Post-void residual (ml)	96.0 ± 158	35.0 ± 50.0
Nonresponders		
Madsen score	13.9 ± 4.2	9.6 ± 4.0
Maximum flow-rate (ml/s)	8.3 ± 3.3	7.9 ± 3.0
Post-void residual (ml)	78.0 ± 80.0	67.0 ± 77.0

were analyzed (Figure 4). The amount of energy released during treatment, measured as total energy dose, average dose, and the maximum power output was found to be significantly different in the 2 groups. The higher amount of energy released in the responder group resulted in a higher temperature at the level of the urethra.

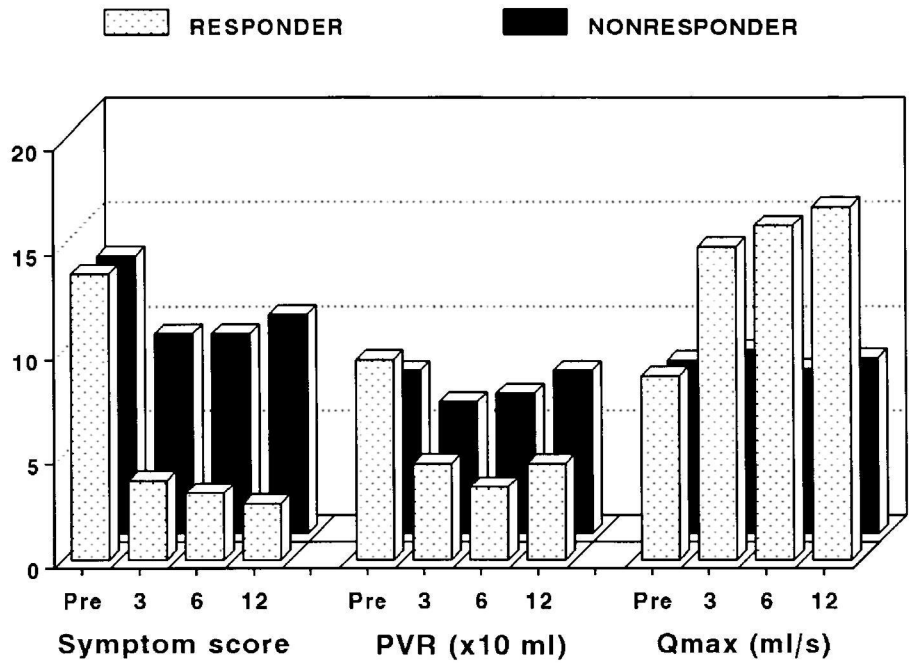
The number of urethral alarms was greater in responders versus nonresponders but the difference was not significant (Figure 5).

Notwithstanding a higher energy release in responders, temperatures recorded at the level of the rectal wall were comparable in the two groups; nevertheless fewer rectal alarms was observed in responders when compared to nonresponders

DISCUSSION

Variance analysis of data obtained has shown how our patient population did not differ significantly among the various sites and it is comparable with the BPH

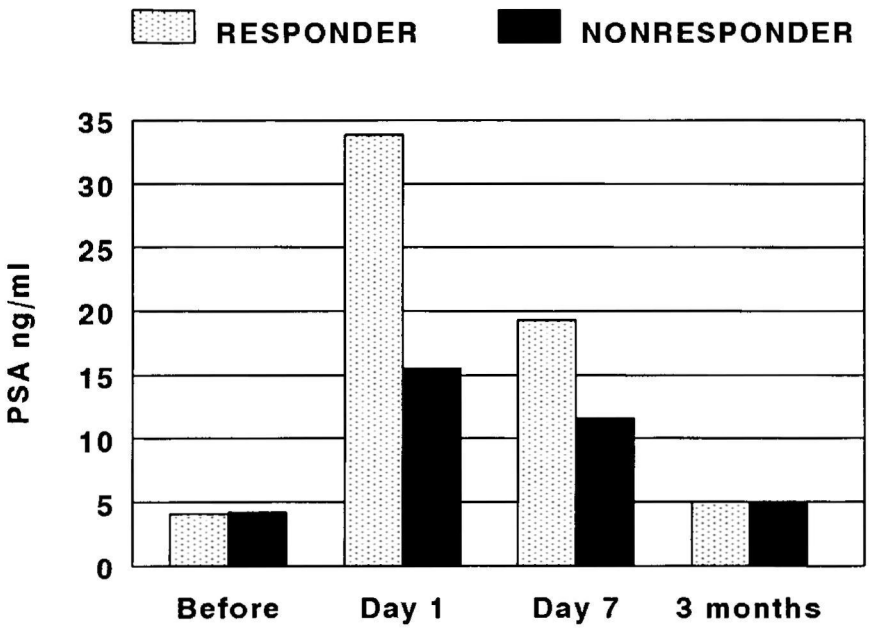
Figure 2. *Difference in symptom score, post-void residual volume (PVR) and maximum flow rate (Qmax) between responders and nonresponders at baseline (Pre), 3, 6 and 12 months after treatment.*



population enrolled in previous studies. The use of 2 discrete populations of responders and nonresponders instead of one single group was designed to achieve a balance between the two groups which is otherwise dependant on patient selection in the individual sites. Moreover, it is easier to perform such an analysis determining treatment parameters that predict outcome of treatment.

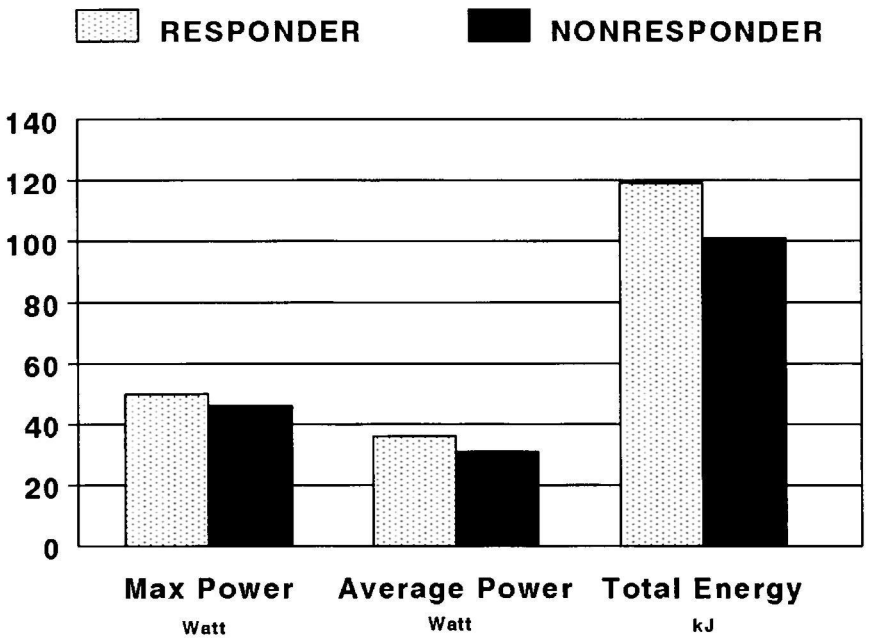
The outcome of thermotherapy has been shown to be variable between different sites in previous studies.[3,5,7,8,12] To identify selection criteria that could possibly predict successful treatment outcome, a large series of patients was evaluated according to the response of treatment. Responders and nonresponders characteristics at screening were not statistically different, which further supports a previous supposition from our group that currently only baseline urodynamic

Figure 3. *Changes in PSA level (ng/ml) between responders and nonresponders at baseline, 1 day, 7 days and 3 months after treatment.*



parameters can predict clinical outcome from microwave treatment.[9] Provided the 2 groups of patients were comparable at baseline, a different microwave treatment profile could have been responsible for the different outcome in the 2 populations. The treatment profile reflects the energy delivered to the prostate and depends on the number of the rectal and urethral alarms (Figure 1). The alarms result in a safe treatment but they may limit the emission of microwave energy. In view of the results achieved with higher energy levels we think that the safety of treatment obviously interferes with efficacy. One can not have high temperatures within the prostate using low power levels.[10] We know that the amount of heat produced within the prostate is correlated with objective clinical outcome but such parameters are not available in this series. Nevertheless, we still have an indirect measure of intraprostatic temperatures which is given by the elevation of PSA in the days following transurethral microwave thermotherapy. We do not know

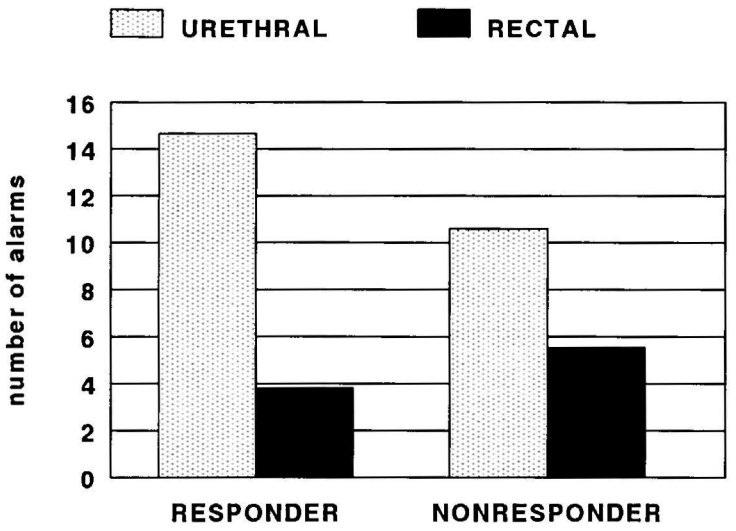
Figure 4. *Difference in maximum (max) power, average power and total administered amount of energy between responders and nonresponders.*



wether epithelial cell damage is of any importance in clinical response to microwave therapy but is certainly one of the three major cellular components of BPH. Interestingly, the variation of the PSA level within 1 week after treatment was significantly different in the 2 groups. Variation among the individual patients is high and it reflects the different response of the individual prostate to microwave treatment, which we observed in previous studies. The kinetics of the PSA increase is outside the objectives of our study but they certainly deserve attention in the future. The concept was confirmed in a recently conducted placebo controlled study.[3]

The key questions are why some patients achieve higher intraprostatic temperature than others and whether this is dependent on differing tissue architecture blood supply in some prostates. Answering such questions will significantly influence patients selection and the design of new treatment software

Figure 5. *Difference in number of rectal and urethral alarms between responders and nonresponders.*



in the future. Analysis of different treatment parameters has shown that the amount of energy released during treatment differs significantly in the 2 groups and more energy was delivered in responders when compared to nonresponders. The observation is confirmed by the evaluation of 3 separate parameters, maximum power output during treatment, and total and average energy doses. Interestingly, the energy applied cannot be related to prostate size.

What happened to this higher amount of energy released into the prostate of patients who did well? A higher energy dose produced a higher urethral temperature, which is not evident when examining the peak urethral temperature achieved during treatment but it was clear if we note the maximum urethral temperature sustained for at least 3 minutes. A higher urethral temperature has, of course, triggered a greater number of urethral alarms, although the difference between the 2 groups was not significant because of the high variability of this parameter in different treatments (0 to 150). Transient interruption of microwave emission seems not to be detrimental to treatment outcome or the total energy dose. Therefore, where is all this energy going? The flux of energy emitted by the

microwave antenna passes through the prostate from the urethra to the rectum. As the irradiative energy is absorbed by tissue it is transformed into heat energy and the temperature increases. When temperatures increase, vasodilatation occurs creating a heat sink which may carry away significant amounts of heat. If irradiative energy is largely absorbed by prostatic tissues then rectal temperature cannot increase (by lack of energy) and, consequently, we expect a fewer rectal alarms. Interestingly, this is what happened in the responder group; lower temperatures were measured in the rectal wall of these patients and a fewer alarms were recorded.

A higher energy dose with lower rectal temperature may be dependent on 2 different phenomena: either a higher energy absorption by the prostate tissue with a high intraprostatic temperature or a higher energy dissipation from a major blood supply with little temperature rise within the gland. Because patients with a higher energy deposition and lower rectal temperatures have a more successful treatment outcome, better energy deposition is more likely to be responsible for the lower number of rectal alarms observed in responders.

CONCLUSIONS

None of the baseline parameters used within our study was able to define the ideal patient for and predict the result of treatment. Changes in PSA levels and energy absorption of the prostate merely reflect the heterogeneity of the disease and variability of outcome to this treatment modality. Tissue architecture of the prostate gland and its relative blood supply might have a role in determining the outcome of microwave heating.[12] Investigation of possible correlations among these parameters might be important to understand the mechanism of therapeutic effect of microwave heating on BPH, resulting in more efficient heat induction of the prostate.

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Chapter 3

LONG TERM RESULTS OF LOWER ENERGY THERMOTHERAPY

Based on:

de Wildt MJAM, d'Ancona FCH, Hubregtse M, Carter SStC, Debruyne FMJ, de la Rosette JJMCH

3 Years followup in patients treated with lower energy thermotherapy. Journal of Urology: in press

SUMMARY

A retrospective study was conducted to investigate the long term outcome of patients treated with lower energy TransUrethral Microwave Thermotherapy (TUMT). Three hundred and five patients with lower urinary tract symptoms and benign prostatic enlargement underwent TUMT according to a similar protocol at two centers. After three years followup, 133 patients who had only been treated with TUMT were available. Over this period of observation a significant symptomatic improvement over baseline and improvement in maximum flow of 2.6 ml/s was seen. Hundred and twenty-five patients were retreated with either invasive or medical treatment. After three years followup, lower energy TUMT shows significant and durable improvement of baseline parameters in 52% of patients.

INTRODUCTION

In the last decade many different alternatives to a surgical resection of the prostate in patients with Lower Urinary Tract Symptoms (LUTS) and Benign Prostatic Enlargement (BPE) have been introduced. These include the use of different oral medications, such as 5α-reductase inhibitors and α1-adrenergic antagonists, as well as several minimally invasive approaches [1,2]. Although a surgical resection is effective in relieving bladder outlet obstruction with a consequent reduction in symptoms, the popularity of these alternative therapeutic options in the treatment of BPE is based on the potential reduction in morbidity and costs. The use of heat applied by different generators (e.g., ultrasound, radio-frequency, laser and microwave-devices), appears to be the most promising alternative [3-6]. TransUrethral Microwave Thermotherapy (TUMT) offers great potential as an outpatient anesthesia-free single session procedure. Presently, of the many different thermotherapy-devices, the Prostatron (Technomed, Lyon, France) has received the most attention and has been investigated extensively with more than 25.000 treatments performed worldwide. Several studies of this device report substantial and significant subjective improvement. An overall improvement of about 70% in symptom scores, using the Madsen-Iversen Symptom Score (MSS), compared with baseline is usually noted. The improvement in urinary performance is also encouraging, with an improvement in maximum flow (Qmax) of around 2-3 ml/s (representing about 35%) over baseline and a similar reduction in Post Void Residual volume (PVR) of around 35% [6]. The mechanism of action may be related to thermal damage of prostate tissue and not to the effect of urethral manipulation as shown by several randomized studies of TUMT versus sham [7,8]. More important, a study of TUMT versus TURP by Dahlstrand et al., has shown that the symptomatic improvement after TUMT is statistically identical to improvement in patients treated with TURP [9]. However, the effect on uroflowmetry parameters in TUMT patients is less pronounced when compared

with TURP patients. Both subjective as objective parameters remained stable over 3 years period of observation [6].

The authors have a large experience with the Prostatron device. Since the end of 1990, treatments with the lower-energy protocol (Prostasoft® version 2.0) have been performed. We conducted a retrospective study in patients treated with this protocol at two different centers to discover the results of treatment over a long period of followup.

MATERIAL AND METHODS

From December 1990 to December 1992, Three hundred and five men with LUTS and BPE were treated with the Prostatron device. Pretreatment assessment included patient history (with Madsen-Iversen symptom scores) [10], physical examination (with digital rectal examination), urinalysis and urine culture, transrectal ultrasound of the prostate with calculation of the prostate volume using the formula of Stamey and Terris [11], and uroflowmetry with measurement of PVR by abdominal ultrasound of the bladder using the ellipsoid technique.

The great majority of these patients were included in a range of prospective trials that were conducted according to more or less similar protocols. Criteria to enter the study were an age of more than 45 years, LUTS for more than 3 months, a Madsen symptom score of 8 or more, a urinary maximum flow of 15 ml/s or less, and a Post Void Residual volume of 350 ml or less. Exclusion criteria were urinary retention, prostate carcinoma, acute or chronic prostatitis, urethral stricture, intravesical pathology (stones, neoplasm), neurogenic bladder dysfunction, urinary tract infection, isolated enlargement of the middle lobe, use of drugs influencing bladder or prostate function, disorders of blood flow or coagulation and diabetes mellitus. The TUMT treatment in general has been described before [12]. After treatment, patients were asked to remain in the department until satisfactory

voiding had been established. In case of retention, a urethral catheter was placed usually for one week. All patients were treated at least 3 years ago. Data on symptom scores and uroflowmetry results were analyzed retrospectively at baseline, 12, 24 and 36 months after treatment. The maximum flow was corrected for artefacts by two independent observers using the 'two second method' [13]. The voided volume was correlated with the Post Void Residual volume (PVR) to give a 'voiding fraction', using the formula: voiding fraction (%)= voided volume / (voided volume + PVR)[14]. In case of further treatment by either surgical or medical intervention, the date and type of treatment were noted. When a patient did not return for further followup and no record of the patient's fate was in the patient's file, a detailed questionnaire with an enclosed Madsen symptom score was sent to the patient. If the Madsen symptom score was missing at the three-year visit to the outpatient clinic, a Madsen symptom score was obtained by telephone interview. A patient was considered lost to followup if no knowledge was available of his fate after his last visit to the outpatient clinic, despite several attempts to contact him by either mail or telephone. If a patient was not satisfied with the result of the TUMT treatment and therefore changed to medication for his lower urinary tract symptoms (either 5α- reductase, α-blocker or anticholinergics) or underwent an operation, the uroflowmetry or symptom score data were not taken into consideration in evaluation of the followup. Finally, post treatment morbidity was noted if the patient experienced urinary incontinence, a urethral stricture or other treatment related complaints.

RESULTS

Of the total 305 patients, 73 patients were treated in the London center and 232 in Nijmegen. The English patients at average had smaller prostates, voided with larger volumes and had a larger post void residual volume and consequently

smaller voiding fraction. All other parameters used in the study were equally distributed and statistically similar (table 1) For the total group the mean age at baseline was 65.3 ± 7.3 years (range 45 - 87).

Table 1 *Baseline characteristics for the two centers*

	Mean ± SD		
	Nijmegen	London	
	n = 232	n = 73	p-value
Age (yrs)	64 9 ± 7 2	66 8 ± 7 5	0 051
Prostate volume (cm^3)	49 9 ± 19 7	43 6 ± 23 4	0 031*
Madsen score	12 7 ± 3 5	13 5 ± 3 4	0 070
Uroflowmetry			
Qmax (ml/s)	9 0 ± 2 8	9 4 ± 2 7	0 375
Voided volume (ml)	223 ± 113	258 ± 121	0 045*
Post-void residual (ml)	65 ± 68	139 ± 98	<0 001*
Voiding fraction (%)	79 ± 18	68 ± 19	<0 001*

* Significant difference using Student-T test (α = 0 05)

Table 2 *Number of patients, additional treatments and losses in the followup*

	Number of patients				
	Baseline	1 year	2 years	3 years	Total
TUMT only	305	233	112	133	133
Medication		18	11	16	45
Invasive procedure after prior use of medication		2	9	5	16
Invasive procedure		22	23	19	64
Death		1	2	3	6
Lost to followup		17	19	5	41
Missed visit		12	69	-	-

The average prostate volume was 48.6 ± 20.7 cm^3 (range 15 - 133). After three years followup 133 patients who had no additional treatment by either medication or an invasive procedure were available. The fate of the other patients is given in table 2. In total 140 letters were sent to the patients of which 99 were returned. The remaining 41 were considered lost to followup. If no data at one and/or two-year followup was available and the patient returned for further followup after three years or when he filled out the mailed questionnaire, he was considered a missed visit at one and/or 2-year followup.

Table 3 *Followup paired data of baseline parameters of patients treated with TUMT without additional treatment*

	Mean					
	Baseline	1 Year		2 Years		3 Years
		base	12 mths	base	24 mths	base	36 mths
Madsen Symptom Score							
N=	305	208		66		113	
Mean score	12 9	12 8	5 6*	13 0	6 1*	12 2	8 1*
Uroflowmetry							
N=	305	228		110		63	
Qmax (ml/s)	9 1	9 2	11 4*	9 3	11 2*	9 4	11 9*
Voided Volume(ml)	228	235	224	254	239	230	216
Post Void Res (ml)	82	75	48*	74	50**	62	48**
Voiding Fraction (%)	77	79	85**	80	84***	80	84

Significant using the Wilcoxon Matched-Pairs Signed Ranks test (α=0 05) with (*p<0 001,**p<0 01,***p<0 02)

Table 3 shows the paired data of improvement from baseline of the main indices. After one year there is a 56% reduction in symptom score that gradually

declines to 53% and 34% at 2 and 3 years followup respectively Nevertheless, the symptomatic improvement remains statistically improved over baseline values The improvement in maximum flow stays stable at 24% after one year, and 20% and 27% after two and three years followup respectively The improvement in post void residual and voiding fraction also remains constant over the three-year period of observation, although the improvement in voided percentage over baseline is no longer statistically significant at three years followup This may be due to the small number of patients that have uroflowmetry data available at this visit

Table 4 *Response rates of main indices after 1 2 and 3 years in patients only treated with TUMT shown as a percentage of available patients*

	Percentual improvement from baseline parameter			
	< 25%	≥ 25% ≤ 50%	> 50%	> 75%
Madsen score				
1 year	19%	21%	60%	34%
2 years	23%	15%	62%	26%
3 years	48%	13%	39%	27%
Qmax (ml/s)				
1 year	54%	20%	26%	15%
2 years	57%	20%	23%	14%
3 years	51%	22%	27%	18%

Stratification of the data of patients treated only with TUMT by the percentage change in outcome at 1, 2 and 3 years followup, as a definition of success as suggested in the Food and Drug Administration (FDA) guidelines, is shown in table 4 The proportion of patients that have 50% or more symptomatic improvement remains stable at the first two years and declines to 39% at three years followup The proportion of patients that have 50% or more improvement of the maximum flow remains durable at 26%, 23% and 27% at one, two and three

years followup respectively. Apart from the greater symptomatic improvement at one year followup for the English patients, there appeared to be no statistical difference between the London and Nijmegen center in the amount of improvement of any of the main indices (table 5). At 3 years followup, 133 patients had undergone only TUMT that corresponds to 133/258=52% of patients with available data. In total 80/219=31% underwent an invasive procedure with a second TUMT in 8 patients, a transurethral resection of the prostate in 45 patients, an incision of the prostate in 3 patients, a laser prostatectomy in 17 patients, a suprapubic prostatectomy in 5 patients and finally one patient underwent a radical prostatectomy after diagnosis of prostate cancer. In total 60/258 = 23% of patients were not satisfied with the result of TUMT and changed to medical therapy. Of these patients, 42 used α-blockers, 5 patients began 5α-reductase treatment and 12 patients started with anticholinergic drugs. One patient started treatment with flutamide when prostate cancer was diagnosed. Sixteen of these were not content with the medical therapy, and finally underwent surgical intervention.

Figure 1 illustrates the Kaplan-Meier plot of early termination of the study due to starting medication and an invasive procedure. Patients waited at average 1.4 ± 0.8 years (range 0.5 - 2.9) before initiating medical therapy and 1.5 ± 0.8 years (range 0.25 - 2.9) before having a surgical procedure when they were dissatisfied with the result of the TUMT treatment.

No statistical difference in any of the baseline parameters could be found between patients who at 3 year followup after TUMT had a response rate of 50% or more in either symptom score or maximum flow and patients who underwent retreatment by either medication or invasive procedure. After treatment 82 patients (82/305=27%) needed a transurethral catheter due to urinary retention. In the majority of patients this catheter could be removed one week after treatment. Three patients (3/258=1.2%) developed recurrent urinary tract infections for which antibiotic treatments were necessary. Eight patients (8/258=3.1%) experienced

prolonged macroscopic hematuria. One patient (1/258=0.4%) developed a urethral stricture. Four patients (4/258=1.6%) developed urge-incontinence. Finally, four patients were diagnosed with prostate cancer by prostate biopsies (n=2) and by histology of resected tissue after TURP (n=2).

Table 5. *Difference in improvement of baseline parameters between the*

	Mean ± SD		
	London	Nijmegen	p-value
Madsen score			
1 year	9 2 ± 4 6	6 5 ± 4 9	0 001*
2 years	8 5 ± 5 8	5 8 ± 5 7	0 065
3 years	5 9 ± 6 2	3 8 ± 5 9	0 210
Qmax (ml/s)			
1 year	2.7 ± 3 8	2 0 ± 3 7	0.249
2 years	1 6 ± 3 8	1.9 ± 4 3	0 701
3 years	1 7 ± 7 2	2 6 ± 4 0	0 560

* Significant using T-test for independent samples (α = 0 05)

DISCUSSION

The aim of any treatment in patients with LUTS and BPE is to achieve symptomatic relief with a corresponding reduction of bladder outlet obstruction. Symptomatic improvement is determined by a decrease in symptom scores. Traditionally, symptomatic treatment efficacy in TUMT is evaluated with the Madsen-Iversen symptom score that at the time of the first trials (1991) was the only commonly used symptom score. Reduction of bladder outlet obstruction is usually evaluated by increased urinary flow rate since urodynamic pressure-flow studies are not usually applied. A treatment outcome can be expressed either as mean changes of the parameters, or by a percentage improvement of the parameters. Short term results using these methods of treatment evaluation, and

morbidity of TUMT have been extensively reported [6]. However, data as to the durability of this treatment and the retreatment rate is limited to only few publications [9 15 16].

The 56% improvement at one year followup in the present study appears lower than the approximately 70% improvement reported in literature. The same accounts for the objective maximum flow improvement of 2.2 ml/s (or 24%) that is also slightly less comparable with data from literature that report around 3-4 ml/s (or approximately 35%) improvement in maximum flow. Finally, the 36% reduction of post void residual urine seems more comparable although data are limited and with reports varying from a 22 - 69% improvement[6]. On the other hand, the percentage improvement over baseline of the main outcome indices, using the FDA stratification guidelines, appears to be very similar to earlier papers. The present study reports 50% or more improvement in symptom scores and maximum flow in 60% and 26% of patients respectively. Data from literature notes 50% or more improvement in symptoms and maximum flow in 62% and 36% of patients respectively [8]. Furthermore, the present study shows that the achieved improvement in both symptoms and urinary performance remains durable and more or less stable over a three-year observation period. This is in accordance with Dahlstrand et al. who reported on two and three years followup data in a randomized study of TUMT versus TURP [6 9]. Nevertheless, one should acknowledge that there appears to be a trend toward a deterioration of the symptoms with the duration of the followup and that at three years followup the mean Madsen symptom score is 8.1 which is just above the entry level of this study, especially when taking into account that the patients who at three years followup are still without additional treatment, represent the best responders.

So where should TUMT-treatment be positioned among all the available treatment options for patients with LUTS and BPE? The objective improvement after lower-energy TUMT is not comparable to what is achieved after a surgical resection of the prostate as has been shown in the study of Dahlstrand et al [9]. The

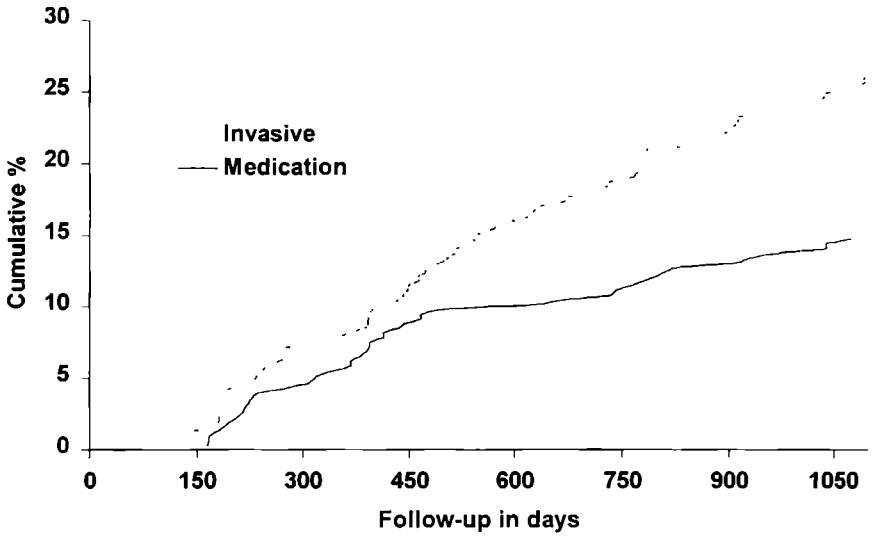
magnitude of improvement in urinary performance seems more in the ranges achieved with medical therapy. Stoner reported a significant improvement over baseline values of 2.4 ml/s in maximum flow of patients (n=156) treated with finasteride in an open extension North American study after 36 months after initiation of the treatment [1]. Lepor published similar changes in 103 patients, which were treated with terazosin after three years followup. The improvement in maximum flow ranged from 2.3-4.0 ml/s above baseline value between 3 months and 42 months followup with 30% or more improvement in flow in 40-59% of patients [2]. However, patients who are still using medication at three years of followup should also be considered as the best responders that inherently skews the data. Table 3 and 4 show similar improvements from TUMT after three years followup, with an improvement in flow of 2.5 ml/s with a 25% or more improvement in 49% of patients. Also, the symptomatic improvements of the alternative treatment options seem more or less comparable. Since the studies reporting on long term followup use different symptom scores to evaluate treatment outcome, the only way to compare these studies is by using the relative or percentage improvement. Lepor documents a 30% or greater improvement in symptom score in 62-77% of patients in a 3-42 months observation period. Stoner reports a mean reduction in symptom score of 3.6 points after 36 months in the extended study of finasteride. However, although the improvement is significant compared with baseline values and to the placebo control group, it only accounts for about a 18% improvement. The present study on TUMT shows that the symptomatic improvement after three years is 4.1 points that account for 34% improvement over baseline. Furthermore, a 25% or more improvement is achieved in 52% of patients (table 3).

Another point that needs to be addressed in the evaluation of TUMT treatment is the retreatment rate. Every treatment option for LUTS and BPE has its failure rate. In the case of initial surgical treatment, a further surgical intervention occurs because either of complications (urethral stricture/ bladder neck sclerosis) or for

recurrent disease. Table 2 shows that retreatment with an invasive therapy after initial TUMT treatment occurs in 24/287=8% of patients that have available data at 1 year followup, in 32/224=14% and 24/173=14% of patients after two and three years followup respectively. This accounts for a total of 80/258=31% retreatment rate over three years. The U.S. Prostatron TUMT group recently presented the long-term results of their FDA Study at the 91st AUA Annual Meeting in Orlando [17]. In contradistinction to the present study, they reported a significant lower retreatment rate of 11% with a TURP procedure. However, 29% reported to have changed to some medical treatment. These differences are likely to be explained by difference in department policy. In the present study a large number of patients were retreated with laser prostatectomy due to several protocols that were conducted with this modality at that time. Whereas in the U.S. it appeared that medication was the treatment of first choice when patients didn't experience improvement after their TUMT treatment. Nevertheless, both the U.S. and the present study report comparable and significant improvement in 52% and 51% of patients at three and four year followup respectively. Available data in literature on retreatment rates after a surgical resection of the prostate has some flaws since the reported 1.8-15.5% retreatment mainly depends on the observation period [18]. The largest documented retrospective study is the study by Roos et al, who documented 50.000 patients undergoing a TURP between 1963-1985. The retreatment rate for a second prostatectomy amounts to 2.3-4.3%, 8.9-9.7% and 12.0-15.5% after 1, 5 and 8 years respectively [19]. In this respect the U.S. long-term results appear to be quite comparable. And since none of the TURP studies reported a retreatment by medication, the overall retreatment rate after TUMT or TURP might actually be quite similar. Unfortunately, neither the finasteride nor the terazosin studies report on the fate of the patients who were considered a treatment failure.

The retreatment rate in the present study of patient treated with TUMT is

Figure 1 *Kaplan-Meier plot presenting early termination of the study. Each individual line represents the cumulative percentage of drop outs of patients (..... . = invasive retreatment, _____ = medication retreatment)*



higher than after TURP. However, a price has to be paid in terms of morbidity. In this respect TUMT seems favorable. The present study only reports a minor complication rate of TUMT, except for the TUMT treatment related retention rate of 27% that appears much higher than the reported 6.5% after surgical intervention[20]. Since TUMT is an invasive transurethral procedure, a urethral stricture rate of 0.4% (1/258) can be considered small compared with surgery that report a 2-20% incidence [21]. No patient reported development of stress-incontinence yet four patients (1.6%) experienced urge-incontinence after TUMT possibly from detrusor instability. Finally, the incidence of prostate cancer in only four patients (4/258=1.6%) appears low in comparison with available data on prostatectomy studies. This may be explained by the fact that patients were screened before entry into the study and that only 50/258=19% of patients actually have histology data from resected tissue available.

The present study, like several other clinical papers on TUMT, has shown that

there is a great inter-individual difference in treatment outcome of objective and subjective parameters. This has led many investigators to search for selection criteria that could predict clinical outcome. A multi center study of responders versus nonresponders to TUMT concluded that none of the baseline clinical parameters could predict treatment outcome [22]. The present study supports this conclusion since no difference in the main treatment indices was found between the patients that could be considered good responders at three years followup and the patients that were actually treatment failures. Until now, the only predictive factor for treatment outcome can be obtained from urodynamic studies with pressure-flow analysis as demonstrated by Tubaro et al. in a European multi center study. Patients with the presence of a constrictive urodynamic obstruction showed favorable improvement in both symptoms as voiding parameters over patients who have a predominantly compressive obstruction [23].

Furthermore, thermometry studies have shown that not all prostates reach the maximum temperature intended, because the thermoregulation of the tissue in every individual patient differs significantly [24]. In addition, the correlation between the achieved intra prostatic temperature and treatment outcome suggest that the higher the intra prostatic temperature, the better the clinical results [25]. This has led to modification of the treatment software by increasing rectal threshold temperature and energy levels, resulting in fewer interruptions during treatment and a mean increase of 40% of total energy delivered to the prostate [26]. First clinical experience in Phase II studies with high energy TUMT treatments (using Prostasoft® version 2.5), has indeed shown an increased objective improvement with comparable symptomatic improvement [26,27]. The relieve of urodynamic bladder outlet obstruction and the presence of a cavity on transrectal ultrasound of the prostate three months after the high energy TUMT treatment, might also be indicative for an improved efficacy and durability on the long term.

CONCLUSION

Lower energy transurethral microwave thermotherapy results in significant symptomatic improvement in 52% of patients, while the objective improvement is in the range of 3 ml/s at three years followup The short and long term morbidity is acceptably low

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Chapter 4

HIGH ENERGY THERMOTHERAPY

Based on:

JJMCH de la Rosette, MJAM de Wildt, K Höfner, SStC Carter, FMJ Debruyne, A Tubaro.

High energy thermotherapy in the treatment of benign prostatic hyperplasia. Results of the European BPH study group.
Journal of Urology ***156****: 97-102, 1996*

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High energy transurethral microwave thermotherapy. A thermoablative treatment for benign prostatic obstruction.
Urology, in press

RESULTS OF THE EUROPEAN BPH STUDY GROUP

SUMMARY

We documented the results of high energy transurethral microwave thermotherapy in the treatment of benign prostatic hyperplasia. We evaluated 116 patients following transurethral microwave thermotherapy according to symptom scores, transrectal ultrasound, free voiding and pressure-flow study parameters. Significant improvement was noted in all objective and subjective parameters. Moreover, cavities in the prostatic urethra were observed in almost 40% of the patients. High energy transurethral microwave thermotherapy is an effective therapy for benign prostatic hyperplasia. Patients with larger prostates and moderate to severe bladder outlet obstruction seem to be the best candidates for this higher energy thermotherapy protocol, although morbidity is increased.

INTRODUCTION

Bladder outlet obstruction in men has been a clinical problem throughout medical history. As early as the 17th century it was suggested that benign prostatic hyperplasia (BPH) could result in mechanical obstruction of the bladder outlet tract, which may eventually cause lower urinary tract symptoms, inefficient bladder emptying with poor urinary flow and/or post-micturition residual urine[1]. At this juncture the patient usually seeks medical advice either because of troublesome symptoms or complaints secondary to the worsened voiding, for example recurrent urinary tract infections.

Presently, transurethral resection of the prostate is the gold standard therapy for BPH, affording excellent results in the hands of the experienced operator. The success of transurethral resection of the prostate is defined by the immediate removal of obstructing prostatic tissue resulting in the formation of cavities. Long lasting improvement in symptoms and voiding parameters is achieved within a few days of treatment. However, this operation is not to be taken lightly. Although the mortality rate has decreased to 0.5%,[2] the morbidity rate after transurethral resection of the prostate is still 18% and has not altered significantly within the last 15 years. Consequently, despite the proved safety and efficacy of this procedure, its morbidity as well as its relatively high cost and invasive nature have led many investigators to search for an alternative treatment.

Many techniques that minimize the physiological effects associated with prostatic surgery are currently being assessed, including use of prostatic stents, transurethral needle ablation, high intensity focussed ultrasound, transurethral microwave thermotherapy and laser therapy.[3-7] The question as to which technique is appropriate in any individual is answered largely by knowing the outcome of each of these therapies. Despite the encouraging results claimed by all of the new techniques, transurethral resection of the prostate continues to surpass its competitors. However, the results of high energy thermotherapy seem to shed a

new light on this discussion.

The results reported with lower energy thermotherapy using Prostasoft® 2.0 (Technomed Medical Systems, Lyon, France) in the treatment of BPH are promising. Overall symptomatic improvement has been reported in the majority of patients in conjunction with improvement of voiding parameters[8-10]. The Madsen symptom score decreased from a mean of 13 before treatment to about 4 after treatment, while mean maximum flow change ranged from 2 to 3 ml/s. It has been suggested that the placebo response with this modality may contribute considerably to treatment outcome. However, 5 sham controlled studies have demonstrated that the effect of transurethral microwave thermotherapy is greater than can be accounted for by either the associated urethral instrumentation or by any placebo effect.[11] The re-treatment after transurethral microwave thermotherapy using Prostasoft® 2.0 was reportedly 0.5% to 11% at one year followup.[9,10,12]

An increase in thermal dose can be seen with the evolution of thermal treatment modalities. The elevation of intraprostatic temperatures as measured by invasive thermometry during transurethral microwave thermotherapy using version 2.0 operating software has been shown to be broadly correlated with clinical outcome.[13] Program version 2.0 was modified to provide more power at a maximum of 70 Watts and uses a higher rectal threshold leading to an increase in the energy delivered to the prostate. This new version of the operating software known as Prostasoft® version 2.5 is currently under evaluation. In contrast to earlier reports on results achieved with lower energy thermotherapy, the results with these higher energy levels seem to be excellent, and in a subgroup of patients they are even comparable to those of surgical therapy. We present the results of a multicenter study using high energy thermotherapy for the treatment of BPH.

PATIENTS AND METHODS

Patients recruited for the study had a Madsen symptom score of 8 or more, maximum flow rate of 15 ml/s or less, post-void residual volume of 350 ml or less and voided volume of 100 ml or more. Assessment of these patients included history with symptom scores, physical examination with digital rectal examination, biochemistry investigations including prostate specific antigen, urinalysis, urine culture, transrectal ultrasonography of the prostate, uroflowmetry, post-void residual volume measurement and a urodynamic investigation including pressure-flow studies. The results of high energy thermotherapy in 116 men with lower urinary tract symptoms and BPH were evaluated, and outcome was correlated with prostate size, International Prostatic Symptom Score (I-PSS), Madsen symptom score, free flow voiding parameters and grade of bladder outlet obstruction. Followup was performed at 4, 12, 26 and 52 weeks after treatment.

We used the Prostatron device with a C00 treatment catheter consisting of a microwave dipole antenna positioned 10 mm below the Foley balloon and mounted in a water cooled transurethral probe. Version 2.5 of the high energy operating software provides power at a maximum of 70 watts with a rectal threshold set at 43.5°C. Transurethral microwave thermotherapy has been described previously.[14]

Uroflowmetry was performed, and the post-voiding residuals were determined by transabdominal ultrasound using the ellipsoid formula. Urodynamic investigations were performed with a transurethral catheter equipped with an intravesical microtip pressure sensor for bladder pressure recordings. The abdominal pressure was recorded intrarectally with a microtip sensor catheter. Commercially available equipment was used to record the pressure and flow data. The digitally stored data were translated to a urodynamics analysis computer program developed at our department. To provide objective and precise grades of obstruction, pressure-flow study graphs were fitted to a passive urethral resistance

relation curve. The minimal urethral opening pressure and theoretical urethral lumen were calculated automatically.[15] The urethral resistance factor was computed to enable the classification of patients on a continuous, 1 parameter scale of obstruction.[16] We also added a nonparametric analysis of obstruction using a classification according to the linear passive urethral resistance relation pressure-flow study nomogram.[17]

RESULTS

Between April 1993 and July 1994 a total of 116 patients were treated with high energy transurethral microwave thermotherapy using the Prostasoft® 2.5 software. Patient age at baseline ranged from 50 to 87 years (mean 66.6) and average prostate volume plus or minus standard deviation was 51 ± 21 cm^3 (range 20 to 154). Madsen symptom score ranged from 8 to 23 (mean 13.6 ± 3.6). Uroflowmetry parameters show a maximum flow rate of 3 to 15 ml/s (mean 9.6 ± 3.3), voided volume 100 to 697 ml (mean 227 ± 127), and post-void residual 0 to 350 ml (mean 73 ± 79). An average of 147 ± 44 kJ (range 28 to 209) of microwave energy were administered during treatment.

Of the patients 67 have reached a 1 year followup, while 105 were followed 26 weeks. Among the 11 patients who were not seen at 26 weeks 2 died of nontreatment related causes (1 of terminal hart failure 4 months after treatment and 1 of pulmonary failure due to α1-antitrypsin deficiency), 3 underwent transurethral resection of the prostate, and 6 were lost to follow up. Mean Madsen symptom score at baseline was 13.6 and improved to 9.4 at 4 weeks, 6.0 at 12 weeks, 5.5 at 26 weeks and 4.9 at 52 weeks of followup (figure 1a). The I-PSS showed a similar pattern, with improvement from a mean of 17.5 at baseline to 13.9 at 4 weeks, 8.2 at 12 weeks, 7.9 at 26 and 7.1 at 52 weeks of followup (figure 1b). Maximum flow rate improved from 9.6 ml/s at baseline to 9.8 ml/s at 4 weeks, 15.2 at 12 weeks and 14.1 at 26 weeks followup. These improvements were sustained to 52 weeks

with a maximum flowrate of 14.5 ml/s (figure 1c). The voided volume during follow up increased slightly (figure 1d), while the post void residual decreased significantly from 73 ml at baseline to 40 ml at 4 weeks, 27 at 12 weeks, 33 at 26 and 25 at 52 weeks followup, respectively (figure 1e). Mean duration of transurethral drainage was 14.3 ± 15.2 days (range 0 to 105 days).

Transrectal ultrasonography at 3 months followup identified a cavity in 37% of the patients (figure 2). There appeared to be a good statistical correlation between the presence of cavities and uroflowmetry improvement ($p=0.003$). Maximum flow rate improved from 9.7 ml/s at baseline to 17.9 ml/s in patients with a cavity on TRUS and from 9.6 ml/s to 13.6 ml/s in those without a cavity. Currently, data for 83 patients are available for urodynamic analysis. At 6 months after transurethral microwave thermotherapy, a statistically significant improvement was noted for all parameters, which is also clearly illustrated in the Abrams-Griffith nomogram (figure 3 and table 1).

Baseline parameter stratification versus treatment outcome showed that particularly patients with larger prostates and moderate to severe bladder outlet obstruction respond best to high energy transurethral microwave thermotherapy (table 2). These patients showed a significant improvement in objective and subjective parameters. The relationship between maximum flow rate at baseline and treatment outcome was much less. There appeared to be no relation between treatment outcome and the Madsen symptom score at baseline.

High energy thermotherapy treatment resulted in considerable morbidity. Irritative voiding complaints were noted in a large number of patients for up to 2 to 4 weeks, and transient hematuria was present in most patients during the first days after treatment. Finally, retrograde ejaculation was documented in a third of the patients who had antegrade ejaculation before treatment.

Figure 1a. *Improvement in Madsen score at baseline, 4, 12, 26 and 52 after treatment.*

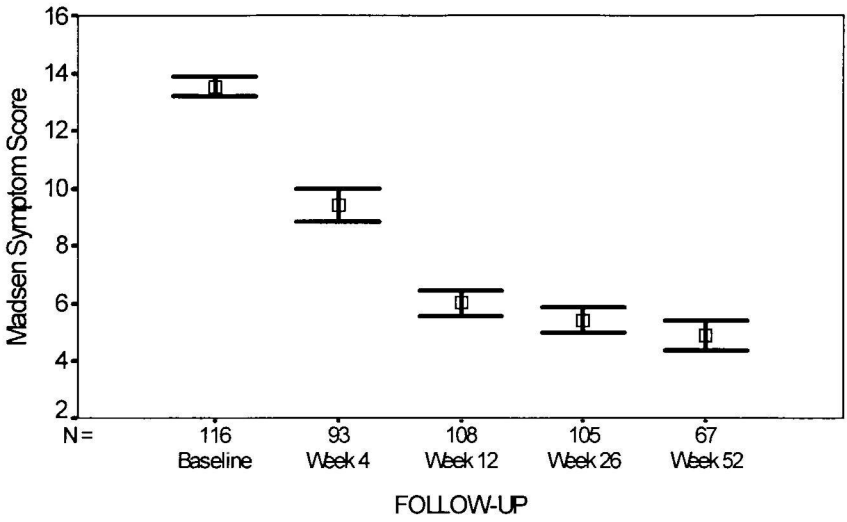


Figure 1b. *Improvement in I-PSS at baseline, 4, 12, 26 and 52 after treatment.*

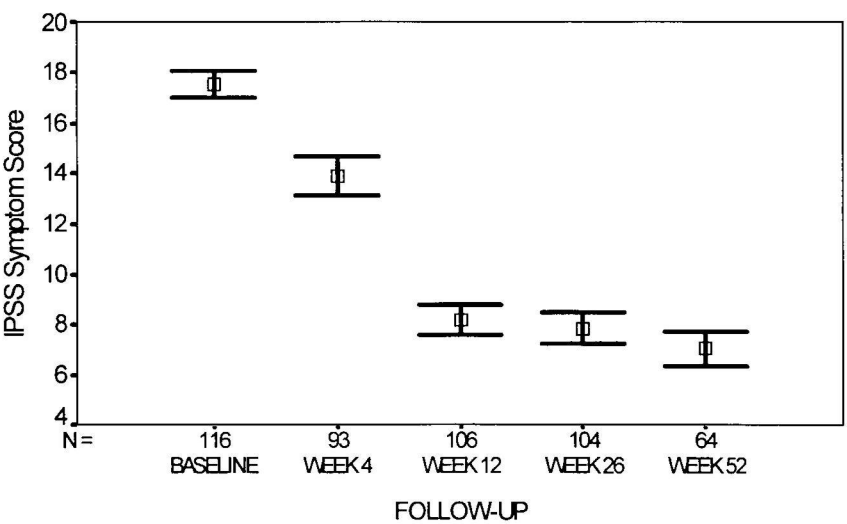


Figure 1c. *Improvement in maximum flow at baseline, 4, 12, 26 and 52 after treatment.*

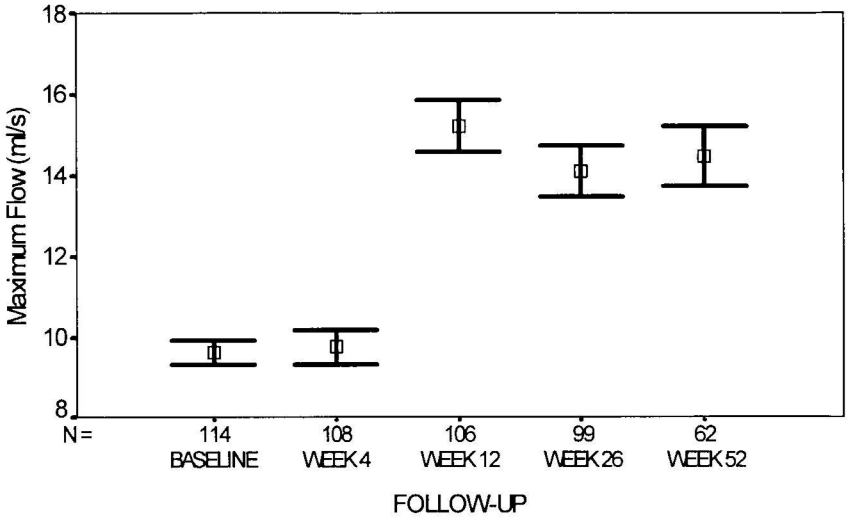


Figure 1d. *Improvement in voided volume at baseline, 4, 12, 26 and 52 after treatment.*

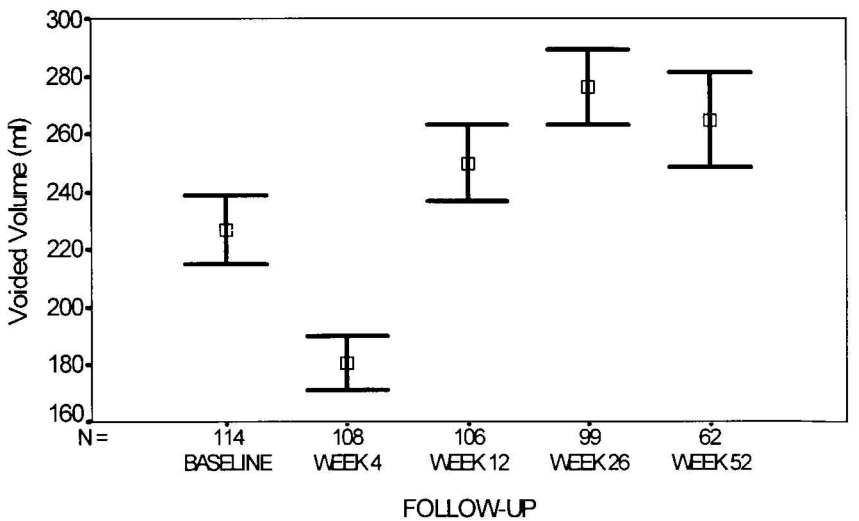


Figure 1e. *Improvement in post-void residual at baseline, 4, 12, 26 and 52 after treatment.*

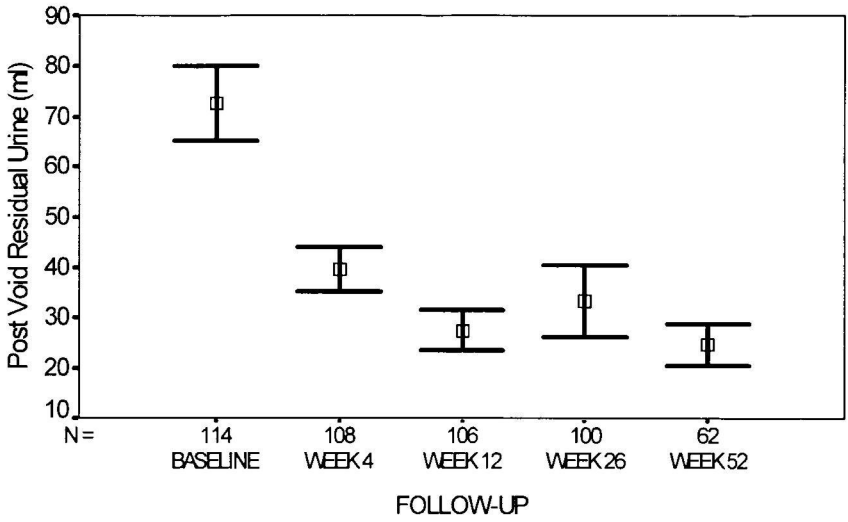


Table 1. *Changes in pressure-flow study parameters before and 6 months after treatment*

	Mean ± SD	
	Before	6 months
p_{det}atQmax (cmH_2O)	64 ±23	39 ± 16
linPURR	2.9 ± 1.3	1.3 ± 1.1
URA (cmH_2O)	41 ± 15	23 ± 11
p_{muo} (cmH_2O)	33 ± 17	16 ± 9
A_{theo} (mm^2)	2.8 ± 1.3	6.2 ± 5.1

DISCUSSION

It is generally believed that enlargement of the prostate results in bladder outlet obstruction, leading to clinical manifestations of BPH. The term BPH describes histopathological abnormalities of the prostate. However, it is usually used to

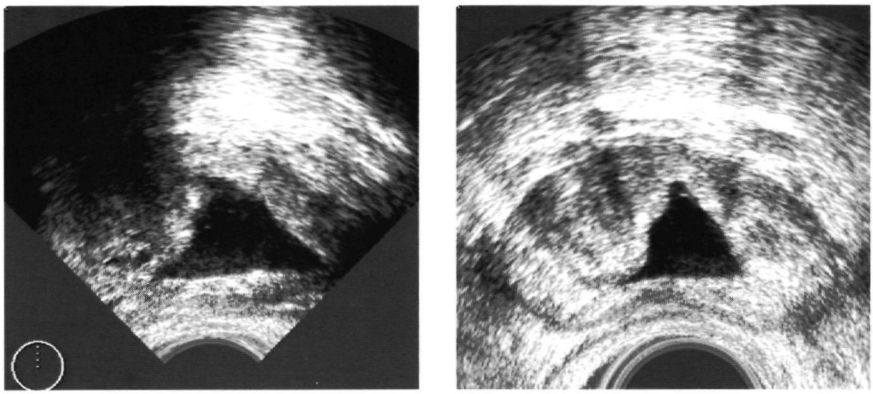
Table 2 *Outcome of main indices at 3 months stratified according to baseline values*

		Mean ± SD					
		Madsen score		Qmax (ml/s)		p_{det}atQmax (cmH_2O)	
	N	Before	3 months	Before	3 months	Before	3 months
Qmax (ml/s)							
≥ 12	36	13 8 ± 3 7	5 0 ± 4 9	13 5 ± 1 2	18 3 ± 5 9	67 ± 21	37 ± 17
< 12	80	13 5 ± 3 6	6 5 ± 4 4	7 9 ± 2 2	14 0 ± 6 4	62 ± 24	39 ± 15
Prostate vol (ml)							
≥ 40	77	13 4 ± 3 6	5 8 ± 4 3	9 8 ± 3 4	16 5 ± 7 1	68 ± 21	38 ± 16
< 40	39	13 8 ± 3 7	6 4 ± 5 0	9 3 ± 3 0	13 2 ± 4 6	53 ± 24	41 ± 15
IinPURR							
≥ 3	52	13 7 ± 3 5	5 7 ± 4 4	9 5 ± 3 4	16 9 ± 7 1	78 ± 15	42 ± 17
< 3	31	14 2 ± 3 9	8 0 ± 4 6	9 1 ± 3 1	14 0 ± 6 5	40 ± 10	33 ± 13

describe a condition that can be characterized by nonhistological criteria such as voiding symptoms, an enlarged prostate and bladder outlet obstruction.[18] The majority of elderly men will eventually experience some voiding symptoms and will seek therapy.[19] The only generally accepted treatment for BPH is transurethral or open prostatectomy. Since men with BPH are often of advanced age with cardiopulmonary diseases and high operative risks, a minimally invasive treatment has been sought, including medication[20,21] and instrumentation.[3-7] With the concept of transurethral microwave thermotherapy as an outpatient and anaesthesia-free procedure, and the encouraging clinical results achieved to date, much effort has been concentrated on developing this treatment modality.

Application of higher energy levels using Prostasoft® 2.5 was first reported by Devonec[6] and de la Rosette[11] et al, who demonstrated clinically significant improvement. Our present multicenter study confirms these results. The changes in subjective parameters using the high energy Prostasoft® 2.5 software, is similar to the improvement noticed in patients treated with the Prostasoft® 2.0 version.[6]

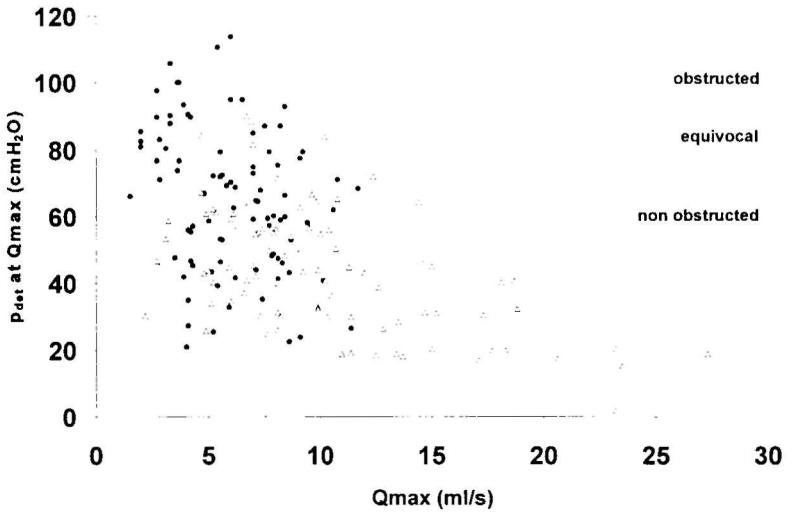
Figure 2 *Ultrasonograms of the prostate identifying a cavity 3 months after TUMT (**a**, longitudinal, **b**, transverse section)*



However, when comparing the objective parameters, a significantly better outcome in terms of urinary peakflow change was noted. A statistically significant increase in maximum flow was found of 9.6 to 15.2 ml/s was noted at 12 weeks after transurethral microwave thermotherapy, which was sustained to at least one year. Mean post void residual values also improved significantly from 73 to 27 ml at 12 weeks and 25 ml at one year. This objective improvement in uroflowmetry results was much more pronounced than in patients treated with the lower energy software. Transrectal ultrasound imaging of the prostate identified a cavity in 37% of the patients at 3 months after treatment (figure 2). A positive correlation between the presence of such a cavity and urinary flow rate improvement was observed. One may conclude that more energy delivered to the prostate seems to result in greater improvement in objective parameters, which may be explained by the creation of cavities within the prostate. However, when such a cavity is absent the treatment should not be regarded as a failure because uroflowmetry may improve independent of cavity formation.

Although flowmetry is an excellent method documenting the act of micturition, and it may indicate whether an abnormality is present, its role in defining the grade of obstruction is limited.[22] For transurethral microwave thermotherapy to be

Figure 3. *Abrams-Griffiths nomogram of obstruction of patients before TUMT (●) and 6 months after TUMT (Δ)*



regarded as proper therapy for BPH, it must be able to relieve the outlet obstruction. Advanced urodynamics, including pressure-flow study analysis, are considered the best methods to document changes in the grade of obstruction.[22] The changes in pressure-flow study parameters were only moderate with the lower energy Prostasoft® 2.0 software. We concluded that only a certain type of obstruction responded favorably to thermotherapy.[23,24] In general, however, severe obstruction is not cured following low energy thermotherapy. Analysis of the urodynamic data at 6 months after transurethral microwave thermotherapy using Prostasoft® 2.5 showed that 80% of obstructed patients appeared to be cured (Abrams-Griffiths nomogram, figure 3). A significant decrease in all obstruction parameters was noted overall (table 1). One can conclude that transurethral microwave thermotherapy using Prostasoft® version 2.5 is able to relieve bladder outlet obstruction.

From an earlier study we learned that no single clinical parameter could predict which patients would respond best to low energy thermotherapy.[25] Using high

energy thermotherapy it appears that patients with more severe outlet obstruction and larger prostates will respond best. Further studies are required to explain this phenomenon. A possible explanation for the favorable outcome of treatment of larger prostates is a difference in tissue composition and tissue perfusion. It is well known that stromal tissue responds different to heat than glandular tissue.[26] Larger prostates may have a different distribution of stromal and glandular tissue and consequently they may respond differently to thermotherapy. We also know that the temperature increase in the prostate depends strongly on the tissue perfusion, and that perfusion is known to increase with temperature during thermotherapy.[27,28] One can speculate that in larger prostates the tissue perfusion is less efficient than in smaller prostates, and that perhaps as a consequence higher temperatures can be achieved resulting in necrosis with formation of a cavity. Current thermotherapy systems do not consider the effect of tissue perfusion on the efficacy of the treatment.

Although urine flow is improved, the morbidity caused by high energy transurethral microwave thermotherapy is increased compared to lower energy protocols. The high energy treatment is well tolerated by the patients but pain medication must be administered before or during therapy in most cases. On a trial and error basis, 30 mg morphine sulfate administered 2 hours before therapy resulted in an almost complaint-free treatment. If requested, patients also were given either 10 mg diazepam and/or 0.10 mg fentanyl during treatment. Perception of discomfort during transurethral microwave thermotherapy may vary from a mild feeling of perineal warmth and a mild urge to urinate to significant discomfort. However, the morbidity is clearly lower with transurethral microwave thermotherapy than with transurethral resection of the prostate. Transurethral microwave thermotherapy can still be performed as an outpatient procedure without general anaesthesia, and is particularly well suited for patients in poor health. Occasionally, hematuria and tissue slough are noted, and urinary retention is expected in almost all patients. Catheterization interval averaged 14.3 days

(range 0 to 105), and patients with larger prostates required longer catheterization periods than those with smaller prostates. The findings of retrograde ejaculation in a third of our patients is in contrast to those documented with lower energy thermotherapy, in which antegrade ejaculation was unchanged in the majority of patients.[29]

No bladder neck contraction or urethral strictures have been noted to date. Treatment with transurethral resection of the prostate was repeated in 3 patients because they where not satisfied with the result. From the long-term followup data using Prostasoft® 2.0 we have learned that re-treatment rate at 1 year is estimated up to 10%,[30] while 3 year follow up data by de Wildt and de la Rosette,[27] and Dahlstrand et al [31] indicate that clinical benefit is sustained for this period. One may expect that the results achieved with the higher energy software are at least as good.

CONCLUSION

High energy transurethral microwave thermotherapy shows significant subjective and objective improvement. The best candidates are patients with moderate to severe bladder outlet obstruction and larger prostates. Formation of cavities after treatment correlated well with better clinical outcome.

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1 YEAR FOLLOWUP OF HIGH ENERGY THERMOTHERAPY

SUMMARY

High energy transurethral microwave thermotherapy (TUMT) was developed to increase treatment efficacy over former low energy treatment protocols as an outpatient-based, anesthesia-free procedure for patients with benign prostatic obstruction A Phase II study was conducted to evaluate treatment outcome and to enlighten possible prognostic factors Eighty-five patients with lower urinary tract symptoms were included in the study A Madsen symptom score of 8 or more, a maximum flow less than 15 ml/s and a postvoid residual urine volume (PVR) of under 350 ml were the main requirements for entry Eleven patients were lost to followup, making 74 patients evaluable at one year followup Significant improvement was noticed in all indices the Madsen symptom score improved 58% from baseline, the maximum flow rate improved from 9 4 to 14 9 ml/s, with a decrease in PVR of 80 ml to 25 ml, bladder outlet obstruction could be relieved in 78% of patients, and prostate volume decreased by 20% , with cavity formation in 42% Patients with bigger prostates (greater than 40 cm^3) and patients with more severe bladder outlet obstruction appeared to be the best responders Post-treatment morbidity consisted of a prolonged need for transurethral catheter drainage (mean 16 days), with correlated irritative voiding complaints for an average of 2 to 3 weeks Overall improvement of high energy thermotherapy now shows comparable results to surgical resection of the prostate

INTRODUCTION

Benign prostatic obstruction (BPO) is a common disease in men that is creating an increasing demand on the health care system. It is estimated that eventually one third of all males will require an operation for relief of lower urinary tract symptoms (LUTS) due to BPO.[1]

For more than 50 years, the treatment for BPO has been decreasing gland volume. The surgical removal of prostate tissue is still considered the reference standard. Besides being the most commonly performed surgical procedure in elderly males, it comprises a large part of the urologist's workload.[2] Complications and side effects include infection, incontinence, retrograde ejaculation, urethral stricture, and impotence. In addition, some patients have a severe medical illness that increases anaesthetic and surgical risk, which may predispose them to postoperative sepsis or a cardiovascular event.[3,4]

Currently, the management of BPO is under evaluation. Medical treatment is becoming an increasingly important option in patients with moderate LUTS.[5,6] In addition several minimally invasive treatment options have been tested. The use of heat (applied by different heat generators such as ultrasound, radio-frequency, laser and microwave-devices) appears to be the most promising alternative.[7,8,9,10] Of these different applications, microwave energy has been most extensively investigated. Continuous developments have led to transurethral microwave thermotherapy (TUMT) that makes it possible to obtain high temperatures deep inside the prostate lateral lobes while still preserving the urethral mucosa; 1296 MHz microwave radiation is applied from a transurethral antenna, and the mucosa is simultaneously cooled by circulating fluid within the applicator (Prostatron device, Technomed Medical Systems, Lyon, France). This concept allows an outpatient-based, anesthesia-free procedure. Significant symptomatic improvement and increase in objective parameters such as maximum flow rates and postvoid residual urine volume (PVR) are reported.[10] The clinical improvement has been

shown not to be due to a placebo effect or the result of the associated urethral instrumentation in randomized trials of TUMT versus sham.[11,12] Although in a randomized TUMT versus transurethral resection of the prostate (TURP) trial the symptomatic improvement is similar to improvement seen after TURP, the objective improvement is less pronounced and the durability of the treatment is unclear.[13] Interstitial thermometry studies during TUMT treatments have shown that there is a strong correlation between the treatment outcome and the obtained temperatures within the prostate.[14] This has led to the development of a new software protocol that operates the Prostatron unit (Prostasoft® 2.5), enabling higher energy levels (intraprostatic temperatures up to 75°C) with an average increase of total energy delivered to the prostate of 40%, thus creating tissue necrosis and cavity formation within the prostate; this is termed thermo-ablation.[15,16]

We conducted a Phase II study using this high energy protocol. Besides documenting treatment outcome, we will also try to determine possible prognostic factors that contribute to the better results.

MATERIAL AND METHODS

Between October 1993 and August 1994, 85 patients were treated with the Prostasoft® 2.5 protocol approved by the hospital's ethical committee. All 85 men, aged 50 to 85 years (mean: 64.7 ± SD 8.6), had LUTS related to BPO and, in principle, were candidates for either (TURP) or an open prostatectomy. Inclusion and exclusion criteria are mentioned in table 1.

Twelve patients (14%) were in poor cardiac or pulmonary health (ASA 3 to 4). At baseline, all patients underwent the following investigations: general history; complete physical examination with digital rectal examination (DRE); estimations of full blood count, blood urea and creatinine; and urine microscopy and culture.

Urine cytology and prostate specific antigen (PSA: Hybritech, Texas) levels were always measured to exclude coexisting malignancy. Upper urinary tract dilation and renal pathology were excluded by ultrasound investigation. Prostate configuration was assessed by performing transrectal ultrasound (TRUSP), volume being calculated by a planimetric technique (Kretz Combison 330 with a 7.5 MHz transrectal probe; multi 3-D VRW 77AK). In case of an abnormality detected by DRE, PSA level, or TRUSP, ultrasound-guided prostate biopsies were performed. Flexible urethrocystoscopy (Storz) was carried out to judge the patency of the (prostatic) urethra for the presence of strictures or an isolated obstructing prostatic middle lobe and to exclude intravesical pathology.

Table 1 *Inclusion and exclusion criteria for high energy TUMT*

INCLUSION CRITERIA	EXCLUSION CRITERIA
Age ≥ 45 years	Acute prostatitis or urinary tract
Prostatic urethra measured by flexible cystoscopy ≥ 2.5 cm	Prostate carcinoma
	Isolated obstructed prostatic middle
Madsen symptom score ≥ 8	Diabetes mellitus
Qmax ≤ 15 ml/s	Intravesical pathology
Postvoid residual volume ≤ 350 ml	Neurological disorders
Voided volume ≥ 100 ml	Drugs influencing bladder function

Patient symptoms were evaluated using a physician-guided Madsen symptom score allowing comparison with previous studies reporting on TUMT.[17] In addition the self-administered International Prostate Symptom Score (I-PSS) was used.[18]

A Dantec Urodyn 1000 flowmeter was used to register the maximum flow rates (with corrections for flow artefacts using the two second method) and voided volume. Post-void residual volume (estimated by suprapubic ultrasound with an ellipsoid technique), and voiding percentage (that is, [voided volume/(voided volume + postvoid residual volume)] x 100 as a measure of voiding efficiency,

were also recorded.

To quantify the grade of bladder outlet obstruction, urodynamic investigation with pressure-flow (PQ) analysis was performed. Intravesical and rectal pressures were recorded using 8F catheters mounted with microtip-sensors (MTC, Dräger, Germany), and detrusor pressure was calculated as the difference between both. The digitally stored pressure and flow-data were analyzed by a program developed at our department (UIC/BME Research Center, Department of Urology, Nijmegen, The Netherlands). The following parameters derived from the PQ-analysis were used: detrusor pressure at maximum flow (P_{det}at Qmax in cmH_2O), maximum flow rate PQ-Qmax in ml/s), and the linPURR (obstruction grading according to Schäfer).[19,20] A patient is considered urodynamically obstructed when P_{det}at Qmax falls into the obstructed area of the linPURR nomogram when the linPURR is 3 or greater.

After correct positioning of the urethral heat applicator and rectal-temperature probe, a 60 minute microwave treatment was performed. A more extensive description of such a treatment has been reported elsewhere.[21] Two hours before treatment a 20-40 mg dose of morphine sulphate was administered orally. If necessary, additional intravenous sedation with a combination of diazepam and fentanyl was given when patients experienced major discomfort during treatment; this was mostly expressed as an intense urge to void, sometimes in combination with an urge to defecate. Initial experience showed urinary retention in nearly all patients; therefore, all patients were given a urethral catheter with leg-bag directly after treatment. Patients were seen 1, 4, 12, 26 and 52 weeks after treatment. Uroflowmetry with PVR volume, symptom scores and blood analysis, and urinalysis were repeated at each visit. Ultrasonography of the prostate was repeated at 12 and 52 weeks. Finally, the urodynamic investigation was repeated 26 weeks after treatment. Statistical analysis was done with the Student's t-test (α=0.05) and the Wilcoxon signed-rank test (α=0.05). Correlations were tested using the Pearson correlation (α=0.05)

RESULTS

At baseline 85 patients entered the study. At a 1-year followup, 74 patients were available for analysis. The followup scheme is presented in table 2.

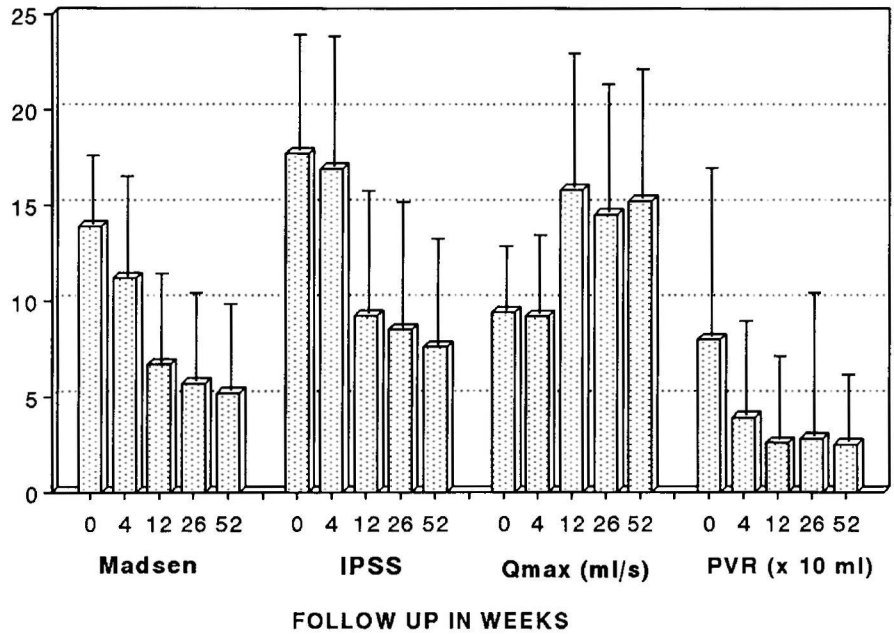
Table 2. *Followup of the 85 patients at 3, 6 and 12 months from baseline*

Number of patients			
Baseline	3 months	6 months	1 year
85	83	81	74
1 TURP elsewhere 1 died of terminal heart failure non treatment related	1 died of pulmonary failure due to α1-antitrypsine deficiency 1 refused further visits to out-patient clinics	3 underwent TURP because of un-satisfactory result 2 refused further visits to outpatient clinics 1 died of metastasized gastro-intestinal tumor 1 underwent laser prostatectomy	

Treatment

In 40 patients (47%) additional intravenous sedation was necessary during treatment. None of the treatments had to be stopped before 60 minutes nor did the energy level have to be reduced. The total amount of energy delivered to the prostate ranged from 50.0 kJ to 208.9 kJ (mean: 154.7 kJ ± SD 36.4). In 3 patients (5%), it was not possible to insert a transurethral catheter immediately after treatment, so a suprapubic catheter was inserted.

Figure 1. *Mean improvement of main indices at baseline, 4, 12, 26 and 52 weeks after treatment*



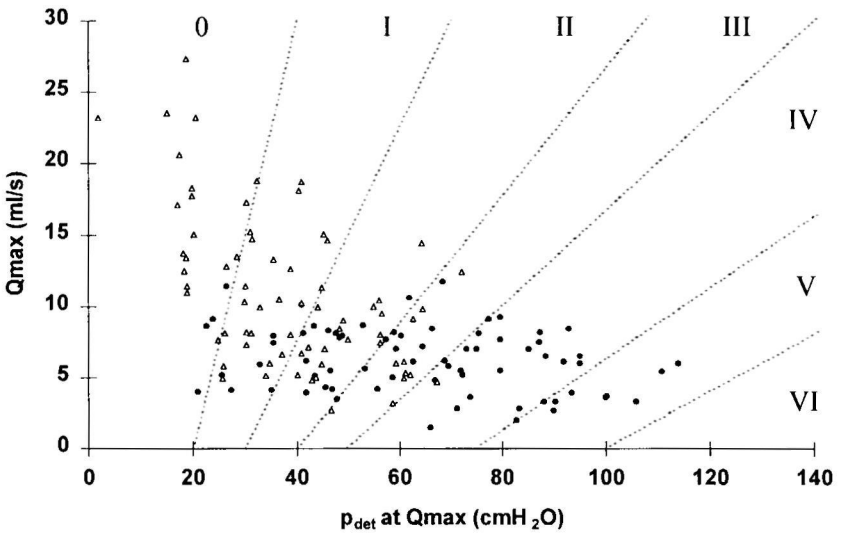
Subjective results (symptom scores)

The complete group showed significant changes in both symptom scores. The mean Madsen symptom score decreased by 58% at 12 months followup. With an initial improvement from a mean 13.9 ± SD 3.6 at baseline to a mean of 6.7 ± SD 4.6 at 3 months, stabilizing occurred at 5.7 ± SD 4.6 at 6 months and 5.8 ± SD 4.7 at one year followup. Comparable changes were noticed in the I-PSS scores. The mean I-PSS at baseline of 17.6 ± SD 6.0, decreased to 9.2 ± SD 6.4 at 3 months, 8.5 ± SD 6.5 at 6 months and 8.0 ± SD 5.8 at a year followup indicating a mean I-PSS decrease by 55% at 1 year (figure 1).

voiding parameters

For the complete group the mean maximum flow rate showed significant improvement from 9.4 ± SD 3.3 ml/s at baseline to 15.8 ± SD 7.0 ml/s at 3 months followup and remained stable at 14.4 ± SD 6.7 ml/s at 6 months and 14.9 ± SD 6.7 ml/s at 1 year followup.

Figure 2. *Changes in p_{det}atQmax (cmH_2O) before (●) and 6 months after TUMT (△) in the linPURR-nomogram for obstruction*



Similar improvements were noticed in the post void residual urine and voided percentage. A mean PVR of 80 ± SD 88 ml at baseline improved to 26 ± SD 44 ml/s at 3 months, stabilizing at 28 ± SD 75 ml at 3 months and further improving to 25 ± SD 35 ml after 1 year. The voided percentage improved from a mean of 77 ± SD 18% at baseline to 92 ± SD 10% at 3 months, 93 ± SD 13% and 92 ± SD 11% after 1 year followup (Figure 1).

Urodynamic investigation with pressure flow studies

At baseline, two investigations were excluded because pressure-flow analysis was not available due to unreliable recording of the voiding phase; therefore the urodynamic data of 83 patients were available. After 26 weeks the urodynamic investigation was repeated in 71 patients. In total, 8 patients refused a second investigation, the remaining 4 patients were the ones who were lost to followup (table 2). The urodynamic parameters significantly improved: the p_{det}atQmax improved from a mean of 63.6 ± SD 22.7 cmH_2O at baseline to 38.9 ± SD 15.7 cmH_2O at 26 weeks; the PQ-Qmax improved from a mean of 6.3 ± SD 2.3 ml/s at baseline to 11.0 ± SD 5.4 ml/s at 26 weeks; the linPURR improved from a mean of 2.9 ± SD 1.3 at baseline to 1.3 ± SD 1.0 at 26 weeks.

Figure 2 gives a graphical representation of changes in detrusor pressure at maximum flow rate (p_{det} atQmax) before and 6 months after TUMT using the linPURR-nomogram for obstruction. At baseline, 46 patients (65% of 71) could be considered obstructed with a linPURR of 3 or more. Using the linPURR classification for obstruction, 36 of these 46 patients (78%) can no longer be considered obstructed 6 months after treatment.

Trans rectal ultrasound imaging of the prostate

At baseline, the mean prostate volume on ultrasonographic investigation was measured at 53.9 ± SD 22.8 ml (range 30 to 154). The repeated measurement at 3 months showed an average volume of 45.1 ± SD 19.1 ml (range 21 to 122 ml) thus indicating a significant volume reduction of 8.8 ± SD 12 ml ($p < 0.001$). This reduction was confirmed at 52 weeks with a mean prostate volume of 43.4 ± SD 19.3 ml (range 15 to 119). Furthermore, in 35 patients of the available patients at 3-month followup (42% of 83) a cavity could be observed (Figure 3). The presence of a cavity was positively correlated with improvement in urinary performance and

relief of outlet obstruction. The difference in Qmax improved was significant ($p=0.02$): the mean improvement in Qmax is 8.5 ± SD 7.3 ml/s (from 9.4 to 17.9 ml/s) in patients with a cavity and 4.8 ± SD 5.4 ml/s in patients without a cavity (from 9.7 to 14.5 ml/s). In accordance there is greater relief of outlet obstruction in patients with a cavity ($p=0.002$): the mean p_{det}atQmax improves 36.8 ± SD 27.1 cmH_2O (from 70.4 to 33.6 cmH_2O) in patients with a cavity and 17.7 ± SD 25.6 cmH_2O (from 59.3 to 41.6 cmH_2O) in patients without a cavity.

PSA levels

The mean PSA level at baseline was 5.0 ± SD 3.3 ng/ml (range 0.5 to 14), and it increased to a mean 40.8 ± SD 28.3 (range 1.8 to 120), 1 week after treatment. It ended below baseline level of 4.0 ± SD 2.9 after 12 weeks, 4.0 ± SD 2.6 at 6 months and 4.3 ± SD 2.7 at the 1 year followup. The amount of prostate volume reduction is significantly correlated with the decrease below baseline of the PSA-levels (Pearson correlation coefficient of 0.51 and $p < 0.001$).

Sexual function

Of the 85 patients at baseline 77 indicated being sexually active. Prior to treatment already 35 of these 77 patients (45%) had already reported a decrease in erectile function, and 14 of the 77 (18%) had diminished or absent ejaculation. At least 3 months after treatment, none of the 41 remaining patients with normal erectile and ejaculatory function reported erectile dysfunction, 18 of the 41 (44%) claimed a retrograde ejaculation, and 6 of the 41 (15%) experienced diminished ejaculatory volume at evaluation.

Response criteria

Analysis of the 3- month followup data shows different response rates when taking some of the baseline parameters into account. Table 3 shows the response rates in percentage and mean improvement as expressed by Madsen and I-PSS symptom scores, Qmax and p_{det}atQmax, given the stratification of some baseline parameters. Regarding this table, it seems that patients with bigger prostates and urodynamic obstruction are the best responders to high energy TUMT.

Table 3 *Mean value and % improvement 3 months after treatment of stratified baseline*

		% and Mean ± SD							
Baseline		Madsen score		I-PSS score		Qmax		p_{det}atQmax	
	N	%		%		%		%	
Madsen score									
< 15	51	48	5 6 ± 4 4	40	6 7 ± 7 3	88	6 5 ± 7 0	32	27 1 ± 27 7
≥ 15	34	56	9 8 ± 5 1	48	11 0 ± 8 4	69	5 6 ± 6 6	31	21 5 ± 28 4
Qmax (ml/s)									
≥ 12	26	64	9 5 ± 4 8	59	11 3 ± 6 3	39	5 3 ± 5 5	36	23 4 ± 29 9
< 12	59	45	6 3 ± 5 0	36	7 2 ± 8 4	99	6 6 ± 7 3	30	25 3 ± 27.5
Prostate vol (ml)									
≥ 40	62	54	7 7 ± 5 0	45	8 6 ± 7 2	84	6 7 ± 7 3	39	29 5 ± 28 9
< 40	23	43	6 2 ± 5 3	38	8 0 ± 9 9	72	4 9 ± 5 2	13	13 5 ± 22 1
lnPURR									
≥ 3	52	58	8 1 ± 4 6	50	9 4 ± 7 1	98	7 3 ± 7 3	44	36 5 ± 24 8
< 3	31	40	6 2 ± 5 7	33	7 1 ± 9 3	53	4 5 ± 5 8	9	6 3 ± 17 3
lnPURR ≥ 3 and pros vol ≥ 40 ml	40	62	8 6 ± 4 3	53	9 9 ± 6 3	102	8 0 ± 7 4	46	39 0 ± 26 4

At the first visit (1 week after treatment) micturition had been restored satisfactorily in 57% of the patients and the transurethral catheter could be removed. The mean catheter placement time was 16 days, with a prolonged catheter time necessary in 10% of patients (range 30 to 105 days). This mainly concerned patients with bigger prostates and patients with severe outlet obstruction. The most common complaints noted during the time of an indwelling catheter were bladder spasms with urine leakage past the catheter in 25%, perineal discomfort in 7%, and hematuria in 76% After removal of the catheter, 60% of patients experienced temporary irritative complaints of urgency and frequent micturition. These irritative complaints could successfully be treated with anticholinergic medication (oxybutinin) sometimes (in combination) with anti-inflammatory drugs (diclofenac). All patients received systemic antibiotic prophylaxis (cotrimoxazol) prior to treatment and was continued for 5 days. In 29% of patients the antibiotics were resumed either because of positive culture or empirically in the case of substantial complaints. Six patients (7%) developed epidydimitis after treatment. On average the treatment-related complaints ended 2 to 3 weeks after treatment. In total 18 of 85 (21%) patients were using anticoagulants of whom 5 (6%) coumarin derivatives. One of these patients had to be admitted to the urology ward for bladder rinsing because of blood clot retention due to dysregulated anticoagulant medication.

DISCUSSION

Transurethral resection or open prostatectomy in the treatment of BPO still results in the best symptomatic improvement and urinary performance. Various new surgical techniques are comparable in their results.[7,8,9] The major drawback of

most of these treatments is that hospital admission and anesthesia are still necessary. Although TUMT does not result in TURP-like objective improvement, the question was raised if it was necessary to reach "supranormal" flow rates achieved with TURP since age-matched asymptomatic patients appear to have a flow rate (13 ml/s) more comparable to that of TUMT.[22] It appeared that the mechanism of action using this lower energy thermotherapy is substantially different from the volume reduction and cavity formation obtained with TURP. However, this most likely contributes most to the durable effect of TURP in the long term. Although this study does not concern a randomized study of TURP versus TUMT, it is the first report that shows that it is indeed possible to achieve TURP-like results with an anesthesia-free procedure without major post-treatment morbidity.

The symptomatic improvement obtained using TUMT in this study, expressed as the Madsen symptom score, is in agreement with ranges previously reported. The entry level score is usually around 13 and the expected outcome around 4, with an overall improvement of around 65%.[10] The present study is comparable to these data with an average improvement of Madsen symptom score from 13.9 at baseline to 5.8 at week 52, representing an overall improvement of 58%. Improvements in I-PSS score show a similar decrease when compared with other studies of minimally invasive treatment for BPO. These studies represent an entry level I-PSS of around 20 with improvement to around 7 at the 12-month followup, representing an improvement of 65%.[23] The present study shows comparable results with a mean I-PSS of 17.7 at baseline and improvement to 8.0 at week 52, with an overall improvement of 55%.

The improved efficacy of high energy TUMT compared with former low energy protocols is mainly expressed in a significantly better outcome in all objective parameters. The far better urinary performance is expressed in changes in uroflowmetry, which demonstrates a substantial increase in maximum urinary flow rate with reduction of PVR and an increase of voiding percentage.

Improvements in maximum flow rate are now in the range that are usually seen in patients treated with TURP or open prostatectomy.[24,25] Such an improvement can only contribute to a more durable effect in the long term if this is indeed based on relief of outlet obstruction. Previous studies on urodynamic changes after TUMT with low energy levels, reported little change in urodynamic obstruction parameters. This was not comparable to urodynamic changes seen after TURP, but seemed to be founded on an increased elasticity of the prostatic urethra.[26] On the contrary, high energy TUMT can achieve TURP-like urodynamic relief of obstruction, which in the present study is evidently shown in the improvement of the mentioned urodynamic obstruction parameters. In 78% of patients who could be considered obstructed at baseline, outlet obstruction is relieved. This substantial improvement is best illustrated with the changes in pre-treatment and post-treatment detrusor pressure at maximum flow using the linPURR-nomogram (figure 2). It shows a general trend from the obstructed pre-treatment region towards the unobstructed region after treatment, although some patients remain obstructed. This shift is comparable to the changes found in patients who are treated with TURP.[27]

Further evidence of the substantial effect on prostate tissue produced by the high energy TUMT, is shown in the significant reduction of prostate volume at 1 year by a mean of 10.5 ± SD 12 cm^3 which represents an overall reduction of a mean 19.4 ± SD 21.8%. Available studies on prostate volume decrease after TURP show a higher amount of tissue (around 60%) removal.[28]

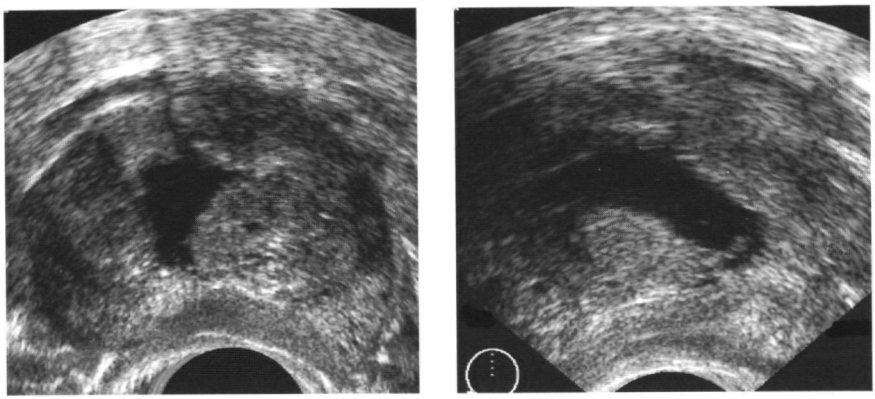
Changes in PSA levels shortly after TUMT have always been associated with the amount of effect that microwave energy causes on prostate tissue. In TUMT versus sham studies, no rise of PSA was seen in the sham-arm, whereas the TUMT group showed increase to a mean of 25 ng/ml.[29] In a retrospective responder versus nonresponder study it was shown that responders to TUMT had a significantly higher rise of PSA 1 week after treatment when compared to nonresponders.[30] In the present study, the PSA levels rose to mean levels of around 40 ng/ml.

Interestingly, the present study shows a significant correlation between the decrease of PSA below baseline level and the amount of prostate volume reduction that is achieved, which is in accordance with what is found after TURP.[31] Tissue damage not only can result in prostate volume reduction but also in cavity formation. Previous studies with lower energy TUMT failed to show this effect on the prostate. In contradistinction, the present study notes a cavity, comparable to cavities that can be seen after TURP, in 42% of patients (figure 3). The absence of a cavity does not, however, necessarily imply worse treatment outcome. Although the mean improvement of several parameters might be less, the standard deviations indicate moderate amount of variation. Therefore, good response can also be seen on an individual basis.

However, there is a price to be paid in terms of morbidity. The present trial showed that there is an increased morbidity mainly consisting of a prolonged catheterization time and irritative complaints after treatment. Whereas patients treated with lower energy TUMT are reported to have a retention rate after treatment of around 20%, all patients treated with the high energy protocol needed a catheter for at least 1 week. Although irritative complaints - such as frequency, urgency, dysuria and hematuria - were also reported with lower energy TUMT treatments, they are more frequent and pronounced during the first 2 to 4 weeks in patients with high energy treatments. Nevertheless, the high energy treatments are still possible on an outpatient basis in a single 1 hour session without the need for anesthesia. Moreover, in the present study with 74 patients followed up for at least 1 year, there were no urethral strictures, no bladder neck contractures, and no stress incontinence.

As a consequence of a more effective treatment, the effect on ejaculatory performance is substantially changed. Patients treated with low energy TUMT report a 5% to 10% retrograde ejaculation after treatment; in the present trial, this occurred in 44%, with an additional 15% of patients reporting a diminished ejaculatory volume. These results indicate that the high energy TUMT is also

Figure 3 *Ultrasonograms of the prostate 3 months after treatment identifying a cavity (**a**, transverse, **b**, longitudinal section)*



capable of changing the bladder neck function, which, besides causing retrograde ejaculation, is probably responsible for better urinary performance and reduction of bladder outlet obstruction. Finally, one also has to keep in mind that a large number of patients who are unfit for surgery because of poor physical health, profit from this ambulatory anesthesia-free therapy. In this study, the twelve patients in ASA 3 to 4 group all responded favorably.

Although the objective and subjective improvement all point to TURP-like results, not all patients experienced equal response. Previous clinical results of low energy TUMT showed clear separation between patients who respond favorably in both subjective and objective terms and patients who do not respond at all. In a retrospective multicenter study of responders versus nonresponders, it was concluded that none of the baseline parameters (such as prostate volume, uroflowmetry results, or symptom scores) were able to define the ideal patient for treatment and to predict the result of the treatment.[30] In another multicenter study using urodynamic parameters, it was concluded that, with pressure-flow study parameters, it was possible to identify the patients who would respond favorably.[32] Data analysis with stratification of baseline parameters in the present study, shows favorable results in patients with moderate to severe bladder outlet obstruction and

bigger prostates (table 3). Nevertheless, there still is considerable difference in treatment outcome among individual patients. The clinical benefit appears to be related to the achieved intraprostatic temperatures, that result from a complex interaction between the biologic response to microwaves and the pattern of energy provided during treatment in any individual.[14] This interaction is probably greatly depending on prostate vascularization and tissue composition of the prostate.[33,34] Further research should, therefore, be directed towards gaining better insight in these matters.

CONCLUSION

High energy TUMT results in improved objective outcome with comparable subjective response when compared to low energy TUMT treatments that were reported previously. Overall, the improvement now attains results that are comparable with surgical resection of the prostate and bladder outlet obstruction is similarly relieved. Nevertheless, stratification of baseline data showed improved efficacy in patients with bigger and urodynamically obstructed prostates. However, post treatment morbidity is substantial and should be given more attention in future prospective randomized trials.

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Chapter 5

PRESSURE-FLOW STUDY ANALYSES AND HIGH ENERGY THERMOTHERAPY

Based on:

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Pressure-flow study analyses in patients treated with high energy Thermotherapy

Journal of Urology, in press

SUMMARY

We evaluated the urodynamic changes after high energy microwave thermotherapy in patients with lower urinary tract symptoms and benign prostatic enlargement. A total of 120 patients was available for analysis with urodynamic investigation and pressure-flow studies before and 6 months after treatment. Several obstruction parameters were used to evaluate treatment outcome. A significant decrease ($p < 0.001$) in all obstruction parameters was noted. Mean detrusor pressure at maximum flow decreased from 64.7 cmH_2O to 39.1 cmH_2O, urethral resistance factor from 41.8 cmH_2O to 23.5 cmH_2O and linear passive urethral resistance relation from 3.0 to 1.4. Analysis of subgroups showed better results in patients with greater grades of obstruction. High energy thermotherapy results in significant and substantial decrease of bladder outlet obstruction.

INTRODUCTION

Presently, there is no agreement on the role of urodynamic studies in assessment of patients with lower urinary tract symptoms and benign prostatic hyperplasia (BPH).[1,2] Most urologists agree that the main feature of the enlarging prostate is bladder outlet obstruction, eventually resulting in lower urinary tract symptoms. Most surgical therapies attempt to decrease obstruction and relieve symptoms. Since the results of surgery for BPH are generally favorable, there has been little enthusiasm for use of resource consuming investigations, such as advanced urodynamic studies.

However, an increasing number of urologists are becoming aware of the additional benefit of urodynamic studies with pressure-flow analysis in assessment and followup of patients with lower urinary tract symptoms and BPH. It is well-known that 25 to 30% of patients treated surgically do not have bladder outlet obstruction.[3-5] Although postoperative results are impressive and the procedure is reasonably safe, the morbidity of the operation is still considerably great.[6] Furthermore, the outcome in patients with minimal obstruction is less favorable,[3,5,7] and most urologists will agree that a treatment designed to relieve obstruction in patients without bladder outlet obstruction is unjustified. Also, during the last decade many alternatives to prostatectomy have surfaced, ranging from the pharmacological approach to numerous procedural alternatives.[8-13] While none of these alternatives have reached subjective and objective results comparable to those noted postoperatively, morbidity is significantly decreased and one may question whether transurethral prostatectomy-like results always must be obtained to achieve a good outcome. Urodynamic studies can also be useful in the selection of patients who are candidates for alternative treatment.[14,15]

For the last 5 years, we performed transurethral microwave thermotherapy in the treatment of patients with lower urinary tract symptoms and BPH. Although subjective improvements using the lower energy protocol (Prostasoft® 2.0;

Technomed Medical Systems, Lyon, France), objective improvements are less pronounced. Urodynamic studies have been used to investigate the pathophysiology of BPH and evaluate the clinical outcome of various treatments. From a urodynamic viewpoint, only patients with a particular type of obstruction responded favorably using the lower energy using the lower energy protocol.[14] Recently, a higher energy software version has been introduced to improve the outcome of this procedure, and a significant improvement in all objective and subjective parameters was observed. In a subgroup of patients, the results even seemed competitive with surgical therapy.[9] We report on the urodynamic results of this high energy thermotherapy in patients with lower urinary tract symptoms and BPH. We used pressure-flow study parameters to describe the power of this high energy thermotherapy to relieve obstruction, and compared this method to other (alternative) therapy options. We also studied which patients improved the most with this new thermotherapy protocol and to identified specific urodynamic selection criteria.

MATERIAL AND METHODS

Since April 1993, patients with lower urinary tract symptoms and BPH were included in a prospective study of TUMT using the high energy thermotherapy protocol. Inclusion criteria were Madsen symptom score of 8 or more, maximum flow rate of 15 ml/s or less, post void residual volume of 350 ml or less, and voided volume of 100 ml or more. All patients underwent screening with physical examination (including digital rectal examination), blood chemistry studies (including prostate specific antigen with the Hybritech assay), urinalysis and urine culture. Transrectal ultrasound of the prostate was performed with planimetric measurement of prostate volume. All patients underwent urethrocystoscopy to measure prostate length, and assess the size of the middle and lateral lobes. In

cases of a suspicious digital rectal examination, transrectal ultrasound or elevated prostate specific antigen, prostate biopsies were obtained to exclude malignancy.

We used the Prostatron device with a treatment catheter consisting of a microwave dipole antenna with the hot point positioned just below the Foley balloon. The catheter was mounted in a water cooled transurethral probe. The high energy operating software (Prostasoft® 2.5) provides a maximum power of 70 W with a transrectal threshold set at 43.5°C. Transurethral microwave thermotherapy generally has been described previously.[16]

Urodynamic investigations were performed with an 8F transurethral lumen catheter with an intravesical microtip pressure sensor, and abdominal pressure was recorded intrarectally with an 8F microtip sensor catheter. Before cystometry, the bladder was emptied through the lumen of the transurethral catheter, and filled with sterile saline at room temperature and a filling speed of 50 ml per minute with the patient supine. Pressure and flow data were recorded with commercially available equipment. The digitally stored data were translated to a urodynamic analysis computer program, developed at our department. Precise fitting of the automatically computed passive urethral resistance relation curves to the pressure-flow plot, with correction for artefacts, was done by hand. Patients with detrusor failure or chronic urinary retention were excluded from this study. Several different parameters were used to document obstruction, including detrusor pressure at maximum flow (p_{det} at Qmax in cmH_2O) with grading according to the Abrams-Griffiths nomogram[17], intersection of the quadratic urethral resistance relation with the pressure axis (URA in cmH_2O)[18], parameters calculated from the passive urethral resistance relation (p_{muo} = minimal computer derived detrusor pressure with ongoing flow in cmH_2O, and A_{theo}= theoretical cross-sectional area of the urethra during voiding in mm^2)[19] and, finally, linear passive urethral resistance relation (linPURR) which is an approximation of the resistance relation by means of a straight line through minimal voiding pressure and detrusor pressure at maximum flow rate with grading according to the Schäfer nomogram[20].

Our patients were evaluated at baseline and at 26 weeks. To evaluate subjective parameters, patients had to complete international prostatic (I-PSS) and Madsen symptom score questionnaires. Objective parameters were evaluated by free urinary flow rate using a uroflowmeter and urodynamic studies with pressure-flow study analysis.

Student's t-test was used for statistical comparison of preoperative and postoperative data of the entire group. The Wilcoxon matched pairs signed ranks test and the Kruskal-Wallis test were used to compare improvement in the different stratified groups.

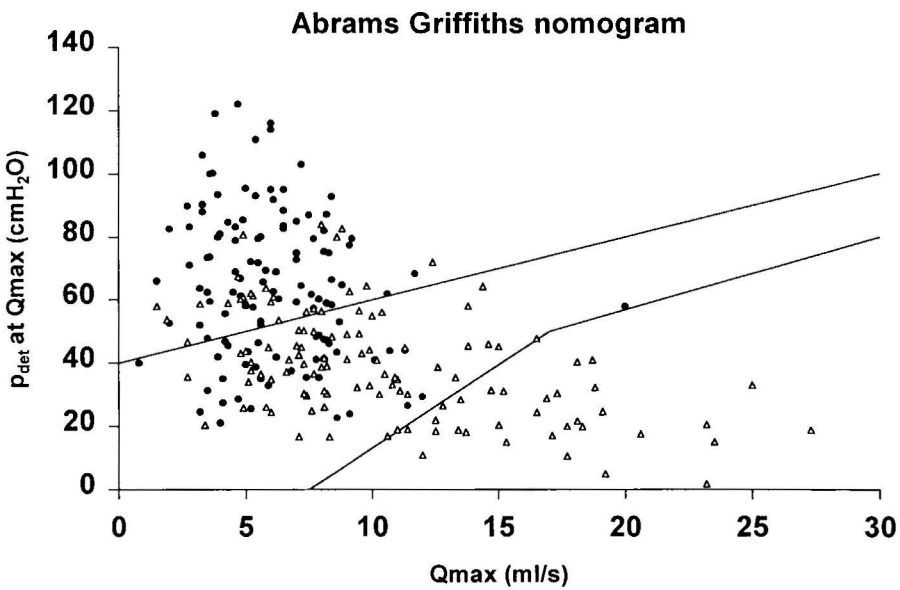
Table 1. *Changes of mean baseline symptomatic, uroflowmetry and urodynamic parameters with standard deviation SD (n=120)*

	Mean ± SD		
	Baseline	6 Months	p-value*
Symptoms			
Madsen score	13.9 ± 3.6	5.3 ± 4.5	< 0.001
IPSS score	17.7 ± 6.0	8.0 ± 6.0	< 0.001
Uroflowmetry			
Maximum flow (ml/s)	9.4 ± 3.1	14.1 ± 6.2	< 0.001
Post-void residual (ml)	72 ± 86	29.2 ± 78	< 0.001
Voided volume (ml)	222 ± 127	296 ± 134	< 0.001
Urodynamics +			
p_{det} at Qmax (cmH_2O)	64.7 ± 23.4	39.1 ± 17.1	< 0.001
Qmax (ml/s)	6.1 ± 2.6	10.5 ± 5.3	< 0.001
URA (cmH_2O)	41.8 ± 15.4	23.5 ± 11.7	< 0.001
p_{muo} (cmH_2O)	33.6 ± 16.6	16.1 ± 10.4	< 0.001
A_{theo} (mm^2)	2.7 ± 1.4	6.1 ± 5.2	< 0.001
linPURR	3.0 ± 1.3	1.4 ± 1.2	<0.001

* all parameters significant according to Student's t test (α=0.05)

A total of 120 patients with repeated urodynamic investigations was available for analysis. Only 15% of the initially treated patients had no second urodynamic evaluation because of difficulty to introduce the microtip catheter or because the patient refused another study. There was no difference in outcome between these patients and the 120 studied. Mean patient age plus or minus standard deviation was 67.0 ± 8.8 years (range 45 to 89). The average prostate volume was 58.1 ± 25.0 cm^3 (range 30 to 154). Symptomatic, uroflowmetric and urodynamic pressure-flow parameters at baseline and 6 months after treatment demonstrated highly significant and substantial improvement (table 1).

Figure 1. *Detrusor pressure at maximum flow (p_{det} at Qmax) before (●) and 6 months after treatment (Δ) of 120 patients in an Abrams Griffiths nomogram of obstruction.*



Depending on what obstruction parameter was used, the incidence of pretreatment urodynamic obstruction ranged from 66 to 78%. Of the 120 patients 79 (66%) were considered obstructed according to linPURR of 3 or more, 81 (68%) according to the Abrams Griffiths nomogram and 93 (78%) according to URA of more than 29 cmH_2O. After treatment 18 to 30% of the patients still had obstruction: 21 (18%) according to the linPURR classification, 23 (19%) according to the Abrams Griffiths nomogram and 36 (30%) according to URA. Figure 1 shows the pretreatment and posttreatment values of detrusor pressure at maximum flow using the Abrams Griffiths nomogram of obstruction.

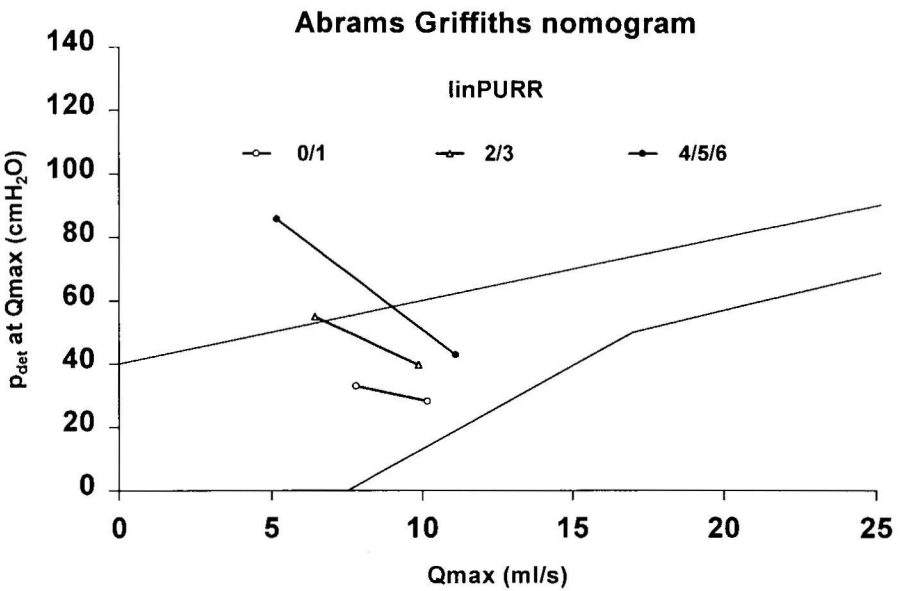
When stratifying the patients according to the grade of obstruction at baseline, the changes and mean improvement in objective parameters showed

Table 2. *Improvement in parameters stratified according to baseline obstruction grade*

	Mean ± SD						
	linPURR 0 /1		linPURR 2 / 3		linPURR 4 / 5 / 6		
	before	after	before	after	before	after	p-value
Symptoms							
Madsen score	12.9±2.9	5.3±4.1	14.6±3.5	6.5±3.7	13.7±3.5	4.3±3.7	0.23
I-PSS score	16.5±6.7	8.4±5.8	18.6±5.9	9.9±4.1	17.3±5.9	6.1±4.1	0.28
Uroflowmetry							
Qmax (ml/s)	9.6±2.8	13.3±5.5	10.1±3.3	12.4±7.0	8.7±3.3	15.9±7.0	0.002*
Post-void res. (ml)	53±83	83±7	64±94	33±81	87±94	35±81	0.70
Urodynamics							
p_{det}atQmax	33±9	28±13	55±14	40±19	86±14	43±19	<0.001*
Qmax (ml/s)	7.8±4.1	10.2±4.7	6.4±1.8	9.9±6.0	5.2±1.8	11.1±6.0	0.056
URA (cmH_2O)	22±4	18±8.1	35±11	24±13	55±11	25±13	<0.001*
p_{muo} (cmH_2O)	15±5	12±7.5	28±14	16±11	46±14	18±11	<0.001*
A_{theo} (mm^2)	4.2±1.7	6.9±4.6	2.9±0.6	5.8±0.6	1.9±0.6	6.1±5.5	0.07

* significant according to Kruskal Wallis test for independent samples

Figure 2. *The mean value of detrusor pressure at maximum flow before and after treatment stratified according to obstruction class.*
Non/mild: linPURR 0/1; moderate: linPURR 2/3; severe: linPURR 4/5/6



different results (table 2). There was a statistically significant improved efficacy in the majority of the objective parameters in patients with severe obstruction (linPURR of 4 or more) compared to those without or with moderate obstruction (linPURR of 3 or less). There appeared to be no significant difference in subjective parameters in patients with different grades of obstruction. Furthermore, analysis of mean changes in p_{det}atQmax in these 3 subgroups is best expressed with the Abrams Griffiths nomogram (figure 2). One can appreciate that patients with severe obstruction had the most impressive changes. Nevertheless, on an individual basis, those without obstruction showed good improvement but generally the changes were moderate. The same finding accounts for patients with moderate obstruction, although mean improvement was more pronounced.

If the achieved decrease in outlet obstruction is considered a stratification criterion and is compared to baseline subjective parameters, it is confirmed again that the greater degree of outlet obstruction at baseline, the better the objective improvement. No prognostic value could be identified in uroflowmetry parameters nor symptom scores (table 3).

Table 3. *Mean baseline parameters and SD in correlation with urodynamic*

	Mean ± SD			
	≤ 0 classes	1 - 2 classes	≥ 3 classes	
	n = 30	n = 57	n = 33	p-value
Symptoms				
Madsen score	14.0 ± 3.8	14.4 ± 3.5	13.0 ± 3.3	0.23
I-PSS score	17.9 ± 6.1	17.6 ± 5.8	17.6 ± 6.2	0.98
Uroflowmetry				
Qmax (ml/s)	10.2 ± 2.8	9.1 ± 2.8	9.2 ± 3.6	0.24
Post-void res. (ml)	71 ± 91	65 ± 79	85 ± 93	0.48
Urodynamics				
p_{det}atQmax	49.0 ± 23.2	61.2 ± 19.1	85.0 ± 15.1	<0.001*
Qmax (ml/s)	6.6 ± 2.4	6.3 ± 3.1	5.3 ± 1.7	0.09
URA (cmH_2O)	32.3 ± 13.2	39.5 ± 13.5	54.2 ± 12.3	<0.001*
linPURR	2.0 ± 1.3	2.9 ± 1.2	4.2 ± 0.6	<0.001*

* significant according to Kruskal Wallis test for independent samples

DISCUSSION

Urologists have recently renewed their interest in the treatment of symptomatic BPH because of the availability of less invasive methods. However, to compare these alternative therapies to the gold standard of transurethral resection, previous reports have questioned which method is the best for describing the individual physiological problem. The pathological triad of symptoms, prostate size and

obstruction described by Hald et al is well recognized, and it is also acknowledged that the 3 variables are independent.[21] It is important to know whether new treatments have the same effect on each variable as does the classic transurethral resection of the prostate. If there are differences in the way that a new treatment affects patients, it is possible that this information could be used to select patients for less invasive therapies. The main question is whether heat treatments such as transurethral thermotherapy, high intensity focused ultrasound or laser therapy truly offer an alternative to classic ablative operations such as transvesical enucleation or transurethral resection of the prostate.

Changes in symptoms scores, prostate size and flow rate are the most commonly cited evidences of efficacy for alternative treatments. However, at best there is only questionable evidence to support an association between these parameters and obstruction as defined by urodynamic studies.[22-24] The latter has always been accepted as the only diagnostic method for determination of lower urinary tract obstruction, although the use of routine urodynamics has yet to be established.[25] Alternative treatments are able to relieve subjective symptoms but the question remains whether the objective improvements in obstruction parameters as documented by pressure-flow studies are changed. An effective decrease in outlet resistance as shown by pressure-flow measurements has been documented for transurethral resection of the prostate, indicating the efficacy of the procedure in the elimination of specific mechanical obstruction in BPH.[26]

A promising minimally invasive, anaesthesia-free, alternative treatment options is transurethral microwave thermotherapy. Large series of patients have been treated, using the Prostatron unit with different types of treatment catheters and energy levels.[9] Regardless of the vast experience, it is still not precisely clear how low energy thermotherapy affects the objective and subjective symptoms of patients with BPH. It has been assumed that a potential effect of this form of thermotherapy on decreasing outlet obstruction resistance may be caused by shrinkage of tissue due to tissue necrosis, leading to expansion of the urethral

lumen in the prostatic urethra. Subjective symptoms may be influenced by this decrease of bladder outlet obstruction or the evident effect on the autonomic nervous system.[14,27]

Recently we investigated to what extent low energy transurethral microwave thermotherapy as a nonablative procedure is able to decrease the outlet resistance. It appeared that transurethral microwave thermotherapy exerts a specific effect on outlet obstruction that cannot be compared quantitatively with surgical removal of the prostate. Transurethral microwave thermotherapy only influences the flow-controlling area significantly, which is expressed in changes in the PURR curvature (and thus an increase in theoretical cross-sectional area A_{theo}) without affecting the PURR footpoint (equivalent to an unchanged p_{muo}).[28] Although low energy transurethral microwave thermotherapy is comparable to transurethral resection of the prostate with regard to improvement of subjective symptoms, outlet obstruction is changed little. Therefore, low energy transurethral microwave thermotherapy would prove to be an optimal choice for patients with BPH and lower urinary tract symptoms and low grade bladder outlet obstruction.

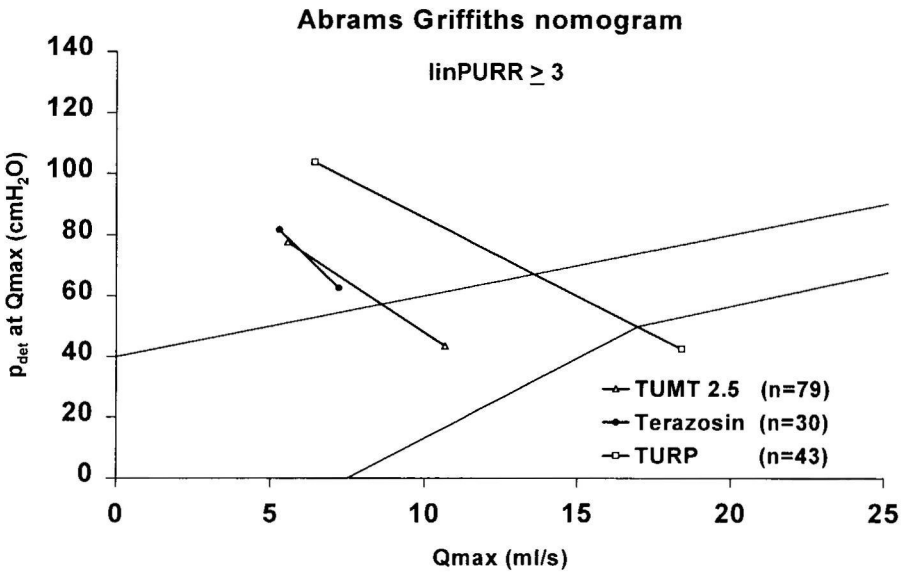
To improve outcome after thermotherapy, high energy levels have been applied. Simple clinical analysis of the outcome by peak flow rate and Madsen symptom scores demonstrates a substantial advantage of Prostasoft® 2.5 over the earlier version. We concluded that "the great change in flow rate we have seen in patients receiving the 2.5 software treatment cannot be explained by anything other than a decrease of urodynamic obstruction, assuming the same contractility".[9] Our present study shows that symptomatic improvement is in the same range as is reported in previous studies on low energy thermotherapy.[29] The Madsen symptom score usually shows a baseline value of approximately 13 with an expected outcome of approximately 4. Our study is comparable with a mean improvement from 13.9 at baseline to 5.3, 6 months after treatment. The same degree of improvement may be seen in I-PSS. Our study shows improvement from 17.7 at baseline to 6.0 after 6 months, which is comparable to available data on

other minimally invasive treatments for BPH that use the I-PSS for subjective evaluation.[30] Furthermore, analysis of the stratified data shows that, except for the urodynamic parameters, neither subjective nor uroflowmetric parameters could be identified as prognostic factors. This finding agrees with previous studies of low energy transurethral microwave thermotherapy.[14,31]

The improvements in uroflowmetry results are significantly better compared to former low energy transurethral microwave thermotherapy. For the entire group, there is an average 50% improvement in maximum flow from baseline of 9.4 to 14.1 ml/s after 26 weeks. However, stratified data show that the improvement can range from 23 to 38% in the no to moderate obstructed group, to 83% in the severe obstruction group. This finding shows that high energy transurethral microwave thermotherapy results in almost doubling of the maximum flow in severely obstructed cases which is significantly better than results of low energy transurethral microwave thermotherapy in the same group, whereas patients with no to moderate obstructed patients show improvement, which is still comparable with the best results achieved with the low energy protocol. Our study demonstrates that improvement in maximum flow is indeed due to decreased bladder outlet obstruction as indicated by a significant improvement in all obstruction parameters. In addition, it is shown that patients with greater degrees of obstruction seem to respond best, showing a substantial decrease of p_{det} at Qmax of 86 cmH_2O at baseline to 43 cmH_2O after treatment, with a similar improvement in maximum flow from 5.2 ml/s before treatment to 11.1 ml/s at 6 months. This substantial decrease in bladder outlet obstruction with associated subjective improvement might possibly lead to increased durability of this treatment in the long term.

Where should we position high energy thermotherapy in the armamentarium of treatment options? As noted earlier, an effective decrease in outlet obstruction according to pressure-flow measurements has been documented for transurethral resection of the prostate, indicating the efficacy of the procedure in the elimination

Figure 3. *The mean value of detrusor pressure at maximum flow before and after treatment in obstructed patients (linPURR ≥ 3)*



of specific mechanical obstruction in BPH. This fact indicates that transurethral resection of the prostate is effective because of the tissue ablation involved. For comparison of the urodynamic changes after alternative treatments with those noted in patients who underwent transurethral resection of the prostate in a nonrandomized fashion, a number of patients from Bristol, England were evaluated before and after transurethral prostatectomy.[32] Furthermore, the urodynamic changes after medication (terazosin) are also compared with the results of the current study of high energy thermotherapy and are presented as the mean changes of p_{det} at Qmax before and after treatment in a Abrams Griffiths nomogram.[33] However, when judging and comparing data of the aforementioned studies, one should consider that at baseline these were different groups. The transurethral resection group mainly consisted of patients with severe obstruction, whereas the terazosin group included those with mild-to-moderate obstructed.

Therefore, to make the data of these studies more comparable, we selected only patients who at baseline had clear obstruction (linPURR of 3 or more), and compared these data with those of our present study (figure 3). The improvement after transurethral microwave thermotherapy is in the range of what is achieved after transurethral resection of the prostate, and significantly greater than noted after medication. However, although changes are impressive, one should acknowledge that results are not equal to those after transurethral resection of the prostate. In this regard, high energy thermotherapy should be positioned between medication therapy and operative intervention. Similar conclusions were drawn by Devonec et al., who compared symptomatic and objective improvements in uroflowmetry parameters of different treatments [34]. They also positioned high energy transurethral microwave thermotherapy between medication therapy and surgical intervention, with ranges noted more towards those achieved with surgery. Nevertheless, case selection should identify the most favorable patients for high energy thermotherapy to improve further treatment efficacy and finally achieve results comparable to those of surgery with lower morbidity. Since patients with greater degrees of obstruction respond most favorably to higher energy transurethral microwave thermotherapy, they are the best candidates for this treatment. Thus, patients with minimal bladder outlet obstruction should preferably undergo medical treatment or lower energy thermotherapy, since subjective improvements with these treatments are significant with only minimal morbidity. However, such an algorithm can be used only if urodynamic studies with pressure-flow studies are included in the assessment of patients with BPH. In view of the benefit to the patients, when using urodynamic studies with pressure-flow analysis as a selection criterion for therapy, we believe it worthwhile to include these so-called invasive, time consuming investigations in the assessment of patients with BPH.

CONCLUSION

High energy thermotherapy using the Prostatron device with the Prostasoft® 2.5 operating software results in significant and substantial subjective and objective improvement in the majority of patients. Patients with greater degrees of bladder outlet obstruction are the best candidates for treatment.

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Chapter 6

TRANSURETHRAL MICROWAVE THERMOTHERAPY: A REVIEW

Based on

MJAM de Wildt and JJMCH de la Rosette

Review Transurethral microwave thermotherapy an evolving technology in the treatment of benign prostatic enlargement

British Journal of Urology, 76 531-538, 1995

HISTORY

The use of heat in treatment of prostatic diseases has been advocated for over a century. In 1866 Busch showed that malignant tissue was especially susceptible to heat.[1] Since then, many different and ingenious methods for the beneficial application of heat have been described.

In prostatic tissue there are several temperature thresholds: below 40°C cells are affected little; between 41 and 45°C malignant cells are more susceptible to permanent damage than benign tissue and this effect is termed hyperthermia; in the range of 45-60°C cell death can occur and is defined as thermotherapy. Thermal treatment in excess of 70°C destroys all human living tissue and is termed thermoablation.[2]

Hyperthermia was first introduced in the early 1980s, initially to treat prostate carcinoma.[3] The alleviation of symptoms of prostatism and the reduction of tumor bulk seen in patients treated with hyperthermia also led to application of hyperthermia in patients with benign prostatic hyperplasia (BPH).[4] Many studies have been published on the use of hyperthermia in treatment of BPH. Although they reported significant symptomatic relief, the effect on objective improvement was very limited. Moreover, in a multicentre study transrectal hyperthermia was shown to be ineffective when compared with sham treatment,[5] transurethral hyperthermia is still under investigation as has proved to be more effective than the transrectal route and better than sham treatment.[6,7] The results achieved with hyperthermia suggested that higher temperatures would be more effective. Transurethral microwave thermotherapy (TUMT) was designed to apply microwave energy deep within the lateral prostatic lobes whilst simultaneously cooling the urethral mucosa. Currently the application of high energy thermotherapy in the treatment of BPH is being evaluated.

MICROWAVE TISSUE INTERACTION.

The applicability and outcome of microwave treatment is influenced by the microwave frequency used, the tissue composition and vascularization, and patient's tolerance of the heat treatment.

The appropriate electromagnetic spectrum comprises microwaves in the range from 300 to 3000 MHZ, but the two frequencies most commonly used are 915 MHZ and 1296 MHZ. When applied transurethrally, the isothermic field of the latter shows a concentric heat distribution more or less following the anatomical borders of the transition zone of the prostate and not reaching maximum temperature in the rectal mucosa; this frequency thus seems best fitted for the treatment of prostatic diseases. The effects of microwaves on tissue depends on tissue composition and water content. Penetration is greater in fat, which has a high water content, than in muscle which has a lower water content. The depth of penetration also depends on the microwave frequency: the higher the frequency of the microwaves, the less the penetration. However, penetration is also influenced by tissue temperature and refraction, reflection and dispersion of the microwaves in heterogenous tissue. Furthermore, heat conduction and convection are influenced by perfusion of the tissue causing spatial differences in tissue temperatures.

Cell death is achieved when temperatures exceed the cytotoxic threshold, which depends on the cell type; In prostate adenomatous tissue the thermal threshold is 45°C for 30 minutes. Therefore when heterogenous tissue is treated, not all cells within the treated area will die. Furthermore, small capillaries are thrombosed whereas larger vessels are spared because they are cooled by blood flow. Thus, the size of the necrotic area is not only determined by the tissue composition but also by tissue vascularization.[2]

To allow treatment with no anesthesia, heating of the urethral mucosa, which is rich in pain receptors, should be avoided because 45°C is not only the

thermotoxic level but also the thermal pain threshold. The transition zone of the prostate has fewer nociceptors and can therefore be heated to more than 45°C. Urethral obstruction associated with BPH arises from anatomical compression by the periurethral adenomatous tissue from the bladder neck to the verumontanum, and partly by a dynamic obstruction resulting from the tone of the prostatic smooth muscle.[8] Theoretically, the optimal treatment is the one that spares the urethral mucosa, heats the periurethral prostate tissue to above cytotoxic temperatures, and spares the adjacent rectal mucosa. Thermotherapy with urethral cooling allows not only the delivery of increased energy, but higher temperatures, up to 70°C, deep inside the lateral prostatic lobes resulting in tissue coagulation, necrosis and even tissue ablation. Not all patients reach the maximum temperature intended, because the thermoregulation of the tissue differs.[9] Studies correlating the achieved intraprostatic temperatures and outcome of treatment, suggest that the higher the intraprostatic temperature, the better the clinical results.[10]

Thus the clinical benefit and tolerability of TUMT must be related to the achieved intraprostatic temperature, which results from a complex interaction between the biological response to microwaves, the pattern of energy provided during the treatment and the incorporation of urethral cooling.

CLINICAL RESULTS

Many thermotherapy devices have been developed for the treatment of BPH, including the Urowave (Dornier Medical Systems, Germering, Germany), ECP (Prof. H. Wiksell, Stockholm, Sweden), Prostalund (Dantec Medical A/S), T3 (Urologix, Minneapolis, USA), TURAPY (Direx Medical Sytems, Petah Tiqvah, Israel) and the Prostatron device (Technomed Medical Sytems, Lyon, France). The latter has been most widely used and reported on and the authors have experience with over 600 patients treated using this device. Therefore, in the following section

reports this experience with the Prostatron device and compares the results with those available from the other devices and with transurethral resection of the prostate (TURP).

The Prostatron has been used with three software programs which have different features, mainly in controlling the amount of energy applied while ensuring maximum safety for the patient with no need for anesthesia: Prostasoft Version 1.0 (temperatures $\leq$ 50°C); Version 2.0 (temperatures from 50-60°C) and Version 2.5 (temperatures $\leq$ 70°C). Version 2.0 is the most widely used and Version 2.5 is currently under investigation. The procedure for the TUMT treatment itself has been described extensively elsewhere.[11,12]
The results of Prostatron treatment are discussed below.

TUMT using Prostasoft® 2.0

Currently, over 25.000 patients with BPH have been treated with the Prostatron device using Prostasoft® 2.0. The first clinical data was presented by Devonec et al. and Carter et al. in 1991.[11,13] The results achieved for symptomatic improvement and changes in urinary performance were encouraging and impressive.
The overall symptomatic changes, using the total Madsen-Iversen physician-guided symptom score, showed a considerable improvement.[14] The mean entry level is usually 13 (range 11-16) and the expected outcome at 3 months is about 4 (range 2-6) showing an overall improvement of around 70% (Table 1). Similar symptom scores were found in asymptomatic elderly men.[15]

Urinary peak flow rates (Qmax)were also improved, although less pronounced. Mean Qmax at baseline was about 9 ml/s (range 8.2-10.4), improving by 3-4 ml/s after 3 months, representing a mean improvement of 35% over baseline. Unlike those occurring after TURP, improvement in Qmax occurred gradually. Improvement had occurred by 4 weeks after treatment and was more pronounced after 3 months. The final improvement of urinary flows occurred between 6 to 12

Table 1. *Improvement in main treatment indices before, 3 and 12 months after TUMT using Prostasoft® 2.0*

No. of patients	Symptom score			Qmax (ml/s)			Post-void residual (ml)		
	Baseline	3 mths	1 yr	Baseline	3 mths	1 yr	Baseline	3 mths	1 yr
37 [13]	12	8	-	8.4	10.8	-	109	50	-
19 [11]	12	2.8	1.4	8.2	14.3	14.3	64	41	58
37 [35]	8.5*	4.5	-	10.3	11.5	-	-	-	-
60 [36]	13.9	4.8	-	8.9	13.1	-	-	-	-
17 [37]	16.5	-	6.9	7.2	-	10.7	39	-	17
130 [38]	12.9	5.9	6.4	10.4	11.5	11.8	54	49	42
128 [39]	11.3	2.1	-	9.2	14.9	-	100	43	-
140 [40]	11.7*	4.9	4.2	9.0	12.6	13.3	135	81	41
140 [41]	23.7*	10.6	11.6	10.1	12.3	12.4	98	69	76
818 [42]	13.3	5.7	3.5	8.8	13.0	12.6	-	-	-
115 [43]	15.7	3.8	2.6	9.8	13.3	13.7	108	33	22

* Symptom score other than Madsen-Iversen symptom score

months after TUMT and was sustained at the followup 3 years later.[16,17] Post-void residual volume (PVR) also decreased significantly; large initial PVR's were reduced, but better results are found in patients with a PVR of < 200 ml.

The variability in objective outcome between the different centres was considerable. Although the results of TUMT using Prostasoft® 2.0 are very promising, the degree and significance of the a possible placebo effect remained to be evaluated.

Sham treatment versus TUMT using Prostasoft® 2.0

All treatments contain possible 'placebo' effects and thus a precise and general definition of 'placebo' is difficult. Broadly, the placebo effect could be defined as a single, unknowable nuisance variable which is inactive and specific in its effect. To apply this definition to the effect of surgical intervention is a daring concept. There are several controlled studies, using sham treatment, of the clinical use of

thermotherapy for BPH.[18-23] The majority of which show a significant effect of TUMT on both subjective and objective parameters with no significant placebo component (Table 2).

Table 1. *Improvement in main indices before , 3 and 12 months after TUMT using Prostasoft® 2.0*

Type	No pat.	Symptom score			Qmax (ml/s)			Post-void residual (ml)		
		Baseline	3 mths	1 yr	Baseline	3 mths	1 yr	Baseline	3 mths	1 yr
Sham [18]	19	14.2	12.8	-	8.6	9.2	-	118	171	-
TUMT	21	14.5	4.3	-	8.5	13.0	-	147	12	-
Sham [19]	24	12.1	8.2	9.1	9.7	9.5	11.3	-	-	-
TUMT	24	13.2	5.9	3.3	9.6	13.0	14.0	-	-	-
Sham [20]	36	14.9	10.7	-	7.4	9.5	-	-	-	-
TUMT	75	13.9	6.3	-	7.3	11.5	-	-	-	-
Sham [22]	44	12.9	10.4	8.2	9.6	9.7	10.5	85	104	56
TUMT	46	13.7	4.7	4.2	9.2	13.4	13.4	94	34	50
Sham [23]	40	17.5*	9.5	-	9.4	9.5	-	97	106	-
TUMT	40	19.0*	9.5	-	8.8	9.9	-	86	86	-
Control	40	18.0*	17.0	-	8.8	8.5	-	86	83	-

* American Urological Association - 7 symptom score

In addition, the changes in prostate-specific antigen (PSA) levels, seen only after TUMT,[19,20] are further prove that the mechanism of action of TUMT is related to the thermal damage of prostatic tissue and not to the mechanical effect of a single catheterization.

However, to be considered an alternative to surgical therapy in (a subgroup of) patients with BPH, TUMT should be compared with TURP.

TUMT using Prostasoft® 2.0 versus TURP

To evaluate the clinical utility of TUMT, Dahlstrand et al have randomized TUMTagainst the 'gold standard' TURP.[17] Their study showed a statistically identical symptomatic improvement of symptom scores in patients treated with

Table 3. *Results of a randomized controlled study of TUMT vs TURP* [17]

	Mean ± SD				
	Baseline	3 months	12 months	24 months	36 months
Madsen					
TUMT	12.1 ± 3.0	2.6 ± 2.6	2.3 ± 2.4	2.3 ± 2.9	3.0 ± 2.9
TURP	13.6 ± 3.9	1.1 ± 2.8	0.6 ± 1.4	1.2 ± 1.8	2.3 ± 3.7
Qmax (ml/s)					
TUMT	8.4 ± 2.6	11.5 ± 4.2	12.3 ± 4.1	12.3 ± 4.4	11.9 ± 3.4
TURP	8.3 ± 3.2	18.1 ± 7.1	18.9 ± 6.0	17.6 ± 5.9	18.6 ± 7.1
PVR (ml)					
TUMT	97 ± 78	51 ± 51	55 ± 65	47 ± 43	42 ± 51
TURP	104 ± 95	34 ± 32	23 ± 18	27 ± 32	45 ± 27

(TUMT n = 38; TURP n = 32)

TUMT or TURP. This effect was sustained for at least 3 years of followup. The mean Madsen score in those patients undergoing TUMT improved from a baseline of 12.1 to 3.0 after three years of followup and from 13.1 to 2.3 in those undergoing TURP. TUMT had less effect on voiding parameters; the mean Qmax improved from a baseline 8.4 ml/s to 12.8 ml/s 3 years after treatment in those treated with TUMT, whereas those undergoing TURP improved from 8.3 ml/s to 18.6 ml/s. The PVR decreased similarly in both groups, from a baseline 97 to 47 ml after 3 years in the TUMT group, and from 104 to 43 in the TURP group (Table 3). It was concluded that the objective improvements with TUMT were not equal to those with TURP, but the subjective improvement were more or less comparable. The need for TUMT to achieve Qmax seen with TURP was questioned, because asymptomatic age-matched patients only have a mean Qmax of 13 ml/s.[24]

It is clear that the mechanism of action of TUMT, using the Prostasoft® 2.0 software, is substantially different to that which produces the volume reduction and cavity formation obtained with TURP. Clinical outcome could possibly be

enhanced with higher temperatures, resulting in thermoablation and thus cavity formation.

Prostasoft® 2.5

Modifications to the operating software have provided more power at a maximum of 70 Watt and a higher rectal threshold temperature, resulting in fewer interruptions during treatment and a mean increase of 40% in the total energy delivered to the prostate.[25]

Changes in subjective parameters using (high energy) Prostasoft® 2.5 were similar to those in patients treated using Prostasoft® 2.0. The mean Madsen symptom score improved from a baseline of 14, to 6 at the 3-month followup. However, when objective improvement was compared, there was a significantly better outcome in the changes in Qmax (Table 4).[25,26] Indeed, after high energy thermotherapy, values of Qmax were greater than those of patients in the same age group but with no voiding symptoms.[24] The improvements in Qmax were in the range that is observed after TURP, from a mean baseline of 9 ml/s to almost 16 ml/s by 3 months after treatment. Transrectal ultrasonography of the prostate, performed 3 months after treatment, identified a cavity in more than 40% of the patients. There was a positive correlation between the presence of such a cavity and the improvement in Qmax.

Thus, more energy delivered to the prostate seems to result in greater improvement in objective parameters possibly because cavities are created in the prostate. However, the price is an increase of incidence of morbidity. Whereas patients treated with the Prostasoft® 2.0 were reported to have a urinary retention rate after treatment of about 20%, using high energy Prostasoft® 2.5 a catheter was needed in all patients for at least 1 week. Although irritative complaints such as frequency, dysuria and hematuria were also reported after low energy TUMT treatments, they were more frequent and pronounced during the first 2-4 weeks in patients

Table 4. *Some results obtained using high energy thermotherapy devices compared with those using Prostasoft® 2.5*

	No. of patients	Qmax (ml/s)		Symptomatic improvement (%)
		Before	After	
Prostasoft® 2.5 [44,26]				
	116	9.6	15.7	59
	72	9.2	15.2	62
TURAPY 70 [45]	72	5.8	12.3	53
Prostalund [46]	91	8.5	10.2	38
T3 System [47]	103	9.4	14.3	62

receiving the high energy treatment. Nevertheless, the high energy treatments are still possible on an outpatient basis in a single one hour session with no need for anesthesia.

SELECTION CRITERIA

The clinical results of TUMT show a clear separation between patients who respond favorably to TUMT in both subjective and objective parameters and patients who do not respond at all. Consequently, many investigators have searched for selection criteria to predict clinical outcome. Because high energy TUMT is under clinical evaluation, no selection criteria are yet available and the following study was initiated in patients treated with Prostasoft® 2.0.

Responders versus nonresponders

Data of 292 patients from 17 centres were analyzed retrospectively.[27] Using data obtained at the 6-month followup, patients were divided into responders, defined

as having a Madsen symptom score of 3 or less, or 50% or more decrease, a Qmax of 15 ml/s or more, or 50% or more improvement, and a PVR of 50 ml or less, or 50% or more improvement, and nonresponders defined as those with a Madsen symptom score of 8 or more, or 50% or less improvement, a Qmax of 10 ml/s or less, or 20% or less improvement, and a PVR of 200 ml or more, or 50% or less decrease. There were no differences in any of the baseline clinical parameters (i.e. age, prostate volume, symptom scores, Qmax and PVR) between the groups and it was concluded that none of the baseline parameters used in this study were able to define the 'ideal' patient for treatment or to predict the result of treatment. However, compared to nonresponders, the responders had significantly different curves of the urethral and rectal temperatures during treatment, possibly because there was a better energy absorption by the prostate tissue. This absorption eventually causes tissue damage, which may be reflected in change of PSA level. Indeed, the responders showed a significantly greater increase of PSA level 1 week after treatment when compared to that of nonresponders, suggesting a more pronounced effect of treatment on prostatic tissue.

There has been increased interest in urodynamic investigation, using pressure flow analysis (PFA), in the assessment of patients with voiding complaints. In the aforementioned study,[27] urodynamic studies with PFA were not performed. Therefore, a multicentre, retrospective urodynamic study was conducted to evaluate the role of PFA in TUMT treatment to determine whether it predict the clinical outcome of TUMT treatment.[28]

The role of pressure flow analysis

Urodynamic studies have been used to investigate the pathophysiology of benign prostatic disease and to evaluate the clinical outcome of various treatment modalities.

The (change of) elasticity of the prostatic urethra seems to play an important

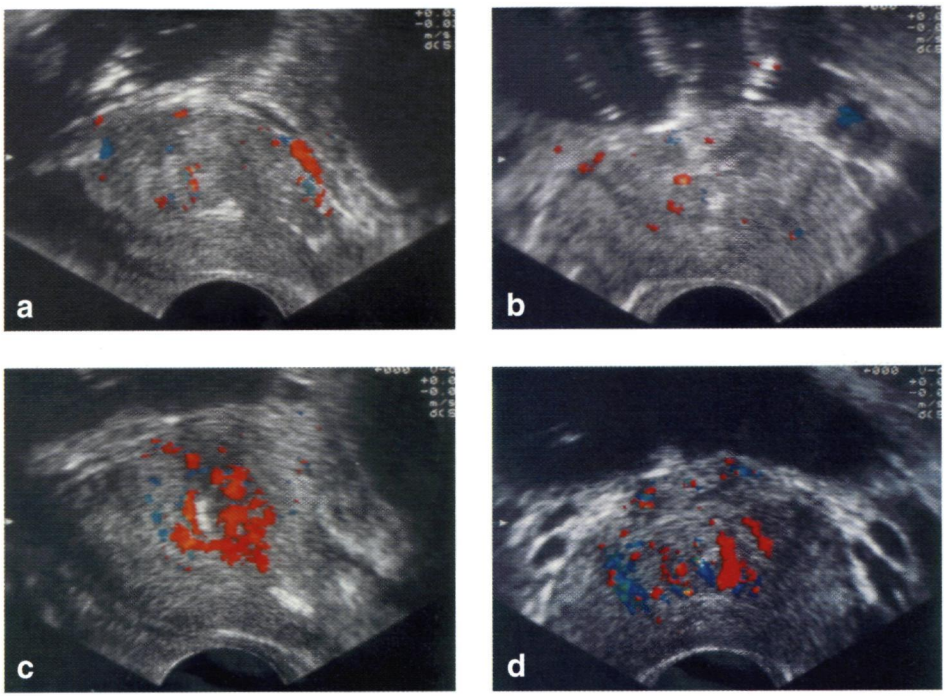
role in treatment of BPH using TUMT.[29-31] If TUMT is able to modify elasticity of the prostatic urethra, patients suffering from reduced elasticity should be ideal candidates for study. This hypothesis was tested in a retrospective analysis of a large European multicentre study,[28] which showed that no single subjective or objective parameter was significantly correlated with clinical outcome after TUMT. However, there was a trend towards a better outcome in patients with less obstruction. Schäfer defined two types of obstruction, constrictive and compressive.[32] When the patients were divided according to this definition, both groups were still comparable at baseline but differed significantly after treatment. The severity of symptoms of BPH was significantly modified in both groups, with a greater decrease in severity in patients with constriction than in those with compression. The change in objective parameters after treatment also differed significantly in both groups; those with predominantly constrictive obstruction had a greater improvement in voiding parameters, than did those with compressive obstruction. It was concluded that PFA may be used to identify the patients who respond favorably using Prostasoft® 2.0.

DISCUSSION

Since 1990, TUMT using Prostasoft® 2.0 has been used for the treatment of men with lower urinary tract symptoms. There are several advantages of the minimally invasive approach in TUMT; patients are treated on an ambulatory basis, complications are extremely rare and patients suffer minimal discomfort, which arises mainly from the 20%, who need catherization for about 1 week after treatment.

The results of TUMT treatment have been encouraging, but there has been some scepticism as to the place of TUMT in the urological options available for the treatment of BPH. Several studies have demonstrated that there is significant clinical effect, with a reduction in symptom scores. However, the changes in Qmax

Figure 1. *Ultrasonograms of the prostate with color Doppler mapping using the Hitachi EUB555 with a transrectal probe (V33W; 6.5 MHz multipurpose endoprobe), before (**a,** longitudinal and **b**, transverse) and immediately after TUMT (**c,** longitudinal and **d**, transverse).*



are less impressive and do not attain those achieved after TURP. The advocates of TUMT treatment have argued that thermotherapy eventually results in changes of voiding parameters after treatment comparable to those in asymptomatic elderly men. In this respect, TURP could even be considered as an 'over treatment' in achieving a supra-normal Qmax after surgery.

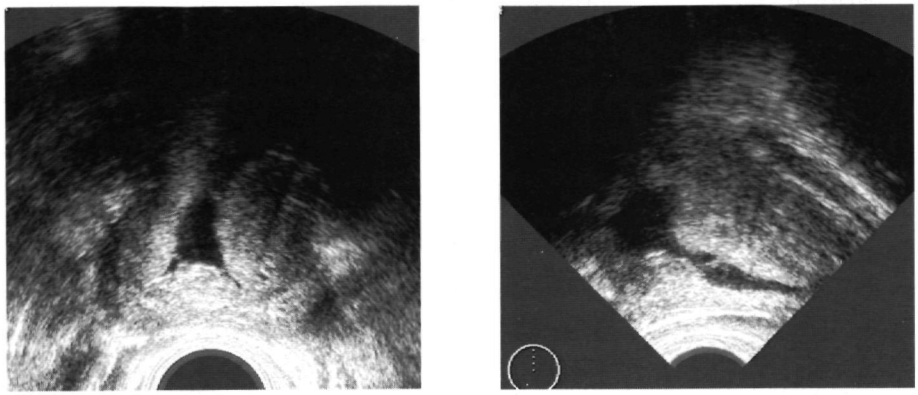
In contrast to surgical therapy, the clinical results after TUMT treatment show a wide range in outcome variables. Recent results have produced a better understanding of how microwave heating of the prostate can achieve clinical benefits and suggest better selection criteria which may allow us to take advantage of the undoubted benefits of a less-invasive treatment. The clinical benefit seems

to be related to the achieved intraprostatic temperature, which results from a complex interaction between the biological response to microwaves and the pattern of energy provided during the treatment in any individual.[9,10] This interaction depends on the heat-sink formed by the veins of the Santorini's plexus, and on the heterogeneity of each individual's prostatic structure. Overall, in unselected patients, there is a 60% improvement in subjective and a 30% improvement in objective variables after 1 year. Unless predictive factors can be identified and/or the efficacy of TUMT treatment is improved, opponents of TUMT treatment will not accept this minimally invasive therapy as a valuable alternative for treatment of BPH.

The outcome of TUMT may be closely related to the vascularization and tissue composition of the prostate. Tubaro et al. showed that TUMT significantly changed intraprostatic blood perfusion.[33] Color Doppler flow analysis performed immediately after treatment showed a mean 12.5-fold increase in the number of visible vessels within the prostate. This effect appeared to be restricted to the adenomatous area (Figure 1). Presently, there are few published studies concerning the vascularization of the prostate. Because it has a major impact on treatment outcome, this subject demands further investigations, as does the influence of composition of the prostate.

Thermotherapy relies on a predictable zone of heating within homogenous prostatic tissue; however, it is well known that prostatic tissue is heterogeneous. Because glandular and stromal tissue respond differently to heat, it is obvious that thermotherapy will have a different impact on individual prostates. Studies to test this hypothesis and provide selection criteria based on histological variables are under way. Complications after TUMT are minimal and patients tolerate the treatment well. Many patients who are unfit for surgery, because of poor physical health, may profit from this ambulatory anesthesia-free therapy. The re-treatment rate 1 year after TUMT using Prostasoft® 2.0, is acceptable and ranges from 1 to 13%.[34] To determine the durability of response, a longer followup is necessary and

Figure 2. *Ultrasonograms of the prostate showing cavity formation 3 months after TUMT using the Prostatron and Prostasoft® 2.5 (**a**, transverse. **b**, longitudinal section)*



the three years followup results of Dahlstrand et al., are very encouraging.[17]

To improve the treatment outcome, high energy software and devices have been developed (Prostasoft® 2.5; TURAPY 70; Prostalund; T3 System). The early results of these high energy thermotherapies are very promising and more comparable with the results of TURP. Indeed, the efficacy of increased heating has improved and the conclusion 'the hotter the better' seems correct (Table 4). Cavities are frequently detected by ultrasonography after treatment (Figure 2), which may account for the improvements found so far. Larger prostates with moderate to severe bladder outlet obstruction seem to be best candidates for the higher energy thermotherapy treatment. However, there is an increased morbidity, mainly arising from prolonged catherization and irritative complaints after treatment. From these preliminary results it seems obvious that high energy thermotherapy is the way forward.[25]

Therefore, we conclude that the objective must be to determine the thermal dose which will maintain a safe treatment with clinically significant improvements in objective and subjective variables, whilst causing minimum morbidity after treatment. Moreover, a maximum benefit will be guaranteed only when proper selection criteria are identified and applied.

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SUMMARY AND FUTURE PERSPECTIVES

SUMMARY

For many decades, the only solution for male bladder outlet obstruction has been the surgical removal of prostate tissue. In the past sixty years, the transurethral resection of the prostate has been perfected to the extent that it is now an acceptably safe procedure. However, the morbidity and costs involved with the procedure and the patients demands for non-surgical treatment, has led to development of numerous medical and procedural alternatives that aimed to reduce the burden on both the patient and the health care expenses.

Nearly all procedural modalities are based on the application of some form of heat to the prostate aiming at destruction and consequent removal of tissue. Although many different heat applicators are available, the use of microwaves has been most extensively investigated and reported on. This thesis reports on several clinical trials that have been conducted using TransUrethral Microwave Thermotherapy or TUMT for the treatment of elderly men with lower urinary tract symptoms and benign prostatic enlargement. Furthermore, we enlighten improvements of this technique and possible predictive factors and subjects for future research efforts.

Early experience and the first reports on TUMT results, showed significant subjective improvement. However, the objective improvement was less pronounced and not comparable to results achieved with surgical intervention. To investigate the role of a possible placebo effect, we conducted a randomized controlled study of Sham versus TUMT treatment. **Chapter 1** shows that although a placebo response indeed is present, compared to the genuine treatment the improvement seen after sham accounts for little of the observed benefit.

Nevertheless, the TUMT results demonstrated a high variability between patient's response in both subjective and objective variables. In **chapter 2** we discuss possible factors that might predict or enhance treatment outcome based on data derived from a retrospective trial in 292 patients at 17 centers worldwide. We

demonstrated that responders to thermotherapy had a significant higher total energy dose administered with significant higher urethral temperatures and fewer rectal alarms. Furthermore, the PSA levels after treatment, as an indirect measure of intraprostatic temperature, were measured significantly higher in the responder group. However, none of the baseline variables used within our study was able to define the ideal patient for and predict the result of treatment.

The durability of response of thermotherapy is discussed in **chapter 3**. We report on a retrospective study on 305 patients that underwent TUMT in two European centers. After 3 year follow-up, a total of 133 patients that only had TUMT treatment were available. We showed that the improvement in symptom score and urinary performance stayed stable over this observation period, with a slight symptomatic deterioration after three years. The retreatment rate amounts to 48% in 3 years: 80 patients underwent an invasive treatment, and 45 patients turned to medical therapy. We reported only little morbidity on short and long term follow-up.

In order to improve treatment efficacy, changes in the treatment protocol were made to enable application of higher energy levels. **Chapter 4** reports on a Phase II multi center study in 116 patients that were treated with this new protocol. We showed that the subjective improvement remained comparable with the results of former lower-energy protocols. On the other hand, the objective improvement was now in the ranges that can be attained after surgical resection of the prostate. In the majority of patients, further proof of increased efficacy was shown by a significant reduction in bladder outlet obstruction based on urodynamic investigations with pressure-flow studies analyses before and 6 months after TUMT treatment. The presence of a prostate cavity, 3 months after TUMT in almost 40% of patients, also contributes to this. The high energy treatments were still possible without anaesthesia and on an outpatient basis. Nevertheless, the post treatment retention rate of 100% with a mean catherization time of two weeks in combination with irritative complaints during the first 2 to 3 weeks, induced an

increased treatment morbidity.

The initial results of high energy thermotherapy showed that the grade of outlet obstruction and the size of the prostate, might be indicative for better treatment outcome. We further elaborate on these findings in **chapter 5**. The changes in pressure-flow study parameters in 120 patients that underwent high energy TUMT, are discussed. For the total group there appeared to be a substantial and clinically relevant reduction in bladder outlet obstruction, that after treatment is no longer present in 72% of patients. Further analysis of the stratified baseline variables, identified that patients with a prostate volume of more than 40 grams with moderate to severe bladder outlet obstruction appeared to be the best responders.

Finally, **chapter 6** gives a review on thermotherapy with reiteration and comparison of the results of the abovementioned studies with the available data in literature. With regard to the results achieved with high energy thermotherapy and the probable predictive factors for improved treatment efficacy, we bring up some possible answers. The fact that bigger prostates respond better to TUMT might be explained by a different composition and vascularization of prostatic tissue.

In chapter 4 and 5 we showed that the efficacy of thermotherapy could be enhanced by applying higher energy levels to increase the intraprostatic temperature. The results of high energy thermotherapy showed significantly better objective improvement over former lower energy protocols with similar subjective outcome. However, although the results in subgroup of patients were comparable to the results achieved with surgical resection of the prostate, there still was a significant group of patients that did not respond favorably. It became apparent that the size of the prostate and the grade of bladder outlet obstruction were indicative for treatment outcome. This variability might be explained by the heterogeneity of the prostatic tissue. The difference in tissue composition and in particular the vascularization of the prostate in each individual patient, are likely the most important contributing factors. Therefore, to further enhance treatment outcome future research efforts should be focused on gaining better insight in 1) **prostate vascularization,** 2) **tissue composition, and** 3) **temperature mapping** of the prostate which may lead to possible adaptions to the treatment protocol and/or devices. Finally, this should be tested in prospective clinical trials based on proper 4) **selection criteria.**

Prostate vascularization

Little is known about the difference in vascularization in each individual prostate and it's correlation in the response to heat treatment. Tubaro et al. demonstrated that there was an enormous increase in prostatic blood flow directly after TUMT treatment.[1] They tried to quantify the amount of increase in blood flow by using color Doppler imaging. They concluded that there appeared to be a 12.5 fold increase in blood flow mainly in the adenomatous part of the prostate. However, presently color Doppler imaging still lacks high reproducibility and quantification

is difficult. Therefore, also other ways for visualization and quantification should be investigated. Possible solution might be the use of intravascular ultrasound contrast agents.[2] The ideal contrast contains micro bubbles that are inert, have the size of red blood cells with identical velocity profiles and physiologic transit times, do not cause systemic hemodynamic effects, and do not alter the bloodflow. It therefore can be applied to determine bloodflow, volume and/or perfusion. The most important property of ultrasonic contrast agents is their capacity to enhance the backscattered signal. This first of all results in images with greater clarity with better visualization of the blood vessels. Furthermore, additional digital substraction techniques might also be applied to further enhance and to make three dimensional imaging possible.[3] Different contrast agents are currently being tested. Were the first research efforts conducted in the field of cardiology, future research may also allow application in prostate imaging.

Tissue composition

Imaging of the vascularization of the prostate implies a dynamic process. Whereas the determination of the tissue composition of the prostate relies more on a static condition.

The prostate is composed from smooth muscle, fibrous tissue, epithelium and glandular lumen. However, the proportion of the various components differs for each individual prostate and depends on the prostate size as on the location in the prostate.[4] This heterogeneity of tissue, with different reactions to microwaves of each component, might partly explain the variety of treatment outcome since the TUMT theory is essentially based on the application of heat to homogenous tissue. Therefore, to correlate treatment outcome with prostate composition, histology is necessary. Hefty et al. showed that a there was difference in the stromal-epithelial ratio of the transition zone of the prostate between patients who failed and who were successful to treatment with laser.[5] The specimens for histology were derived

from pretreatment prostatic biopsies. Similar studies to correlate treatment outcome after TUMT are currently being conducted. Drawback of these studies is the invasive way to obtain histology with consequent risks,[6] and the number and positions in the prostate from which the biopsies can be taken are limited. Therefore, possible noninvasive methods that can cover the complete prostate would be ideal. Presently, computerized analysis of ultrasound images is superior to conventional interpretation of transrectal ultrasound imaging of the prostate in the detection of prostate carcinoma. An image analysis technique based on the correlation of statistical texture descriptions computed from ultrasound prostate images with the histopathology of the tissue imaged (AUDEX), makes differentiation between benign and malignant prostate tissue possible.[7] Possibly, similar techniques can be applied when assessing the stromal-epithelial ratio to enable prostate tissue mapping.

Temperature mapping

The abovementioned methods that might give insight in the dynamic and static properties of the prostate composition, do not elucidate the actual effect that heat has on prostatic tissue. Possibly temperature mapping contributes to a better understanding.

The ideal treatment protocol would be the one that continuously measures the intraprostatic temperature at multiple levels in the prostate to form a feedback system with the energy delivery system to regulate the determined temperatures. Thermometry studies have been performed by applying intraprostatic temperature sensors by the perineal route.[8,9] Major drawback is the invasive nature of this procedure which limits the amount of sensors. Furthermore, they only measure the temperature at predetermined sensor locations, which might not correspond to the actual tissue location of interest. Hence, a non-invasive temperature feedback method should be investigated that can cover the whole prostatic region.

Ultrasound is capable to depict tissue temperature changes by measuring shifts in the reflected signals that are proportional to the change in tissue temperature.[10] Therefore, the theory to combine transrectal ultrasound temperature mapping of the prostate with the heat delivery system to establish a feedback system, offers unique opportunities to greatly enhance treatment efficacy.

Selection criteria

Major research efforts should be aimed at achieving insight in the fundamental dynamic and static properties of the prostate to make adaptions to either the treatment protocol and/or devices and initiation of clinical trials with proper selection criteria possible.

The present thesis has shown that from all the baseline parameters, prostate size and bladder outlet obstruction were indicative for treatment outcome. However, although transrectal ultrasound of the prostate is a common assessment tool in patients with benign prostatic hyperplasia, the use of urodynamic investigations with pressure-flow studies is still a matter of debate due to the invasive character of the procedure, the costs and the availability of the equipment and personnel.[11] Therefore, future clinical trials in thermotherapy could greatly benefit from any noninvasive and easy accessible assessment tools, like the options which have been discussed in the above paragraphs, that are able to distinguish between patients and are predictive for treatment outcome.

We close with the observation that the objective for further studies must be to determine the thermal dose that will still maintain a safe treatment with clinically significant improvement in subjective and objective parameters, whilst causing minimum morbidity after treatment. Only by identifying and applying the proper selection criteria, maximum benefit of thermotherapy can be achieved.

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SAMENVATTING EN TOEKOMSTPERSPECTIEVEN

SAMENVATTING

Decennia lang is de chirurgische verwijdering van prostaatweefsel de enige oplossing voor blaasuitgangsobstructie bij mannen geweest. De laatse zestig jaar is de transurethrale resectie van de prostaat zodanig geperfectioneerd, dat het hedentendage een veilige ingreep is. Echter de met deze ingreep samenhangende morbiditeit, het kostenaspect, alsmede de vraag van patienten naar niet operatieve alternatieven, hebben geleid tot de ontwikkeling van diverse minder invasieve als ook medicamenteuze behandelingsvormen.

Vrijwel alle alternatieve minimaal invasieve technieken maken gebruik van warmte die op verschillende manieren kan worden toegediend. Het uiteindelijke doel van deze warmtetoediening is de destructie en de verwijdering van prostaatweefsel. Diverse technieken zijn beschikbaar, echter het gebruik van microgolven wordt het meest toegepast. Dit proefschrift beschrijft diverse klinische studies met betrekking tot een nieuwe behandelingsvorm voor oudere mannen met mictieklachten en een goedaardige prostaatvergroting, de zogenaamde TUMT-behandeling (TransUrethrale Microgolf Thermotherapie). Verder is geprobeerd verbeteringen van deze techniek, mogelijke prognostische factoren, toekomstverwachtingen en onderwerpen voor verder onderzoek, te verduidelijken.

De eerste resultaten van TUMT lieten weliswaar duidelijke symptomatische verbeteringen zien, echter de objectieve verbetering was minder uitgesproken en niet te vergelijken met resultaten die werden bereikt met een operatief ingrijpen. Om uit te zoeken of een mogelijk placebo-effect een rol speelde, is een placebo gecontroleerde en gerandomiseerde studie uitgevoerd. Hoofdstuk 1 maakt duidelijk dat een er inderdaad een placebo effect aanwezig is. Echter in vergelijking met een daadwerkelijke thermotherapie behandeling, draagt het placebo effect slechts weinig bij tot het uiteindelijk verkregen resultaat.

Desalniettemin vertoonden de resultaten een grote interindividuele variabiliteit in de mate van symptomatische en objectieve verbetering.

Hoofdstuk 2 beschrijft een retrospectieve studie van 292 patienten uit 17 internationale centra, waarin werd gepoogd mogelijke predictieve parameters te identificeren die het behandelingsresultaat konden verbeteren of voorspellen. Het bleek dat patienten die goed reageerden op behandeling een significant hogere totale hoeveelheid energie hadden toegediend gekregen waarbij hogere urethrale temperaturen en minder rectale triggers gevonden werd. Tevens bleek dat de PSA-stijging na behandeling, wat indirect een maat is voor het bereikte effect in de prostaat, significant hoger was bij patienten waarbij de behandeling succes had. Echter geen van de basis-parameters was in staat de ideale patient te identificeren. Noch was het mogelijk om hiermee het behandelingsresultaat van thermotherapie te voorspellen.

De lange termijn resultaten en duurzaamheid van de thermotherapie, worden behandeld in hoofdstuk 3. Hierin wordt een retrospectieve studie van 305 patienten beschreven die een TUMT behandeling hadden ondergaan in twee Europese centra. Na 3 jaar waren 133 patienten beschikbaar die alleen een TUMT behandeling hadden gehad. De subjectieve en objectieve verbetering bleef gedurende deze periode min of meer stabiel, hoewel er een geringe symptomatische verslechtering optrad 3 jaar na behandeling. In totaal werd 49% van de patienten herbehandeld. Bij 80 patienten werd alsnog een operatieve behandeling uitgevoerd en 45 patienten stapten over op een medicamenteuze behandeling. De morbiditeit van thermotherapie op zowel korte als lange termijn, bleek gering te zijn.

Om het behandelingsresultaat te verbeteren, werd het TUMT-protocol aangepast om behandeling op een hoger energie niveau mogelijk te maken. Hoofdstuk 4 beschrijft een fase 2 studie van 116 patienten die behandeld werden met dit nieuwe hoge energie protocol. De symptomatische verbetering bleef vergelijkbaar met eerdere protocollen. De objectieve verbetering daarentegen liet nu resultaten zien die te vergelijken waren met de resultaten van een chirurgische interventie. De meerderheid van de patienten liet een significante daling van de

blaasuitgangsobstructie zien. Dit werd duidelijk gemaakt met blaasdrukmetingen die voor en 6 maanden na behandeling werden uitgevoerd. Het vinden van een caviteit in de prostaat bij echografisch onderzoek bij bijna 40% van de patienten, is een verdere aanwijzing dat de behandeling effectiever is. Deze hoge energie TUMT behandelingen zijn nog steeds mogelijk zonder narcose en op poliklinische basis. Daarentegen is er sprake van een toegenomen morbiditeit die zich met name uit in de noodzaak om na de behandeling een transurethrale catheter te plaatsen bij alle patienten. Gedurende gemiddeld twee weken dient deze catheter te blijven zitten en de patient kan in de eerste 2 tot 3 weken irritatieve klachten ondervinden die van voorbijgaande aard zijn.

De eerste resultaten van de hoge energie behandelingen lieten zien dat de grootte van de prostaat en de mate van blaasuitgangsobstructie bepalend waren voor een beter behandelingsresultaat. In hoofdstuk 5 gaan we verder in op deze bevindingen. De verbeteringen in blaasdrukmeting van 120 patienten die werden behandeld met hoge energie TUMT, worden hier beschreven. De gehele groep laat een aanzienlijke en klinisch significante vermindering van de blaasuitgangs-obstructie zien, waar bij 72% van de patienten na behandeling geen obstructie meer aanwezig is. Verdere analyse van de basis parameters laat zien dat patienten met een prostaatvolume van meer dan 40 cm^3 en matig tot ernstige blaasuitgangs-obstructie het best reageerden op hoge energie TUMT behandelingen.

In hoofdstuk 6 wordt een overzicht gegeven van de literatuur met betrekking tot thermotherapie en worden de resultaten van de in dit proefschrift vermelde studies vergeleken met reeds eerder uitgevoerde onderzoeken. Verder wordt ingegaan op het feit dat het betere behandelingsresultaat van hoge energie TUMT behandelingen bij patienten met grotere prostaten verklaard zou kunnen worden door een verschil in bloedvoorziening en samenstelling van het prostaatweefsel.

In het laatste hoofdstuk wordt vervolgens ingaan op de toekomst-perspectieven. Er zal fundamenteel onderzoek verricht moeten worden naar diverse dynamische en statische eigenschappen van prostaatweefsel met

betrekking tot de reactie op door microgolven gegenereerde warmte. De belangrijkste dynamische factor is de bloedvoorziening van de prostaat. Kwantificatie van de vascularisatie met color Doppler behoort tot een van de mogelijkheden. Wellicht kan de toediening van intraveneus echocontrast hier eveneens tot bijdragen. De samenstelling van de prostaat kan middels echogeleide prostaatpuncties worden vastgesteld en gecorreleerd worden met het bereikte behandelingsresultaat. Andere minder invasieve methoden zoals beeldanalyse technieken, behoren wellicht ook tot de mogelijkheden. Bij een ideale thermotherapie behandeling zou het mogelijk moeten zijn een directe terugkoppeling te verkrijgen met de in de prostaat gemeten temperatuur. De temperatuur in de prostaat kan bepaald worden met behulp van in de prostaat geplaatste optische thermosensoren. Nieuwe ontwikkelingen in de echografie, maken het wellicht ook mogelijk op een niet invasieve wijze de temperatuur te meten.

Toekomstige klinische studies kunnen zeker profiteren van de hierboven genoemde technieken. Het zal patientenselectie mogelijk maken en behandelingsresultaat kunnen voorspellen. Om het maximale effect van thermotherapie te realiseren, zal het uiteindelijke doel moeten zijn de juiste energiedosis te vinden die een veilige behandeling garandeert met een zo gering mogelijke morbiditeit en die tevens een klinisch relevante verbetering in zowel subjectieve als objectieve parameters laat zien.

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Het tot stand brengen van een proefschrift doe je nooit alleen. Het is helaas ondoenlijk om een ieder die hieraan op directe of indirecte wijze heeft bijgedragen, persoonlijk te bedanken. Zonder volledig te kunnen zijn, wil ik de volgende personen met name danken.

Allereerst Prof. Dr. F.M.J. Debruyne, Uw inspanningen maakten de afdeling Urologie Nijmegen tot een internationaal toonaangevend centrum. Het is mij dan ook een voorrecht geweest om in een dergelijke wetenschappelijk stimulerende omgeving, promotie onderzoek te kunnen verrichten.

Mijn co-promoter Dr. J.J.M.C.H. de la Rosette is zonder twijfel de belangrijkste persoon geweest in realisatie van dit proefschrift. Beste Jean, jouw onnavolgbare inzet, gedrevenheid, wetenschappelijke interesse en bereidheid tot begeleiding, zijn van onschatbaar belang geweest. De vele avonden en weekends die we samen doorbrachten achter de computer, waren voor mij niet alleen uitermate leerzaam maar waarschijnlijk veel belangrijker nog, ook erg plezierig. Daarnaast maakte je het mogelijk, dat ik ons wetenschappelijk werk op een groot aantal internationale congressen heb kunnen presenteren.

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I like to thank all the people I have worked with during my too short stay in the U.S. It has been a great opportunity for me to have a look behind the scenes of a medical company and its efforts to get a great machine through FDA approval. It has been a great pleasure to have met the American physicians who are also strong believers of thermotherapy.
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CURRICULUM VITAE

De auteur van dit proefschrift, Michel Johannes Antonia Maria de Wildt, werd geboren op 7 December 1965 te Nijmegen. Het Gymnasium β examen werd behaald aan het Dominicus College te Nijmegen op 30 mei 1984. Driemaal werd hij uitgeloot voor de studie Geneeskunde. Derhalve was hij in 1984 met de studie Gezondheidswetenschappen gestart aan de Katholieke Universiteit Nijmegen. Het aanhouden werd uiteindelijk toch beloond met een naplaatsing in het najaar van 1986. Vervolgens is hij overgestapt naar de studie Geneeskunde, eveneens aan de Katholieke Universiteit Nijmegen. Het doctoraal examen behaalde hij op 23 november 1990. Na twee jaar co-schappen werd vervolgens het Arts examen behaald op 4 juni 1993. Aansluitend is hij van 15 juni 1993 tot 1 januari 1996, op de afdeling Urologie van het Academisch Ziekenhuis Nijmegen (Hoofd: Prof. Dr. F.M.J. Debruyne) als arts-onderzoeker werkzaam geweest. In deze periode heeft hij zich onder de directe leiding van Dr. J.J.M.C.H. de la Rosette (hoofd Centrum Prostaatonderzoek), zeer intensief bezig gehouden met klinisch onderzoek naar nieuwe alternatieve behandelingsmogelijkheden voor patienten met een goedaardige prostaatvergroting. Dit resulteerde onder meer in het hier voorliggende proefschrift.

Per 1 juli 1996 is hij werkzaam in het St. Joseph Ziekenhuis te Veldhoven op de afdeling Algemene Heelkunde (Hoofd: Dr. F.A.A.M. Croiset van Uchelen) in het kader van zijn opleiding tot Uroloog.

Stellingen behorende bij het proefschrift

TransUrethral Microwave Thermotherapy

an evolving technology in the treatment of benign prostatic enlargement

door

Michel J.A.M. de Wildt

Nijmegen, 24 september 1996

1 De wonderlijke combinatie van stralingswarmte en koudegeleiding vormt de basis van het thermotherapie principe.
Dit proefschrift

2 Zonder twijfel is thermotherapie meer dan alleen placebo.
Dit proefschrift

3 Hoe groter de prostaat, des te beter het resultaat.
Dit proefschrift

4 Het urodynamisch onderzoek lijkt vooralsnog alleen bij thermotherapie van prognostische waarde te zijn voor het te bereiken behandelingsresultaat.
Dit proefschrift

5 De hoogte van de individuele symptoom score is noch voor de patient noch voor de uroloog van enige waarde.
Dit proefschrift

6 Gezien de goede resultaten van thermotherapie bij BPH rijst de vraag of de transurethrale resectie van de prostaat nog wel als 'gouden standaard' moet worden beschouwd.
Dit proefschrift

7 Nog steeds geldt dat de numerus fixus voor de studie Geneeskunde met name gebaseerd is op kans en niet op de mate van intelligentie.

8 Specialisatie leidt tot artsen die steeds meer weten over steeds minder.

9 Hoe lager de frequentie, des te dieper de penetratie, is niet alleen een fysisch verschijnsel.

10 De behandelend arts van de prostaat-magnetron is net als een chefkok bij het braden met boter: voor het beste resultaat dient hij 'er wel even bij te blijven'.

11 Het als dokter promoveren tot doctor in de Medische Wetenschappen betekent niet per definitie dat de geneeskunde ook ten volle wordt beheerst.

12 'Even at the center of fire there is cold' *(by* ☥ *)*