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REVIEW

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

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History

The use of heat in the 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 45–60°C cell death can occur and is defined as thermotherapy. Thermal treatment in excess of 70°C destroys all living human tissue and is termed thermoablation [2].

Hyperthermia was first introduced in the early 1980s, initially to treat prostate carcinoma [3]. The alleviation of the symptoms of prostatism and the reduction of tumour bulk seen in patients treated with hyperthermia also led to the application of hyperthermia in patients with benign prostatic hyperplasia (BPH) [4]. Many studies have been published on the use of hyperthermia in the treatment of BPH. Although they reported significant symptomatic relief, the effect on objective improvement was very limited. Moreover, in a multicentre study [5], transrectal hyperthermia was shown to be ineffective when compared with sham treatment. However, transurethral hyperthermia is still under investigation as it 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.

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Microwave tissue interaction

The applicability and outcome of microwave treatment is influenced by the microwave frequency used, the tissue composition and vascularization, and the 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 the 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, 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 temperature.

Cell death is achieved when temperatures exceed the cytotoxic threshold, which depends on cell type; in prostate adenomatous tissue the thermal threshold is 45°C for 30 min. 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 determined not only by tissue composition but also by tissue vascularization [2].

To allow treatment with no anaesthesia, 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 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 also higher temperatures, up to 70°C, deep inside the lateral prostatic lobes, resulting in tissue coagulation, necrosis and even tissue ablation. Not all prostates 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, and the authors have experience with over 600 patients treated using this device. Therefore, 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 and with no need for anaesthesia: Prostasoft Version 1.0 (temperatures $\leqslant$ 50°C); Version 2.0 (temperatures from 50–60°C) and Version 2.5 (temperatures $\geqslant$ 70°C). Version 2.0 is the most widely used and Version 2.5 is currently under investigation. The procedure for TUMT treatment 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 about 70% (Table 1). Similar symptom scores were found in asymptomatic elderly men [15].

Urinary peak flow rates (Q_{max}) were also improved, although less pronounced. Mean Q_{max} 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, improvements in Q_{max} occurred gradually. Improvement had occurred by 4 weeks after treatment and was more pronounced after 3 months. The final improvement of Q_{max} occurred between 6 and 12 months after TUMT and was sustained at the follow-up 3 years later [16,17]. Post-void residual urine volume (PVR) also decreased significantly; large initial PVRs were reduced, but better results were 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 possible placebo effect remain 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). In

Table 1 Improvement in main treatment indices before, 3, 6 and 12 months after TUMT. Where available, means are shown with standard deviation

Reference	No. of patients	Symptom score			Q_{max} (mL/s)			Post-void residual volume (mL)		
		Baseline	3 months	1 year	Baseline	3 months	1 year	Baseline	3 months	1 year
[13]	37	12±3.0	8±3.0	–	8.4±2.2	10.8±3.1	–	109±60	50±66	–
[11]	19	12	2.8	1.4	8.2	14.3	14.3	64	41	58
[35]	37	8.5*±2.4	4.5±2.5	–	10.3±5.4	11.5±5.1	–	–	–	–
[36]	60	13.9	4.8	–	8.9	13.1	–	–	–	–
[37]	17	16.5±4.4	–	6.9	7.2±2.1	–	10.7±3.0	39±50	–	17±23
[38]	130	12.9	5.9	6.4	10.4	11.5	11.8	54	49	42
[39]	128	11.3	2.1	–	9.2	14.9	–	100	43	–
[40]	140	11.7*±5.0	4.9±3.3	4.2	9.0±4.2	12.6±4.3	13.3±4.0	135±18	81±27	41±41
[41]	140	23.7*±4.4	10.6±2.7	11.6	10.1±4.7	12.3±3.2	12.4±3.4	98±46	69±29	76±23
[42]	818	13.3	5.7	3.5	8.8	13.0	12.6	–	–	–
[43]	115	15.7	3.8	2.6	9.8	13.3	13.7	108	33	22.4

*Symptom score other than the Madsen-Iversen Symptom score

Table 2 Results of sham-controlled studies. Mean values with standard deviation where available

Reference	Treatment	No. of patients	Symptom score			Q_{max} (mL/s)			Post-void residual urine (mL)		
			Baseline	3 months	1 year	Baseline	3 months	1 year	Baseline	3 months	1 year
[18]	Sham	19	14.2	12.8	–	8.6	9.2	–	118	171	–
	TUMT	21	14.5	4.3	–	8.5	13.0	–	147	12	–
[19]	Sham	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	–	–	–
[20]	Sham	36	14.9	10.7	–	7.4	9.5	–	–	–	–
	TUMT	75	13.9	6.3	–	7.3	11.5	–	–	–	–
[22]	Sham	44	12.9±3.1	10.4±4.7	8.2±4.5	9.6±2.7	9.7±3.3	10.5±4.3	85±68	104±94	56±65
	TUMT	46	13.7±3.4	4.7±3.7	4.2±5.5	9.2±2.5	13.4±5.8	13.4±5.2	94±75	34±47	50±48
[23]	Sham	40	17.5*	9.5	–	9.4±2.8	9.5±2.9	–	97±56	106±85	–
	TUMT	40	19.0*	9.5	–	8.8±2.3	9.9±3.1	–	86±75	86±51	–
	Control	40	18.0*	17.0	–	8.8±2.7	8.5±1.9	–	86±63	83±53	–

*American Urologic Association — 7 symptom score

addition, the changes in prostate-specific antigen (PSA) levels, seen only after TUMT [19,20], are further proof 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 as 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.* randomized TUMT against the 'gold standard' TURP [17]. Their study showed a statistically identical improvement of symptom scores in patients treated with TUMT or TURP. This effect was sustained for at least 3 years of follow-up. The mean Madsen score in those patients undergoing TUMT improved from a baseline of 12.1 to 3.0 after 3 years of follow-up and from 13.6 to 2.3 in those undergoing TURP. TUMT had less effect on voiding parameters; the mean Q_{max} improved from a baseline of 8.4 mL/s to 11.9 mL/s 3 years after treatment in those treated by 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 of 97 mL to 47 mL after 3 years in the TUMT group, and from 104 to 45 mL 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 improvements were more or less comparable. The need for TUMT to achieve the Q_{max} seen with TURP was questioned, because asymptomatic age-matched patients only have a mean Q_{max} of 13 mL/s [24].

It is clear that the mechanism of action of TUMT,

	Baseline	*3 months*	*12 months*	*24 months*	*36 months*
Madsen symptom score					
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
Q_{max} (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

Table 3 Results of a randomized controlled study of TUMT *versus* TURP [17] (TUMT $n=38$; TURP $n=32$). Mean values with standard deviation

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 thermo-ablation and thus cavity formation.

Prostasoft® 2.5

Modifications to the operating software have provided more power at a maximum of 70 W 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 follow-up. However, when objective improvement was compared, there was a significantly better outcome in the changes in Q_{max} (Table 4) [25,26]. Indeed, after high-energy thermotherapy, values of Q_{max} were greater than those of patients in the same age group but with no voiding symptoms [24]. The improvements in Q_{max} 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 Q_{max}.

Thus, more energy delivered to the prostate seems to result in a greater improvement in the objective parameters, possibly because cavities are created in the prostate. However, the price is an increased incidence of morbidity. Whereas patients treated using 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 haematuria were also reported after low-energy TUMT treatments, they were more frequent and pronounced during the first 2–4 weeks in patients receiving the high-energy treatment. Nevertheless, the high-energy treatments are still possible on an out patient basis in a single 1-h session with no need for anaesthesia.

Selection criteria

The clinical results of TUMT show a clear separation between patients who respond favourably 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

Device	*Publication*	*No. of patients*	*Q_{max} (mL/s) Before*	*After*	*Symptomatic improvement (%)*
Prostasoft® 2.5					
	[44]	116	9.6	15.7	59
	[26]	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

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

clinical outcome. Because high-energy TUMT is under clinical evaluation, no detailed selection criteria are yet available and the following study was initiated in patients treated with Prostasoft® 2.0.

Responders versus non-responders

Data from 292 patients in 17 centres were analysed retrospectively [27]. Using data obtained at the 6-month follow-up, patients were divided into responders, defined as having a Madsen symptom score $\leqslant 3$, or $\geqslant 50\%$ decrease, a $Q_{max} \geqslant 15$ mL/s or $\geqslant 50\%$ improvement, and a PVR $\leqslant 50$ mL or $\geqslant 50\%$ improvement, and non-responders, defined as those with a Madsen symptom score $\geqslant 8$ or $\leqslant 50\%$ improvement, a $Q_{max} \leqslant 10$ mL/s or $\leqslant 20\%$ improvement, and a PVR $\geqslant 200$ mL or $\leqslant 50\%$ decrease. There were no differences in any of the baseline clinical variables (i.e. age, prostate volume, symptom scores, Q_{max} and PVR) between the groups and it was concluded that none of the baseline variables used in this study were able to define the 'ideal' patient for treatment or to predict the result of treatment. However, compared with non-responders, the responders had significantly different curves of 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 a change of PSA level. Indeed, the responders showed a significantly greater increase in PSA level 1 week after treatment when compared with that of non-responders, suggesting a more pronounced effect of treatment on prostatic tissue.

There has been increased interest in urodynamic investigations, 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 can 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 the treatment of BPH using TUMT [29–31]. If TUMT is able to modify the 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 the 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 those patients who respond favourably 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 catheterization 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 a significant clinical effect, with a reduction in symptom scores. However, the changes in Q_{max} 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 'over treatment' in achieving a supra-normal Q_{max} 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

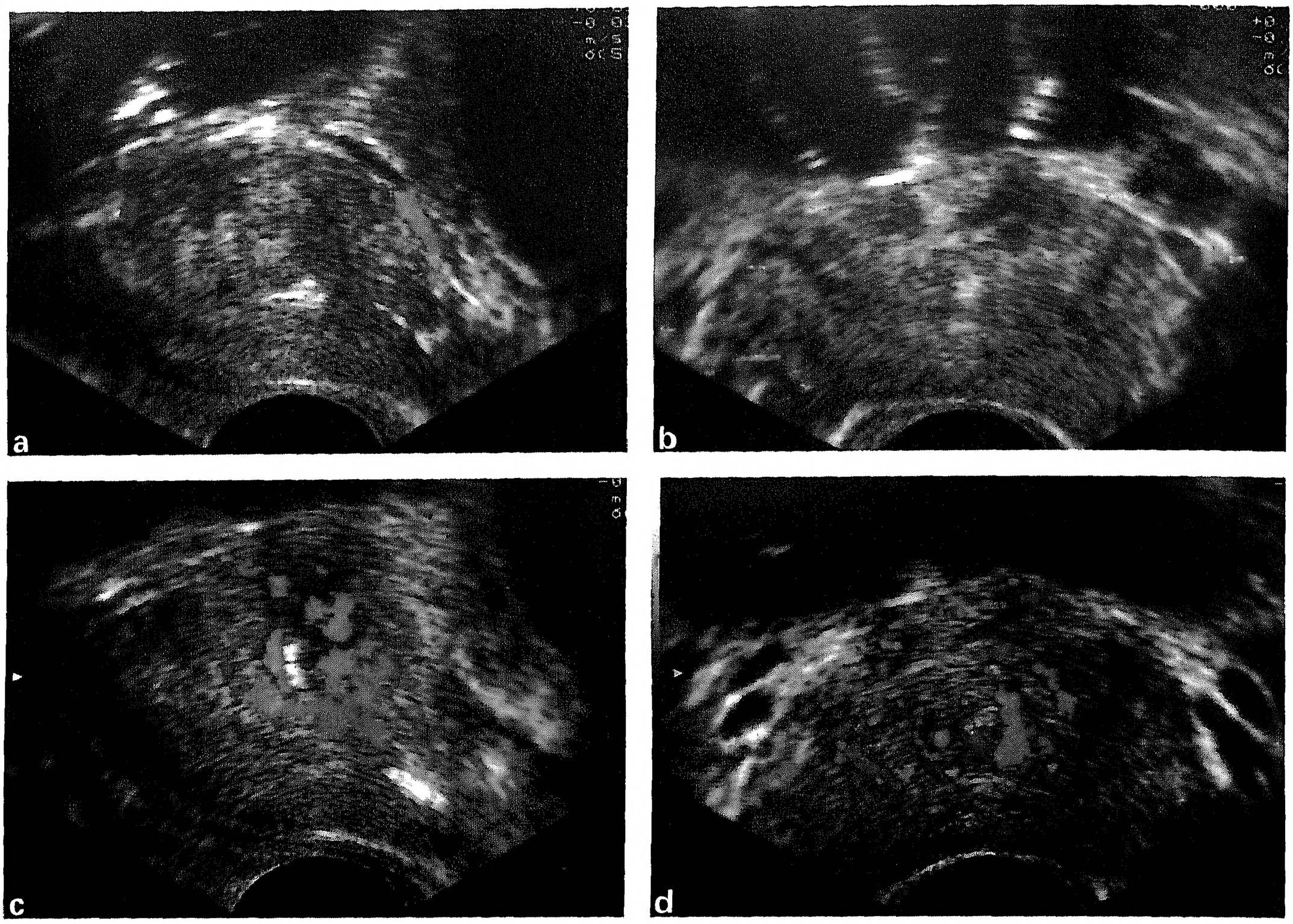

Fig. 1. Ultrasonograms of the prostate with colour Doppler mapping using the Hitachi EUB555 with a transrectal probe (V33W; 6.5 MHz multipurpose endoprobe), before (a, longitudinal and b, transverse) and immediately after TUMT (c, longitudinal and d, transverse).

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 will not accept this minimally invasive therapy as a valuable alternative for the 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]. Colour 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 (Fig. 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 investigation, as does the influence of the 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, anaesthesia-free therapy. The re-treatment rate 1 year after TUMT using Prostasoft® 2.0 was acceptable and ranged from 1 to 13% [34]. To determine the durability of response, a longer follow-up is necessary and the 3-year follow-up results of Dahlstrand *et al.* are very encouraging [17].

To improve 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. Cavities are frequently detected by ultrasonography after treatment (Fig. 2) which may account for the improvements found so far. Larger prostates, with moderate to severe bladder outlet obstruction, seem to be the best candidates for the higher energy thermotherapy treatment. However, there is an increased morbidity, mainly arising from prolonged catheterization 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, maximum benefit will be guaranteed only when proper selection criteria are identified and applied.

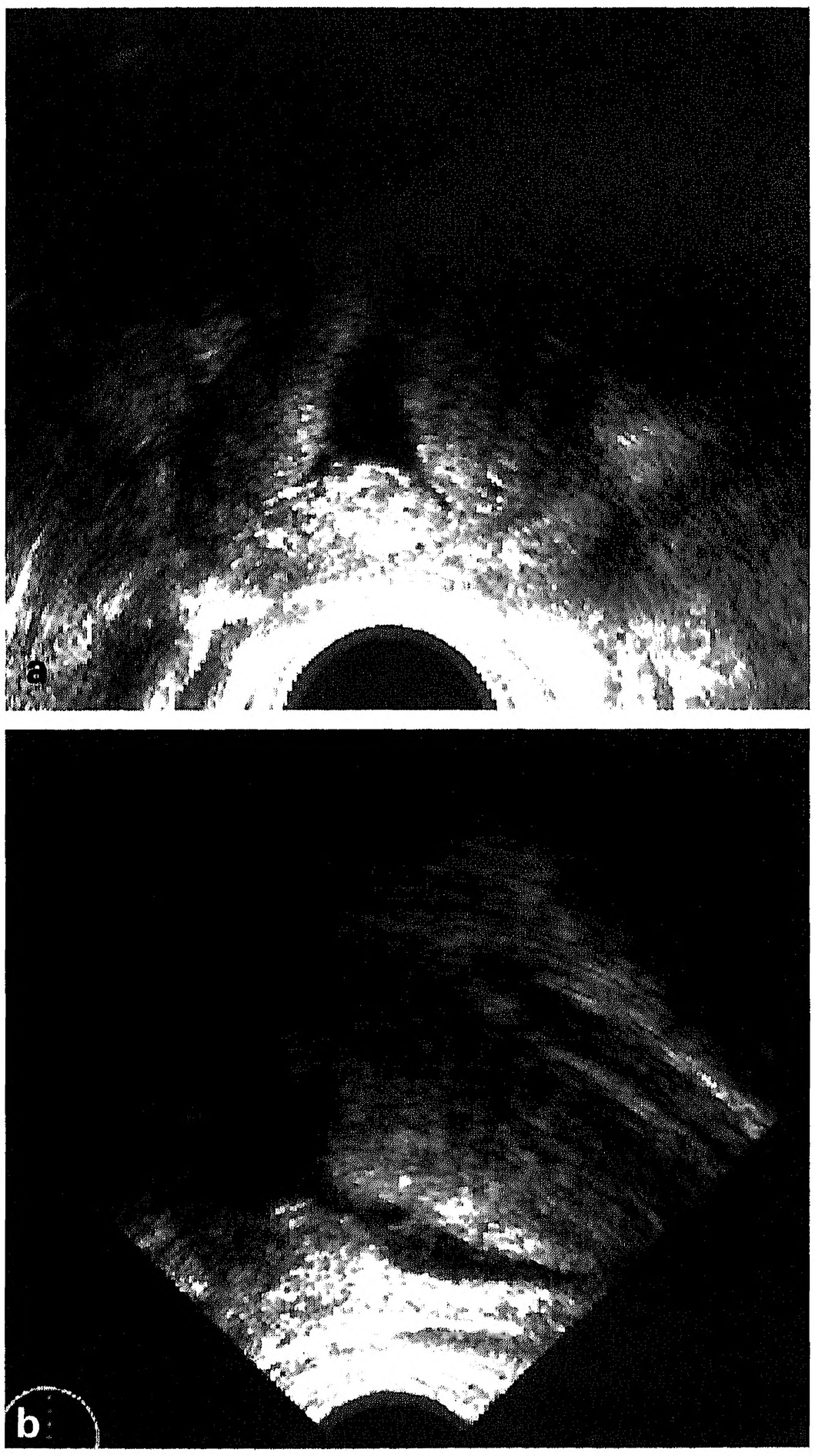

Fig. 2. Ultrasonograms of the prostate showing cavity formation 3 months after TUMT using the Prostatron and Prostasoft® 2.5. a, Transverse section. b, Longitudinal section.

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